Risk assessment for acute toxicity from sheep ectoparasite treatments, including organo phosphates (OPs) used in plunge dipping

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EXECUTIVE SUMMARY (FINDINGS AND RECOMMENDATIONS)

This summary brings together the outcomes and recommendations from the rest of the report. In order that it can be read as a stand-alone document (when taken in conjunction with the glossary) it starts by reiterating the aim of the project.

Project Aim

The aim of the project was to carry out an assessment of the risks to sheep dippers of suffering short-term, ill-health effects associated with organophosphates (OPs). Specifically, the risk considered was that of workers being exposed to doses of OPs during sheep dipping such as to produce overt, acute toxicity accompanied by recognised clinical signs or symptoms. Here, acute toxicity refers to ill-health effects that occur over a short period of time (hours or a few days) immediately following exposure.

The scope of the project included consideration of the chemical methods for sheep ectoparasite control which can be used as an alternative to dipping with OP, namely:

- using pyrethroid dips;
- using pyrethroid pour-ons1; and
- using macrocyclic lactone (ivermectin, doramectin & moxidectin) injectables.

Main Findings

F-1 Quantified risk assessments

In the first stage of the project, we carried out quantified risk assessments for human health. This was based on published information on the toxicology and likely exposures to workers dipping sheep using the organophosphate diazinon2, currently approved for sheep dipping, and the alternative chemical methods of sheep ectoparasite control listed above. We used a similar approach to the published, risk assessment methodology and criteria for worker safety used by UK regulators for the granting of approval/marketing authorisation of pesticides. While the risk assessment methodology is not itself precautionary, the criteria used for making decisions about pesticide product approval that seek to ensure protection from adverse health

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1 'Pour-on' is a generic term used to describe products which are applied by means of an applicator gun, either as a spray-on, spot-on or pour-on.
2 We have also carried out quantitative risk assessments on chlorfenvinphos and propetamphos which, though no longer registered for use, were very widely used for OP sheep dipping from the late 1980s until revocation of their approval (chlorfenvinphos-1994 & propetamphos 2000).
effects for workers and bystanders are precautionary (OGOP,1998; ICPS 2000). We did not use those for veterinary medicines (which sheep ectoparasiticides are classed as) since the details are not published.

The findings from this stage of the project were as follows:

F-1.i For farm-workers\(^3\) dipping using the organophosphate diazinon at fixed dip-baths, the risks related to acute toxicity are such that they very largely meet pesticide approval/marketing authorisation criteria for worker safety, except for the case where workers wear no Personal Protective Equipment (PPE) and are involved in handling the concentrated dip. Our risk assessment supports the importance given by regulators to removing exposure to the organophosphate dip concentrate and wearing appropriate PPE.

Some debate continues in international regulatory circles over the appropriate toxicological endpoint to use when reviewing organophosphate studies in animals. We have chosen to consider significant inhibition (>20%) in the activity of the enzyme acetylcholinesterase in red blood cells or brain following short-term exposure as an appropriate measure of the critical, adverse effect. Here, short-term exposures are those which are over not more than seven working days. The choice of this endpoint is based on the assumptions that acute ill-health is related to inhibition of acetylcholinesterase in nervous tissue and that inhibition of red blood cell acetylcholinesterase is a useful surrogate of inhibition of the same enzyme in both peripheral nerves and the brain. Thus our No-Adverse Effect Level (NOAEL) for short term exposure has been defined from consideration of brain or erythrocyte acetylcholinesterase depression in the available toxicological data set.

We used two approaches to estimate the likely levels of worker exposure. The first approach was to use predictive models which are mostly developed from field study data and expert opinion of occupational hygienists. The second

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\(^3\) We make the important distinction between farm workers who carry out dipping for a few days, two or three times a year, and contract workers who may carry out dipping over extended periods. It was not possible to carry out risk assessments for contractors.
approach was based on using urine biological monitoring measurements of organophosphate metabolites from studies of workers undertaking sheep-dipping, together with data from controlled, low-level exposure studies in human volunteers. These latter studies gave an estimate of the relationship between systemic dose and level of urinary metabolites. The aim of the second method was to attempt to estimate the absorbed dose from all possible exposure routes (dermal, ingestion and inhalation) in real dipping situations. The results from the two approaches are in relatively good agreement. Although the predictive model appears to over-estimate exposure in ‘worst-case scenarios’ compared to the available biomonitoring data.

Both the risk estimate based on the predictive models and that based on urine measurements suggested that for at least 95% of sheep-dipping activity which included both handling of the diazinon concentrate and exposure to the dilute dip, the worker exposure is a factor of 100-fold below the highest level of exposure which does not cause an adverse effect (Margins of Exposure (MOE) >100). Using the worst case for the biological monitoring approach (i.e. using the highest urinary metabolite level seen in a sheep-dipper) gave an estimated MOE of 68, but the lack of PPE and extent of concentrate handling has been noted for these ‘real-life’ monitored studies. We noted a relatively small difference between estimated doses in two published reports of subjects showing serious, acute ill-health from diazinon (15mg/kg) and our defined NOAEL (2.5mg/kg). Therefore we considered the possible use of an additional two-fold uncertainty/assessment factor, leading to an acceptable MOE being greater than 200. This level of MOE was readily obtained when considering the situation where concentrate handling was removed. Therefore we consider diazinon used at a fixed dip without any concentrate handling to fully meet the assessment process.

F-1.ii Similar risk assessments were carried out for the organophosphates propetamphos and chlorfenvinphos, although data was not available to use the biological
monitoring approach for exposure assessment. Our analyses suggested that these organophosphates do not meet our application of approval/marketing authorisation criteria and agree with the revocation by VMD of their approval for use in sheep dipping (final chlorfenvinphos product approval revoked in 1994 & approval for propetamphos products revoked in 2000)

F-1.iii For farm-workers dipping using the pyrethroids, high-cis cypermethrin and flumethrin, at fixed dip-baths, the risks are within the criteria for worker safety. An acceptable MOE of 100 or greater for approval was suggested by the data set. MOEs ranging from 300-1,400 were obtained using the estimated 95th percentiles of the derived exposure assessments and considering the influence of concentrate handling and use of PPE.

The exposure assessment estimated the systemic body dose using the same models as for dipping with organophosphates. Although urine biological monitoring methods for assessing pyrethroid exposure exist, there are no available data that allow this second ‘real-life’ approach to exposure assessment to be undertaken for pyrethroids.

F-1.iv We did not carry out an assessment of the risks to contract workers treating sheep using either organophosphates or pyrethroids because contractors may use a variety of methods, including mobile dip-baths, fixed dip-baths on farms or even ‘off-label’ (i.e. non-VMD approved) methods, such as showering or jetting. We could find no data, except one report on sheep-showering, that has systematically investigated the techniques being employed by contractors or relevant exposure data when using well-established mobile dip facilities. We noted evidence of both the increased use of contractors and ‘off-label’ techniques in general.

We highlight aspects of the toxicology database for organophosphates with respect to contract dipping. While the toxicological endpoint may not change, we consider that the nature of the likely exposure of contractors may mean that appropriate toxicological studies used to identify a NOAEL should be sub-acute,
repeated dose investigations. Such repeated dose experiments are likely to produce a cumulative inhibitory effect in acetylcholinesterase in nervous tissues and surrogates, such as erythrocytes. This would mean a substantially lower NOAEL than that appropriate for farm workers carrying out dipping intermittently and would therefore have implications for any risk assessment of contract organophosphate dipping.

It is unlikely for pyrethroids that the NOAEL would alter in reviewing contract dippers, as the defined NOAELs in this report have largely been derived from relatively long-term repeated dosing studies. Although we have no data to judge the likely exposure for contractors using pyrethroids, the high MOEs derived for farm-workers undertaking intermittent dipping and the unlikely need for a change in the NOAEL would suggest that contract dipping using pyrethroids may pose little problem in the context of risk assessment. However we are not convinced that the same could be said for a risk assessment of contractor dippers using OPs.

F-1.v For the use of the macrocyclic lactones (ivermectin, doramectin and moxidectin) used as injectables, the risks are within the criteria for worker safety.

We base this on a simple worst-case exposure resulting from a single case of self-injection. Ivermectin is widely used as a human medicine to treat certain parasitic diseases. The estimated exposure from self-injection with the current delivery systems would not be substantially greater than the doses which are given to people for therapeutic purposes with no or very little side-effects.

F-1.vi For the use of pyrethroid pour-ons, we had insufficient information on worker exposure to carry out an assessment.

We based this decision on a review of published literature and information from both national and international sources on ‘pour-ons’. However, Veterinary Medicines Directorate were unable to respond within the necessary time scale to
our request for information on how their assessments were carried out and the worker exposure data used.

F-2 Actual incidence of short-term ill-health effects amongst OP dippers

F-2.i We have discussed the limitations of the ‘Suspect Adverse Reactions Surveillance Scheme (SARSS)’ incident reporting scheme in relation to providing information on the number of cases of short-term, ill-health effects amongst dippers using organophosphates; and whether it can be established that it is likely that the reported symptoms are the outcome of organophosphate-induced depression of acetylcholinesterase in nervous tissue. There are long established procedures for primary health care professionals to use biological samples to help in diagnosis of any suggested organophosphate over-exposure. The limitations with the incident reporting scheme were suggested to include the lack of such biological sampling and of proactive investigation of reported cases at an early stage where a clear picture of the symptoms, exposure conditions and confounding factors could be gained from the complainant. This proactive investigation of any report may be particularly important for organophosphate exposure where many of the symptoms are non-specific and could be related a number of confounding causes. We consider that these limitations have, for example, contributed to the current position where not only is the true incidence of what is called “sheep-dippers flu” unclear, but also whether it relates to the classical toxicity caused by OP inhibition of acetylcholinesterase. Unfortunately within the time-scale of the project we were not able to arrange a meeting to discuss the scheme with those involved with ‘SARSS’ at VMD.

In addition to these limitations, we note that improving the quality of the guidance on reporting schemes relating to the use of organophosphates in dipping may reduce the uncertainty in the degree of under-reporting.
Based on the number of reported cases during 1993-1996 inclusive, we have made an extremely crude estimate of the actual incidence per dipping operation of short-term ill-health effects. The incidence was estimated as 1/1000 (0.1%) man dipping operations. We attempted to compare this estimate in the context of available human toxicology related to acetylcholinesterase inhibition and the likely levels of exposure. We also reviewed our database of biological/biological effect monitoring data on sheep dippers and other groups occupationally exposed to organophosphates. This allows us to make some subjective comparisons between occupational cohorts on the level of exposure defined by urine metabolite measurements, the incidence of depressed blood cholinesterase levels and the apparent level of reported non-specific symptoms which may possibly be from acetylcholinesterase inhibition.

The outcome is that, within the very large uncertainties of the estimate from SARSS data, we cannot rule out that such an incidence of subclinical toxicity may not have occurred when concentrate handling was part of the work-tasks. Relatively large volumes of concentrate would need to get on skin and not be properly decontaminated in order to get systemic doses causing adverse effects based on inhibition of acetylcholinesterase. However, we could see how such an occurrence could happen on relatively rare occasions. A review of our biological (effect) monitoring data suggests that most sheep dipping reflects relatively low OP exposure, often indistinguishable from the normal population, and without a high incidence of blood cholinesterase depression. But we have relatively small numbers of blood and urine results for sheep dippers and this makes it difficult to disprove that an accidental over-exposure at level causing an anticholinergic effect did not occur at an incidence rate of one every thousand dips. The two main sources of uncertainty relate to the limitations of the reporting scheme and the paucity of biomonitoring data associated with incidents that allows estimation of dose or the prevalence of acetylcholinesterase inhibition.
We qualitatively considered the adequacy of the control of risks in the workplace within the framework of the approach to risk control set out in the Control of Substances Hazardous to Health Regulations, 1994 & 1999 (COSHH).

F-3.i As found in a recent study commissioned by the Environment Agency (Taylor, 2000), there is potentially scope for reducing the need for, and frequency of usage of, chemical methods for sheep ectoparasite control. This includes both better flock management to reduce the spread of infestations, and reducing multiple treatments arising from misdiagnosis of the type of infestation or using treatments ineffectively. The study identifies raising awareness amongst farmers by means including the provision of better information as key to addressing this. However, this report recognised that chemical treatments will remain a key part of keeping sheep parasites in check.

F-3.ii In addition to improvements in handling the concentrated dip solution, there is continued scope for improving control of worker exposure to OPs during dipping. This includes replacing, or the removal from use, of older poorly designed dips, improvements in both engineering controls (such as the use of ‘splash boards’ to reduce splashing of dippers) and in usage of PPE.

F-3.iii All the chemical methods of sheep ectoparasite control considered have some drawbacks (in addition to worker health issues). There are major environmental concerns about the use of pyrethroids, particularly in regard to incidents of river or waterway pollution. Environmental concerns with regard to injectables have centered on the possible effects on dung beetles. These concerns mean, for example, that the use of injectables had been prohibited by the National Trust on their farms, and by English Nature on any grazing land which is classified as a Site of Special Scientific Interest. As highlighted to us by manufacturers, the development of resistance in ectoparasites to pyrethroids is also of growing concern. Similarly, manufacturers noted that, because the active ingredients in
injectables also control endoparasites, their increased use as ectoparasiticides may promote the development of resistant endoparasites. This could have serious animal health and possible human health implications.

F-3.iv From a farmer’s perspective, a wide range of drawbacks and benefits are associated with the different chemical methods of sheep ectoparasite control. These include; the number of ectoparasites against which a product is effective and the time during which it protects against further infestations; the length of the period after treatment during which animals cannot be slaughtered for consumption; disposal of used pyrethroid and organophosphate dips so as to meet the Groundwater Regulations; how labour intensive the method is; and the cost of the product per animal treated. A particularly important issue is whether farmers have hill or lowland flocks since this is a major determinant in the likelihood of re-infestation and the type of parasites which are prevalent. The study for the Environment Agency referred to above, makes the case that, for lowland farms (specifically for secure and enclosed flocks), substitution for dipping is practicable to some degree. We note that during the current moratorium on sales of organophosphate dips, farmers may have gained practical experience of and insights into the use of alternative methods. This may have included ‘off-label’ uses for some chemicals. However, some available data for 1999 suggests a return to organophosphate dips from using pyrethroid dips, and an increase in the use of both injectables and ‘off-label’ techniques.

F-3 v We have considered whether any chemical methods of ectoparasite control, not included in the scope of this project, merit further study.

We consider that this is the case in regard to contractors who use mobile jetting or showering units to administer organophosphates or pyrethroids. There appears to be a growing trend in the employment of contractors. This use of the products does not have marketing authorisation. Information on the implications for the health of the contract workers appears to be limited. There are suggestions that,
in terms of ectoparasite control, the efficacy of these methods may be limited thus leading to an increased need for multiple chemical treatments.

F-3 vi  In terms of the risk assessments carried out for organophosphate and pyrethroids dips, both chemicals meet the approval process which uses the criteria of ensuring the health of the farm worker. Therefore, if dipping is carried out appropriately there is no case for substitution on health grounds alone. Substitution would be driven by a combination of factors including efficacy against the parasite in question, risk of environmental pollution, man-effort involved, etc.

F-3 vii  There has been a considerable amount of guidance on sheep dipping, specifically when using organophosphates. However most field studies have highlighted a substantial level of non-compliance with this guidance.

F-4  Consideration of the Appropriateness of Cost Benefit Analyses

We outline the use of cost benefit analysis in the regulation of workplace safety. We conclude that, in our view, it would not at this time be appropriate for HSE to carry out cost benefit analyses in relation to the alternatives to current practice in dipping with OPs. This conclusion is based upon consideration of two questions:

F-4.i  Is cost benefit analysis appropriate because there is a possible case, on the basis of short-term ill-health effects, for banning OP dips in favour of alternative chemical means of ectoparasite control?

We consider that the criteria for the risks to workers of developing ill-health used within the framework of the precautionary approach adopted in the UK for granting marketing authorisation for pesticides are broadly met for the use of OP dips by farm workers in relation to short-term ill-health (F1-i above). Because of the
lack of data needed to carry out a risk assessment, we cannot comment on whether the criteria are met for contract workers (F1-iv above). As such, in our view, on the basis of current scientific understanding, there is not a case for banning OP dips in favour of alternative chemical means of ectoparasite control. However, we consider it essential that data is gathered to enable an assessment of the risks to contract workers to be made.

We emphasise that we have given no consideration to longer-term ill-health effects associated with OPs as this was outside our remit.

F-4.ii Is cost benefit analysis appropriate because there is a possible case for enforcing, as reasonably practicable, the adoption of working practices which go beyond those which are currently good practice?

As outlined at F-3.ii above, we consider that there is continued scope for improving control of the exposure to OPs of workers during dipping. However, this is related to improving compliance with the guidance already given by HSE which we understand to describe measures considered to be good practice.

Similarly, as outlined at F-3.i above, there is scope for reducing the need for, and frequency of usage of, chemical methods for sheep ectoparasite control. However, this is in relation to measures which we understand may be considered to be current good-practice.
Recommendations

Our three main recommendations are as follows:

R-1 We recommend the publication of the risk assessment methodology and criteria used in relation to user-safety for regulatory decisions on whether to grant UK marketing authorisation for veterinary medicines. This would be in line with the stated government objectives of transparency and accountability in regulatory decision making.

R-2 We recommend a review of the SARSS incident reporting scheme in relation to the limitations discussed at F2-i above. This review should include consideration of the wider perspective of improving the quality of both the guidance on reporting schemes relating to the use of organophosphates in dipping and the annual reports.

R-3 We recommend that consideration is given to a ‘post-registration’ survey to confirm the degree of ‘real-life’ exposure to workers dipping with OPs. This could be based largely on measurements of metabolites in urine samples. A survey should cover both fixed and mobile dips. Such a survey would:

- allow an assessment to be made of the risks to contractors (see F1-iv above);
- allow tracking of the effectiveness of improvements in removing concentrate handling and using closed transfer devices;
- address one of the main uncertainties outlined at F2-ii above in relation to the actual incidence of short-term ill-health effects;
- help demonstrate for a work activity that remains contentious, the validity of the risk assessment and approval process in an open and independent manner;
The survey could also be used to collect data on exposures associated with mobile jetting and showering units if this is found to be needed in order to carry out a risk assessment (see the following recommendation).

Additional recommendations are as follows:

R-4 We recommend, in relation to F-3.v above, that an assessment is made of the risk to contract workers’ health associated with the use of mobile jetting or showering units. (Such an assessment could be part of a wider review of not only worker-safety, but efficacy and environmental risk; in essence a veterinary medicine marketing authorisation).

R-5 We recommend, in relation to F-1.vi above that, in discussion with the Veterinary Medicines Directorate, consideration is given to whether exposure data is needed for the use of pour-ons.

R-6 We recommend that consideration is given to whether, within the restrictions imposed by legislation, it would be possible to publish, at least in part, details of the user-safety risk assessments used in granting UK marketing authorisation for specific products as veterinary medicines. This would parallel the situation for UK risk assessments for pesticides as agricultural and non-agricultural products and for some non-UK regulatory bodies which have responsibilities for both veterinary medicines and agrochemicals.

R-7 We recommend a review of the content and dissemination of guidance provided to the sheep farming industry in order to increase its effectiveness in influencing working practices. This may involve identifying barriers that seem to inhibit compliance with good practice.
1. INTRODUCTION

1.1. Reading this report

This report describes the outcome of a project to carry out an assessment of the risks to sheep dippers of suffering short-term ill-health effects associated with organophosphates (OPs). The reader who requires only a detailed summary of the findings and recommendations is referred to the executive summary. It is intended that the latter can, in conjunction with the glossary, be read as a stand-alone document.

1.2. Project aim

The aim of the project was to carry out an assessment of the risks to sheep dippers of suffering short-term ill-health effects associated with OPs. Specifically, the risk considered was that of workers being exposed to doses of OPs during sheep dipping which may produce overt acute toxicity accompanied by recognised clinical signs or symptoms. Here, acute toxicity refers to ill-health effects that occur over a short period of time (hours or a few days) immediately following exposure. This is considered to reflect an acute anticholinergic effect.

1.3. Project scope

The project scope, as agreed at the outset, was as follows.

1. The assessment was to be based on available literature and information.

2. The number of reported cases of short-term ill-health effects associated with OP dipping were to be identified. Based on this, an estimate was to be made of the actual incidence of short-term ill-health effects. This was to be compared to an estimate of the incidence based on available toxicology and worker exposures.

3. Consideration was to be given to the following alternatives to current practice in dipping with OPs for the control of sheep ectoparasites:

   - improving exposure control during sheep dipping;
   - using pyrethroid dips;
   - using pyrethroid pour-ons;
   - using ivermectin and doramectin injectables.

This project was to focus on harmful effects on workers although broader benefits and detriments to animals/environment were also to be identified. It was to include consideration of whether it would be appropriate for HSE to carry out cost benefit analyses. Recommendations were to be made on any other chemical alternatives considered to merit a full study.
1.4 Project background

The exposure of workers to organophosphates during sheep dipping has been an issue of potential concern for some years in regard to both acute and chronic toxicity. The project described here was commissioned by the HSE to review the risks in relation to short-term ill-health effects in the light of a number of recent studies into toxicology, worker exposure, and working practices.

Whether or not exposure to low doses of OP compounds can cause long-term adverse health effects was reviewed in 1999 by the COT (COT, 1999). Long-term adverse effects are not considered in the project described here.

An examination of information regarding all OP products licensed in the UK, with regard to the potential for damage to human health, was carried out by officials under OGOP and reported to ministers in 1998 (OGOP, 1998). Information from that review is included in this report.

1.5 Project approach

A two stage approach to the project was adopted:

1.5.1 Part 1: quantitative risk assessments

In the first stage of the project, quantitative risk assessments were carried out based on the toxicology and likely worker exposures for the active substances and methods of sheep ectoparasite control within the scope of the project. Broadly, the highest dose which it was estimated would not give short-term adverse health effects was compared to the dose which it was estimated likely that workers receive.

For these assessments, published risk assessment criteria on worker safety and the methodology used by UK regulators for the granting of marketing authorisation for pesticides were used. (For regulatory purposes, sheep ectoparasiticides are classed as veterinary medicines rather than pesticides. The criteria and methodology used for worker safety in the granting of marketing authorisation for veterinary medicines was not used since these are not published.)

It should be stressed that while use was made of the published criteria and methodology, a formal risk assessment was not performed in the way it would be done by regulators for the granting of marketing authorisations. Nor was it within the remit of this report to do so. One consideration here is that important aspects of health risks which would be considered in granting marketing authorisation are outside the scope of this project. For example, in regard to OP sheep-dips these aspects include the possibility of long-term adverse health effects and exposure to other people such as fleece handlers in the wool industry. Secondly, a fundamental aspect of the regulatory decision making process is that the risk assessments for different products are all carried out by designated expert groups within the appropriate regulatory

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4 We highlight that a current project looking at OP exposure in fleece-handlers is being carried out in collaboration with HSL, British Woolgrowers and Dr P Mellors.
authorities. This is important in ensuring consistency in the decisions made on marketing authorisations.

For OPs, the criterion of the Occupational Exposure Standard (OES) set under COSHH regulations, (1994) was also considered. This was not done for the alternative methods of sheep ectoparasite control since these do not have OESs.

As part of this first stage we also looked at the available information on the actual incidence of short-term ill-health associated with OP dipping. An estimate was made of the actual incidence per dipping exposure, based on reported cases. The likely incidence was also estimated based on the toxicology and likely exposures, and available routine biological monitoring measurements. The two estimates were compared to examine if, within the very large uncertainties on both, it could be said that there were any discrepancies.

1.5.2 Part 2: qualitative assessment of control of risks in the workplace

The adequacy of the control of risks in the workplace was qualitatively considered. This covered current working practices in OP dipping, the options for substitution with other chemical methods of control and the scope for reducing the need to use chemical methods. These considerations were made within the framework of the approach to risk control set out in the COSHH regulations (1994), and the specific requirement on individual employers to 'ensure that the exposure... to substances hazardous to health is either prevented or, where this is not reasonably practicable, adequately controlled.'

1.6 Project information sources

As noted previously, the scope of the project was to consider available information and literature. It was not within the remit of this project to consult the very wide range of parties interested in or affected by the use of OP dips. These parties span concerns ranging from human health, animal welfare, the environment and sustainable farming practices, to the rural economy and the development of the pharmaceutical industry. However, valuable assistance in aiding our understanding of specific aspects of this project was provided by face-to-face meetings with:

- National Farmers Union (NFU) representatives for background on farmers views and concerns in relation to sheep ectoparasite control and for information specific to current working practices and options for substitution for OP dips;

- National Office of Animal Health (NOAH) Ltd. representatives and members representing a number of sheep ectoparasiticide manufacturers for background on the views and concerns of manufacturers and for information specific to current working practices and options for substitution for OP dips;

- Professor HF. Woods, in his capacity as chairman of the Committee on Toxicity of Chemicals in Food Consumer Products and the Environment and its working group on organophosphates which carried out the study into long-term adverse affects referred to
above (COT, 1999), for information on aspects of that study relevant to short-term adverse effects including the reporting and investigation of poisoning incidents;

- Dr. A. Vale, Consultant physician, National Poisons Unit, Birmingham who is a UK authority on OP poisoning and a Fellow of the Faculty of Occupational Medicine. Dr Vale was also a member of the working group on organophosphates, of the Committee on Toxicity of Chemicals in Food Consumer Products and the Environment.

- Miss L. Stubbings, who was Principal Sheep Advisor with the organisation ‘ADAS’ until 1997 and is now an independent sheep consultant working with farmers, the supply trade and Government Agencies on all aspects of sheep production, specialising in health and management issues, for background on farmers’ views and concerns in relation to sheep ectoparasite control, and for information specific to current working practices and options for substitution for OP dips including that in the report she recently co-authored for the Environment Agency (Taylor et al., 2000);

- Officials from the VMD, PSD and HSE, for background on regulatory issues and concerns in relation to health risks associated with OPs and information specific to regulatory risk assessment criteria and methodologies;

- Mr N. Craig, HSE’s agricultural inspector with responsibility for national coordination of veterinary medicine issues related to inspection, for background on sheep dip surveys and other inspection issues and for information specific to current working practices and options for substitution for OP dips.

A number of other informal contacts on issues associated with this report were made by members of the project team.
2. ECTOPARASITES AFFECTING UK SHEEP AND METHODS USED TO CONTROL THEM

2.1 Introduction

If not controlled ectoparasites can jeopardise the welfare of the approximately 45 million sheep farmed in the UK and cause significant financial loss. For about 200 years plunge dipping has been used to control such pests. Organochlorine chemicals used in plunge dipping were withdrawn in the 1980s due to the persistence of their residues, leaving a number of OP compounds, which had been introduced in the early 1960s, for use in dips. More recently in the mid-1980s synthetic pyrethroids (SP) dips were introduced. Plunge dipping of sheep is still reported to be the most effective way of controlling ectoparasites on sheep in the UK. However, it is labour intensive and time consuming with possible environmental implications for the disposal of the spent dip if not carried out properly. Concerns on the human health risks have also been raised which is the underlying driver for this report. A number of other methods of sheep ectoparasite control have been developed such as pour-on products and injectable endectocides. A number of these chemical control products and their method of application to sheep have been approved for use in the UK by the VMD/VPC. However, there is some evidence that some chemical products are being used in a non-approved application method, known as ‘off-licence use’ or ‘off-label use’.

2.2 Main products available and application methods for ectoparasite control in the UK

The four main currently approved product types and application methods include;

- organophosphate dips (only the specific OP diazinon currently)
- synthetic pyrethroid dips (flumethrin and cypermethrin),
- pour-ons, spot-ons and spray-ons (deltamethrin, cypermethrin & cyromazine),
- endectocide injections (ivermectin, doramectin & moxidectin).

Plunge dips use the complete immersion of the sheep in a bath of diluted dip (OP or SP). ‘Pour, spray and spot-on’ applications use a small hand-held gun which discharges a metered dose to the back of individual animals. The area of application on the back of the sheep depends to some extent on the product being applied. Injectable are given by either subcutaneous or intramuscular injection. Information on the appropriate application of the specific chemical forms part of the approval for use.

Other methods of application of OP or SP products such as jetting, showering and spray-races (some of which are extensively used in other countries) have begun to be used in the UK. The increased use of these methods of application may be due to concerns about potential problems with disposal of spent-dip or dip wash and the regulatory interest of the Environment Agency and the application of the Groundwater Regulations. Currently in the
UK products used for jetting and showering are ‘off-label’ or ‘off-licence’ i.e. not approved by VMD and with no recommendations for their use.

2.3 Ectoparasites affecting UK sheep populations

There are six main ectoparasites affecting UK sheep populations:

- scab (Psoroptes ovis);
- blowfly (Lucilia sericata);
- louse (Bovicola ovis);
- tick (Ixodes ricinus);
- headfly (Hydrotea irritans);
- keds (Melophagus ovinus).

(Taylor 2000, Liddel 2000)

Each of these ectoparasites are reviewed in the following sections:

2.3.1 Scab

Sheep scab is highly contagious and is found in all counties in England and Wales. It is most common in the autumn and winter months, being more inclined to thrive in cooler climates. It is passed from sheep to sheep by direct physical contact or as a result of their rubbing on contaminated fence posts, hedges or contact with farm equipment such as shearing equipment. It is often introduced into a flock with the arrival of new livestock. Sheep scab mites can cause severe reactions and distress to sheep. The disease presents itself as raw, spreading skin lesions, which result from an allergic reaction to the faeces of the minute scab mite (Schering-Plough Animal Health, 2000). The effects include stunting and severe loss of condition, loss of fleece, early embryonic loss and death in severe cases - especially of young lambs (Sargison, 1995). It causes significant problems for both sheep and farmers as it also causes damage to hides, weight loss, low birth rates, low milk yields and poor wool quality (Kirkwood 1980, Taylor 2000). The effects are therefore both animal health and economy related.

Actions to be taken with sheep scab are covered under the 1997 MAFF Sheep Scab Order. Whilst it is no longer compulsory to dip sheep to prevent scab infestation, it is a criminal offence for owners or keepers of sheep to fail to treat sheep visibly affected with sheep scab and all other sheep in the flock, or move sheep visibly affected with sheep scab.

Sheep scab became a notifiable disease in 1870 but plunge dipping had been introduced as a method for controlling ectoparasites since the early 19th century. The first commercial dip (William Coopers) was produced in 1843, containing arsenic and sulphur powder which required the addition of water. Over the next 100 years or so, substances used to control scab have included copper sulphate, boron compounds, tar acid derivatives and sulphur.

The first Sheep Scab Order under the ‘Diseases of Animals Act’, was issued by the government in 1938. The Sheep Scab (National Dip) Order (S.I. 1990/1557) introduced an annual
nationwide compulsory dip. Farmers were required to dip their sheep flocks within six weeks of an appointed date each year, in the autumn months.

Progress towards the eradication of sheep scab was not forthcoming until the approval of hexachlorocyclohexane (HCH) in 1948. HCH is an organochlorine compound which at a single dip concentration of 0.013% eradicated the disease and gave 12 weeks protection against reinfestation. MAFF recommended in 1952 a single annual dip with 0.016% gamma-HCH and subsequently eradication of sheep scab was achieved. The organochlorine, Dieldrin, was added to sheep dip preparations until the mid 1960’s when it was banned following a recommendation by the Advisory Committee on Poisonous Substances in Agriculture. DDT, another organochlorine chemical was also in use at this time. Concerns in MAFF about residue levels of organochlorine compounds in meat led to advise to farmers that organophosphate products were preferred. Organochlorines were finally withdrawn from use as sheep scab treatment in 1984.

Following the eradication of sheep scab in 1952, it re-emerged in England and Wales in 1972, probably having been imported in sheep from the Republic of Ireland. It also reappeared in Scotland, having been eradicated there since 1941. This re-emergence of scab resulted in compulsory national dipping being reintroduced in 1976.

Between 1976 and 1983 inclusive, it was compulsory to dip sheep once a year in the summer, except 1980 when it was only compulsory to dip in South West England and in 1981 when it was only compulsory to dip in England and Wales. From 1984 to 1988 two compulsory dips per year were deemed necessary, in the summer and again in the autumn. Between 1976 and 1988 inclusive, dipping was subject to supervision and by 1988 the number of reported cases of scab had fallen to 16. In 1989, however, the supervisory stipulation was lifted and farmers were only required to give the local authority prior notification of dipping. In 1990 and 1991 no prior notification of dipping was required and in 1992, deregulation occurred when the sheep scab Revocation Order was issued. Sheep scab ceased to be a notifiable disease, thus transferring the responsibility of scab control from MAFF to the farmer. The abandonment of compulsory controls in 1992 resulted in an increase in the number of cases of scab again. A survey by the UK Sheep Veterinary Society showed that sheep scab was present in every county by 1994 and in 1995 it was estimated that there were outbreaks in over 3,000 flocks (Lewis, 1997). This increase in the extent and number of cases resulted in the Sheep Scab Order (1997). It had also been suggested that some farmers were found to have failed in their responsibility to treat sheep infested with scab. However, in general an outbreak of scab is something every farmer/shepherd fears because of the impact on flock performance and subsequent economic effect, and the work involved in eradicating the disease from the flock. Unfortunately sheep scab is now endemic in all parts of the UK, although with different geographic patterns. But because it is no longer notifiable reliable figures on the current extent of the problem are not available.

The farmer is bound by legislation to prevent sheep from the suffering inflicted by sheep scab, even when dipping is not compulsory. Various regulations, including the Agriculture (Miscellaneous Provisions) Act 1968, the Welfare of Livestock Regulations 2000 and Welfare of Animals at Markets Order 1990, provide sanctions against the owners of animals suffering unnecessarily through failure to treat sheep scab.
Sheep scab can presently be controlled by the use of OP and SP dips. OPs applied as plunge dips can achieve 100% kill of mites with protection against re-infestation for a minimum of 3 weeks. SP dips are not as effective and importantly resistance of sheep scab mites to SP dips has been documented (Liddel 2000, Synge 1995, personal communication National Registration Authority, Australia). Moxidectin, ivermectin and doramectin are used as injectables but with differing efficacy. Ivermectin only kills about 95% of mites after two injections, doramectin achieves a similar level of control with one injection and moxidectin kills at least 98% of mites with a single injection. Pour-on products are not effective for purposes of controlling scab.
The image below of sheep scab in sheep is courtesy of The Bristol Biomedical Image Archive and Mark Collett, Massey University, Institute of Veterinary, Animal and Biomedical Sciences.
2.3.2 Blowfly (Lucilia sericata)

The condition blowfly strike (myiasis) is normally caused by the maggots of the Green Bottle fly (L. sericata) but can also be caused by the maggots of the Blue Bottle fly (Calliphora sp.). These flies become active in warm, damp weather and may affect sheep from April to September. All flocks are at risk.

Estimates suggest that about 0.5 million sheep are ‘struck’ by blowfly each year in England and Wales, with 80% of farmers reporting at least one case of blowfly strike in their flocks (French 1995). Blowfly is the most prevalent of all the ectoparasites.

The flies are attracted to open wounds on the sheep or to wool damaged by wetness, urine or faeces. They lay their eggs on the sheep, with the resulting strike occurring as the maggots eat into the sheep causing severe irritation and toxaemia. Sheep with strike are typically dull and isolated and may be seen tail-swishing or biting at the affected area, where the wool will become matted and discoloured (Schering-Plough Animal Health 2000). Lambs with fly strike grow at a slower rate and the carcass is devalued and the hide permanently damaged (Taylor 2000). Blowfly strike and its effect can have a rapid onset and, if not diagnosed, result in the death of the affected animal.

Blowfly strike can be treated and prevented using OP dips and high-cis cypermethrin (SP) dips. The length of protection from SP dips can be less than that of the weeks of protection afforded by OP dips. Blowfly strike can also be prevented using cyromazine and high-cis cypermethrin pour-ons, but cyromazine cannot treat the effects of an established strike as it cannot kill the maggots. Injectable products have no effect against blowfly.
Images courtesy of The Bristol Biomedical Image Archive. Photographs taken by Dr Tony Charleston Massey University, Institute of Veterinary, Animal and Biomedical Sciences

Fly-strike in sheep: the first figure shows back strike and body strike, the second figure shows breech strike with wool loss and staining with exudate
2.3.3 Lice

There are two types of louse affecting sheep in the UK- biting lice (Bovicola ovis) and sucking lice (Lithognathus ovillus). The sucking louse is relatively rare and is thus not considered to be a significant problem but the incidence of the biting louse is increasing, particularly in the south west of England, Wales, Scotland and other upland areas such as the Cheviot hills (Schering-Plough Animal Health, 2000).

Lice become most prevalent in the winter months and autumn dipping has been used as a means to control them. The louse is passed from one sheep to another via direct contact. Deregulation of sheep scab control has resulted in an explosion in the louse population due to the fact that lice were effectively controlled by OP dip compounds used against scab. The demise of compulsory dipping and the more widespread use of endectocides which have very little effect on biting lice, are factors responsible for this population explosion (Taylor, 2000).

While the effect of lice is not as profound as blowfly or scab, sheep affected by lice are irritated, lose wool and have poorer growth rates. Lice infestations can be confused with sheep scab resulting in unnecessary dipping. Economic losses are incurred by the leather trade due to lice damage, which is only evident after the hide has been cured.

Lice are controllable using OP and SP dipping which treats outbreaks and normally prevents further infestation for a season. Deltamethrin, cypermethrin and high-cis cypermethrin as pour-ons also control lice but are not as effective as dips, unless after shearing. Injectables do not have any activity against biting lice.

![Lice Life Cycle Diagram](image)

**Figure.** There are two main groups of lice that can affect sheep: sucking and biting/chewing. Of these by far the most common is the biting/chewing louse or Bovicola ovis. Bovicola are reddish brown in colour and up to 3 mm in length. Adult female lice lay 200-300 eggs (nits). Eggs are usually whitish and are glued to the hair shafts just above the skin surface. There is no true metamorphosis and from the egg hatches a nymph called the first nymph. The first nymph is similar to, although much smaller than, the adult. The first nymph moult to form the second nymph the second nymph moult to form the third nymph and the third nymph moult to form the fully grown adult. The whole life cycle from egg to adult only takes 2-3 weeks.
2.3.4 Ticks (*Ixodes ricinus*)

Ticks can present a serious problem to sheep. Up to 300,000 lambs each year are affected by tick borne diseases, such as louping-ill, tick pyaemia and tick borne fever (ADAS 1992). Ticks may also spread the zoonotic diseases, louping-ill and Lyme’s disease, which can have serious consequences for humans (Taylor, 2000).

The effect of ticks on sheep can be devastating. Many die and others are left with permanently stunted growth and a subsequent significant reduction in value. Such is the effect that the control of these parasites must be viewed as top priority (Taylor 2000).

Ticks are controlled by spring dipping as they are most active in the spring, early summer and autumn (Schering-Plough Animal Health 2000). It has been reported that dips used to control ticks are often twice as concentrated as those used at other times of the year to control other external parasites (Sewell 1999).

The number of flock affected by ticks is relatively small, but ticks can pose a serious problem in upland and hill areas. Scotland has a second tick emergence in the autumn which can be severe (personal communication from Dr J Vipond, Scottish Agricultural College). Ticks in the UK are multi-host parasites, spending only a relatively short period feeding on the blood and tissue fluids of the host sheep but continual re-infestation is common (Schering-Plough Animal Health 2000).

Ticks are controlled using OP and SP dips and deltamethrin, cypermethrin and high-cis cypermethrin pour-ons. The pour-ons are especially relevant for ewes pre-lambing and or newborn lambs in problem areas (Schering-Plough Animal Health 2000, personal communication Dr J Vipond, Scottish Agricultural College).

Several species of tick have been reported on sheep in the UK, but by far the most important is the castor bean tick, *Ixodes ricinus*. *Ixodes* is a three-host tick, meaning that each stage - larvae, nymph and adult - feeds on a different host, detaching and moulting between hosts.
The life cycle from egg to adult takes three years, during which ticks are only parasitic on animals for three weeks, the rest of the time being spent in vegetation.

2.3.5 Headfly (*Hydrotea irritans*)

Headfly only present a problem in specific parts of the UK in warm, wet summers but can cause severe loss in affected flocks. Headfly cause damage to the homed sheep breeds of Southern Scotland and Northern England but there have been reports from Wales and central Scotland (Taylor 2000). It was estimated in 1986 that 2.5 million sheep were at risk of headfly injury (Tarry 1986).

Affected sheep show growth loss and scarring. In lambs where headfly are controlled an additional 2 kg growth is gained. The value of affected livestock is reduced in the autumn sales (Taylor 2000). Headfly has been suggested as a priority target on farms where they are a known threat.
The picture (taken from Novartis publicity material) following shows the damage caused by headfly attack in horned sheep
2.3.6 Keds (*Melophagus ovinus*)

Keds are wingless flies that reside permanently on sheep, causing considerable irritation as they pierce the sheep’s skin to suck blood. This can lead to significant damage to the hide and the fleece (Schering-Plough Animal Health 2000). Although the ked population in the UK has been relatively low due to OP compounds being very effective in their control, they may be undergoing a limited resurgence as control practices change (Taylor 2000).

Keds can be controlled using OP and SP dips and deltamethrin, cypermethrin and high-cis cypermethrin pour-ons.

2.4 Overview of Active Ingredients for Ectoparasite Control

**Table 2.4a Plunge Dips:** [Extracted from Sheep Dipping AS29 (rev 2) HSE 1998 & technical information Greenmount Agricultural college 25/11/00]

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Controls</th>
<th>Tick/Ked/Lice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scab</td>
<td>Blow-fly</td>
</tr>
<tr>
<td>Diazinon</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Flumethrin (non-OP)</td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td>Amitraz (non-OP)</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>High-Cis Cypermethrin (non-OP)</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Table 2.4b Pour-Ons (all non-OP):**

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scab</td>
</tr>
<tr>
<td></td>
<td>Blow-fly-Prevnt.</td>
</tr>
<tr>
<td></td>
<td>Blow-fly-Trmt.</td>
</tr>
<tr>
<td></td>
<td>Tick/Ked/Lice</td>
</tr>
<tr>
<td>Cyromazine</td>
<td>x</td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>x</td>
</tr>
<tr>
<td>Cypermethrin</td>
<td>x</td>
</tr>
<tr>
<td>High-Cis Cypermethrin</td>
<td>x</td>
</tr>
</tbody>
</table>

**Table 2.4c Injectables (non-OP):**

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivermectin</td>
<td>x</td>
</tr>
<tr>
<td>Doramectin</td>
<td>x</td>
</tr>
<tr>
<td>Moxidectin</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓ - Controls          × - Not recommended for control

2.5 Methods used in the UK for sheep ectoparasite treatment

There are five main methods of application of sheep ectoparasite control products:

i. plunge dipping
ii. pour, spray or spot - on
iii. injectable products
iv. jetting*
v. showering*

(products used in these methods are currently ‘off label’ in the UK, but widely used internationally.

(Taylor 2000; NRA 1999)

2.5.1 Plunge dipping

The principle of effective dipping is that the sheep is fully immersed in the dip. For effective scab control this must be for a minimum period of one minute. In recent history plunge dipping was done with a range of OP chemicals, although diazinon, propetamphos and chlorfenvinphos were the most widely used from the 1980s. Currently only the OP diazinon is registered for use, but two SP chemicals are also approved for use.

There are five common dipping methods, described by Niven et. al. (Niven 1993) as follows;

a) short swim; a rectangular bath, plunge or walk through. Most types are shorter than approximately 4 meters including ramp in and out. There may be a pit at the side for the operator. Usually an operator puts the sheep in, but the bath may have a slide entry located at the side of the bath. Sheep usually walk out of the bath to an adjacent draining area which dip should drain back into the bath.

b) long swim; regular swim through type. They are usually longer than 4 meters and can be up to 20 meters. They generally have straight walk-through entries but occasionally they may have side, slide entries. They usually have adjacent draining areas.

c) circular; a round or hexagonal bath made of glass reinforced plastic or concrete. They usually have slide entries and ramps out to draining areas.

d) circular bath with island; similar to the circular type but with an island for the operator to stand on, located in the centre of the bath

e) mobile; baths located on trailers, usually of the short swim plunge type. Mechanical, pumped, self contained systems such as the ‘Mobidip’ are commercially available.

There are generally at least three worker activities involved in dipping,
i. ‘chucker’- responsible for putting sheep into the bath

ii ‘paddler’ - manoeuvres sheep in the bath, ensures that they are submerged usually by using a wooden or metal pole, but sometimes with their foot

iii ‘helper’ - general duties, can involve some chucking. Most of time spent rounding-up sheep or shepherding dipped-sheep.

The bath was usually prepared by filling with a known quantity of water and then the quantity of concentrated dip recommended by the manufacturer’s instructions added. The concentrate was added manually, either direct from the concentrate container or from a measuring device, or it may have been added by an automatic dosing device. The active ingredient is stripped out of the diluted dip as sheep pass through and so the baths must be topped up with concentrate to maintain efficacy of treatment. It is intended that sheep dipping using an OP will only continue to be approved if manufacturers can develop systems that remove any concentrate handling by workers.

2.5.2 pour-on, spray or spot - on

Products are applied to specified areas of individual animals. For example, cyromazine is applied using a small hand held gun which emits a narrow fan spray; deltamethrin is applied as a ‘spot’ between the shoulders and the mid-line; cypermethrins tend to be applied as a line down the back from the shoulders to the rump.

2.5.3 injectable products

Products are given either subcutaneously or intramuscularly depending on the products. For some products an automatic injector is available. It should be noted that the same hypodermic needle may be used to inject 10-12 animals before replacement.

2.5.5 jetting and showering

Products used in these techniques are ‘off-label’ in the UK i.e. non-approved and with no guidance. However, such techniques are used to some extent in the UK although more widely used in other countries (NRA, 2000). There is some evidence that the use of hand-jetting and showering in the UK has increased recently (Dunstone, 2000).

2.6 Numbers of sheep treated by product type

There are currently approximately 44 million sheep in the UK during June when there is the maximum number of sheep & lambs. Data has been calculated for the percentage of sheep treatments by product type during 1993, 1997 & 1999 (Liddel, 2000).
Table 2.6a Data from (Liddel, 2000). Number of sheep in the UK, calculated numbers of sheep treated per year and the average number of treatments per sheep each year

<table>
<thead>
<tr>
<th>Year</th>
<th>1993</th>
<th>1997</th>
<th>1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK sheep numbers (millions)</td>
<td>43.9</td>
<td>42.6</td>
<td>44.2</td>
</tr>
<tr>
<td>Total sheep treated (millions)</td>
<td>62.4</td>
<td>68.8</td>
<td>77.3</td>
</tr>
<tr>
<td>Average number of treatments/animal/year</td>
<td>1.4</td>
<td>1.6</td>
<td>1.7</td>
</tr>
</tbody>
</table>

From audited confidential data supplied by NOAH on the value of sheep ectoparasiticides sold by each product group, Liddel (Liddel, 2000) computed the number and percentage of treatments by the product types. The figure 2.6a shows this breakdown.

**Figure 2.6a Calculation of sheep treatments by percentage of product type (Liddel, 2000)**

<table>
<thead>
<tr>
<th>Year</th>
<th>OP dips</th>
<th>SP dips</th>
<th>Pour ons</th>
<th>Injectables</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>88.0%</td>
<td>12.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>40.8%</td>
<td>33.1%</td>
<td>24.0%</td>
<td>2.1%</td>
</tr>
<tr>
<td>1999</td>
<td>51.5%</td>
<td>9.6%</td>
<td>27.6%</td>
<td>11.3%</td>
</tr>
</tbody>
</table>

Liddel’s analysis suggests that there was a move away from OP dips to SP dips from 1993 to 1997. In 1993 OP dips accounted for 88% of all treatments. By 1997 there had been a reduction in the use of OP dips with pour-ons and SP dips replacing the OP dips. From 1997 to 1999 the use of SP dips declined again with a return to the use of more OP dips and a significant increase in the use of the relatively new injectables.

The data showed that in the last year before the ‘OP dip moratorium’ in December 1999, OP dips still accounted for 51% of all treatments and SP dips had decreased to 10% of treatments. Liddel suggested that this was on account of the broad spectrum activity and adequate persistence of OP dips, whereas SP dips may be beginning to show problems with resistant parasites and also implicated in environmental pollution problems in water courses.
The significant increase in injectables in the 1999 season may reflect the introduction of new endectocides requiring only one injection and which give protection as well as control/treatment against sheep scab.

However, the use of the various treatments is influenced by the geographical risk of the various parasite infestations and the analysis above is based on aggregated UK figures. Data is available from studies carried out in Wales by the Environment Agency during 1997, 1998 & 1999 (Dunstone, 2000; Hutchings, 1999). These studies may reflect recent trends in ectoparasite treatments used in upland sheep farming.

Figure 2.6b. Sheep treatments (1997-1999) from Environment Agency studies in Wales.

The data obtained from upland farms in Wales support the suggestion of a significant increase in the use of non-dipping methods (i.e. injectables and pour-ons) during 1999. The Welsh studies also support the overall UK evidence of a significant decrease in the use of SP dips in 1999. However the Welsh studies do not reflect the re-increase in the use of OP dips during 1999 noted by Liddel (Liddel, 2000). The Welsh studies also highlight the increasing use of non-approved (‘off-label’) techniques, such as showering and jetting, which the methodology of Liddel’s analysis based on chemical sales does not detect. It is possible that the increase in ‘OP dips’ signified by Liddel (Liddel, 2000) reflects the sale of OP (diazinon) which is subsequently used in the ‘off-label’ techniques of showering and jetting.

Historically sales of OP sheep dips were considerably higher than estimates for the period 1997-1999. Figure 2.6c shows the data for the sales of OP active ingredient used in sheep dip from 1984. In the mid- to late 1980s almost three times the amount of OP sheep dip (weight of active ingredient) was sold on an annual basis compared to the period from 1994 to 1998. This may be related to compulsory sheep dipping which was twice a year during the period 1984-1988 and once a year 1988 to 1991. Compulsory dipping was discontinued in mid 1991.
A number of OP products have been registered for sheep dipping since 1972, bromophos, carbophenothion, chlorfenvinphos, chlorpyrifos, coumaphos, crotoxyphos, diazinon, iodofenphos and propetamphos (COT, 1999). However, three of these OP active ingredients have figured large in any discussion concerning sheep dipping and our own experience of being involved in monitoring sheep dipping activities since around the late 1980s. (This may solely reflect the level of their usage compared to other registered products.) These three OPs are:

1. Chlorfenvinphos, a diethoxy substituted phosphate and direct inhibitor of acetylcholinesterase, with products registered for use in sheep dipping between 1972-1994,

2. Propetamphos, a phosphorothioamidate which needs metabolism by oxidative desulphuration after absorption to produce an active inhibitor of acetylcholinesterase. Also there is some data that suggests the spontaneous reactivation of cholinesterase after inhibition by propetamphos is negligible (Mason, 1993). Propetamphos was registered for use in sheep dipping from 1973 to 2000.

3. Diazinon, a diethoxy substituted phosphorothioate which needs metabolism by oxidative desulphuration after absorption to produce an active inhibitor of acetylcholinesterase. Diazinon was registered for use in sheep dipping in 1973 and remains registered.

Figure 2.6c. Trend in annual sales of the active ingredients of OP sheep dips in thousands of kg. Taken from (COT, 1999)
3. ASSESSING THE RISKS TO HUMAN HEALTH FROM CHEMICALS

In this chapter, we outline the approaches to assessing the risks to human health from chemicals which are discussed or drawn upon in the remainder of the report.

The chapter covers background material on risk assessment terminology, concepts and the approach to health risk assessment required of employers under the Control of Substances Hazardous to Health Regulations, 1994 (COSHH). This is the approach used in our qualitative consideration of the adequacy of risk control measures in the workplace in relation to OP dipping. We describe this within the context of the regulation of workplace health and safety under the Health and Safety at Work etc. Act, 1974 (HSW Act) and of the general risk assessment duties on employers under the Management of Health and Safety at Work Regulations, 1999 (MHSWR). We also outline the exposure limits set under COSHH which we draw upon in our quantitative assessment of worker risks from OP dipping.

Finally, we consider the approaches to user health risk assessment used in granting marketing authorisation for pesticides. We draw upon this for risk criteria and methodology to use in our quantitative assessments of risks to workers. We preface this with an outline of the broad approach to assessing the risks to people from exposure to potentially toxic chemicals which has been developed in a regulatory context.

3.1 Risk assessment terminology

A hazard is a situation or a substance with the potential for harm to people or damage to something that they value. For example, a particular chemical may be a hazard with the potential to harm people or damage the natural environment.

Likelihood is how likely something is to occur. It may be expressed either as a frequency (occurrences during a stated period of time) or probability (chance per event).

Risk is the likelihood of a given degree of harm being suffered or damage being realised. For example, the risk of workers who do a particular job developing eye irritation per year as a result. So risk has two elements, how likely it is that something goes wrong, and what the consequences are.

Risk Assessment is the study of decisions subject to uncertain consequences. It consists of risk estimation and risk evaluation.

Risk Estimation - may be either qualitative or quantitative. It includes identifying the hazards, and estimating the magnitude and likelihood of the associated harm or damage. Also important is the identification of the characteristics or nature of the harm, such as whether it is to children or adults, and whether delayed or immediate, reversible or irreversible. The risk estimation stage is sometimes called risk characterisation. However, the latter term is also used to describe part of the process of problem formulation used to decide on the scope and nature of the risk assessment needed.
**Risk Evaluation** is the process of determining the significance or value of the identified hazards and estimated risks to those concerned with or affected by the decision. For example, is the risk of harm with particular characteristics to a particular group of people in a particular context tolerable?

**Risk management** is the making of decisions concerning risks and their subsequent implementation. It flows from risk assessment. For example, a regulator may make a decision on whether or not to ban a workplace activity, while an employer may make a decision on whether or not more needs to be done to control the risks to their workers from a particular machine. Risk management does not mean eliminating risk, rather it is to do with controlling risks from activities in the context of the benefits those same activities provide.

It should be stressed that while risk assessment may be used to inform risk-based decision making, it is only one element in the process.

This terminology is not perfect. It is based on a Royal Society report published in 1992. It is used in this report because it is considered to be very largely compatible with that used in the European Commission and UK legislation and guidance drawn on in this report.

It is necessary to specify the terminology used since there is no universally agreed standard. In many cases this simply reflects the fact that risk assessment methodologies and associated terminologies have been developed over many years for a variety of applications in different parts of the world. In addressing this, much work is ongoing to agree harmonised standards. (For example the European Commission organised an `International Workshop on Promotion of Technical Harmonisation on Risk Based Decision Making’ in May 2000.) However, in other cases, the lack of a universally agreed meaning reflects fundamental shifts in understanding of the whole process of risk-based decision making - see, for example, the discussions in (Hurst, 1998) and (Stern & Fineberg, 1996). Given that understanding of risk-based decision making continues to evolve, it seems likely that the language and terms used therein are set to do likewise.

**3.1.1. Complexity and quantification in risk assessment**

The degree of complexity entailed in a risk assessment will depend on the context.

At one end of the spectrum is the employer in a small business who qualitatively estimates the risks in his workplace and evaluates their significance within a framework of guidance or standards published by the regulator. The sheep farmer deciding how to treat ectoparasites in his flock falls into this category.

Somewhere in the middle of the spectrum is the regulator working in the context of nationally or internationally agreed law whose estimate of the risks associated with an industrial process or activity includes quantitative and qualitative inputs. Carrying out user risk assessments as part of deciding whether to grant authorisation to companies to market veterinary medicines or agricultural pesticides falls into this category.

Finally, at the far end of the spectrum, is the national government faced with making a decision on a 'new' risk with high social, political and economic implications, where criteria
to evaluate it need to be developed and where one input is quantified risk estimates in an area where the underpinning science is little known. BSE may be one such example.

Our remit in this project is to work within the framework of existing methodologies and criteria.

It is important to keep the use of quantification in risk assessment in perspective. In judging the significance of a risk, qualitative characteristics of that risk will be important (for example is the risk to children or to adults) as will be the context. Equally, when deciding how big the risk is, numbers are not necessarily best. In the context of nuclear power stations (HSE, 1992) explains that an advantage of quantified risk assessment is that it ‘ensures a systematic process of the design and its risks, to which judgment and common sense as well as numerical calculations can be applied’ but points out that quantified risk assessments will ‘only be appropriate and cost effective for some situations’.

It is also important that the boundaries of the risk assessment have been clearly established at the outset. For example, are all the risks to a worker from a particular activity being considered, or just a specified subset. The importance of problem formulation within risk-based decision making has been discussed (Stern & Fineberg, 1996).

Finally, it should be noted that the terminology chosen above is not intended to convey the impression that risk assessment necessarily proceeds in a tidy manner from estimation through to evaluation. It is often an iterative process. For example, an assessment might begin with an initial screening to check whether a simple worst-case estimate of the risks would lead to an outcome that the risk is negligible. This would be followed by more detailed approaches to estimation and evaluation only if appropriate. Similarly, when working within a framework of agreed evaluation criteria, these may dictate what it is appropriate to estimate.

3.1.2. Uncertainty in risk estimation

When making a risk estimate, the outcome, whether qualitative or quantitative, will have some degree of inexactitude, or uncertainty, arising from imperfect knowledge. (The distinction is made here from what can also be called uncertainties arising from the randomness inherent in a system - for example the variability in peoples’ responses to the same dose of a toxic substance). These uncertainties can be considered as falling into two categories according to their source:

- **Known Uncertainties** are those arising from sources known to the people making the estimate. For example, a risk estimate may be based on models which are known not to describe certain aspects of a problem, or data which is known to be of limited applicability or accuracy. To take these into account, judgements and assumptions will need to be made in order to provide robust and consistent risk estimates. It is important that these are made explicit in order to help determine how much confidence can be placed in the overall risk assessment as a basis for decision-making.

The development of common approaches to dealing with uncertainty for specific applications is important in promoting consistency. For example HSE’s advice on land-use planning in the vicinity of chemical plant is informed by the use of risk
assessments where the approach to dealing with known uncertainties is to use a ‘cautious best estimate’ of the risk: every attempt should be made to use realistic best estimate assumptions but where there is clearly difficulty in justifying the assumption, some over-estimate is preferred. The aim of this approach is to err on the side of safety while limiting needless restraint or prohibition of workplace practices (HSE, 1989). The common approaches used for regulatory chemicals risk assessment and the handling of uncertainties in the risk estimation are outlined below in section 3.2.

- **Unknown Uncertainties** are those arising from sources which are either not known to those making the risk estimate, or whose significance is not appreciated. For example, unknown uncertainties can arise because not all significant pathways to harm have been considered, or inappropriate models have been used, or information misinterpreted.

The accuracy of a risk estimation is necessarily constrained by what is known to the people making it. For example, this constraint can arise where there is a time lag between improved understanding of an issue, and the dissemination of that information. However, unknown uncertainties can also arise through the way information is used, for example if data is misinterpreted, faulty assumptions are made, or critical thinking is not promoted by the environment in which those making the estimation work. (Guidelines for ‘getting the science right’ which apply to use of science in UK policy making generally are set out in (Office of Science and Technology, 1997).) For these reasons, it is important that risk estimates are kept under review and revised as new information is brought to light, for example as a result of accident investigations or epidemiological studies. Similarly, it is important that the details of the assessment are made transparent.

### 3.1.3. Cost benefit analysis and regulatory impact assessment

In a **Cost Benefit Analysis**, CBA, the benefits associated with reducing a risk and the costs (detriments) are compared by expressing both in monetary terms. When considering worker safety, the benefit is a reduction in the risk of harm - be it death, injury or ill-health.

CBA is sometimes used by industry as part of evaluating workplace risks. In particular, it may be done as part of an evaluation of whether a risk has been reduced as low as reasonably practicable. This is generally only done in instances where very large costs would be incurred by industry. (For example, following the Clapham Junction disaster, CBA was used by the railway industry to successfully argue against installing advanced train protection across the UK rail network.)

In the regulation of workplace safety, CBA is used as part of **Regulatory Impact Assessments**, RIAs. RIAs are required by government for all regulatory proposals, not just those concerned with health and safety, which impact on businesses, charities and voluntary bodies. This includes all proposed new health and safety regulations, Advisory Codes of Practice, and European Directives. It is worth noting that RIAs covering risks to workers’ health are carried out for any individual substances for which a ‘maximum exposure limit’ is set under the
Control of Substances Hazardous to Health Regulations (see below) because of their status under these regulations.

An RIA describes the issue which has given rise to the need for regulation and compares possible options for dealing with it. This includes an analysis of risks, costs and benefits. An RIA is used to help ministers judge whether the proposed regulation is necessary and is also intended to inform public debate. The overall approach is described in (Better Regulation Unit, 1998) while detailed advice on valuation of benefits is given in (HM Treasury, 1997). The latter notes that ‘it is never possible in a real life appraisal or evaluation to put a monetary value on all the important factors’. It discusses the way in which costs and benefits for which there is no market value are more often than not compared on the basis of quantitative, and sometimes only qualitative, assessments.

CBAs are also used in support of policy proposals that would require duty holders to make major investments in safety measures (HSE, 1999).

### 3.1.4. Precautionary approaches and the precautionary principle

The importance of adopting a ‘precautionary approach’ to risk management and risk assessment is often cited. Broadly, the term is often used in the sense of ‘errring on the side of safety’. For example, erring on the side of safety in handling uncertainties in risk estimation is sometimes described as being part of a precautionary approach to risk assessment. Similarly, the term is sometimes used to describe erring on the side of safety in risk management decisions because the consequences of a hazard are considered to be serious (whether or not scientific uncertainty is an issue). The Precautionary Principle (outlined in Appendix A) is one example of a precautionary approach.

The confusion over the form that a precautionary approach should take in UK regulation has been highlighted by the UK Intergovernmental Liaison Group on Risk Assessment (ILGRA, 1998). Following this, the group’s remit currently includes the development of a consistent policy on precautionary approaches including the Precautionary Principle.

### 3.1.5 Regulatory risk-based decision making

HSE (HSE, 1999) notes the ‘pressure on regulators for greater clarity and explanation of their approaches to the regulation of risk’. It gives five important aspects of regulatory risk-based decision making (drawn from the government’s five principles of good regulation) which may be paraphrased as:

**Transparency** - being open on how decisions were arrived at and what their implications are;

**Targeting** - focusing actions on the most serious risks or those where the hazards are less well controlled;

**Consistency** - ensuring that similar risks are treated in a broadly similar way;

**Proportionality** - ensuring that risk management decisions are in proportion to the seriousness of the risks involved; and
Accountability - making clear, for all to see, those who are accountable when things go wrong but without resorting to unfair retribution.

Similarly, the Interdepartmental Liaison Group on Risk Assessment has identified ‘the need to build trust as essential to obtaining public acceptance of risk management decisions. This in turn requires departments and their Agencies to have consistent, fair and transparent approaches to decision making which reflect the values of society’ (ILGRA, 1998).

3.2 Workplace assessments of risks to human health from chemicals

3.2.1 The regulation of workplace health and safety

The risks to health and safety arising from workplace activity in Great Britain are regulated by the Health and Safety Commission (HSC) which is the statutory body responsible for the administration of the Health and Safety at Work Etc. Act 1974 (HSW Act). HSC is advised and assisted by the Health and Safety Executive (HSE) which also has some specific statutory responsibilities, in particular the enforcement of health and safety law.

Fundamental to the HSW Act is that those who create risks from work activities are responsible for protecting workers and the public from the consequences. The HSW Act sets out general duties of care which are supported by goal-setting regulations. (Modern goal setting regulations have replaced the majority of older prescriptive regulations.) These general duties and regulations are amplified by Approved Codes of Practice, guidance and advice.

The approach to regulation adopted by HSC/HSE, described in (HSE, 1999) and (HSE, 1992) is based on the concept of tolerable risk. Tolerability refers to a willingness to live with a risk so as to secure certain benefits and in the confidence that it is being properly controlled. To tolerate a risk means that it is not regarded as negligible or as something we might ignore, but rather as something that needs to kept under review and reduce still further if and when possible.

The approach is summarised in figure 3.2.1a. The main tests that are applied in regulating industrial risks involve determining:

- whether a given risk is so great or the outcome so unacceptable that it must be refused altogether (the unacceptable region); or

- whether the risk is, or has been made, so small that no further precaution is necessary (the broadly acceptable region shown in the diagram as corresponding to an ‘insignificant’ level of risk); or

- if a risk falls between these two states, that it has been reduced to the lowest level practicable, bearing in mind the benefits flowing from its acceptance and taking into account the costs of any further reduction. The injunction is that risks should be reduced to a level which is As Low as Reasonably Practicable (the ALARP regulatory principle). This is the tolerable, or ALARP, region.
Figure 1. HSE criteria for the tolerability of risk

N.B. The meaning of 'risk' in the above figure encompasses more than physical harm and also takes account of other factors such as ethical and social considerations (see paras 20-26).
In terms of costs, this framework means that some irreducible risks may be so serious that they cannot be permitted irrespective of the economic consequences. At the other extreme, some risks may be so trivial that it is not worth spending more to reduce them. In general, risk-reducing measures would be weighed against the associated costs if there is a significant risk, and measures must be taken unless the cost of taking particular action is clearly grossly disproportionate compared with the benefit of the risk reduction. In practice this means that employers must err on the side of safety and strongly so when the risk is seen to be considerable or where the consequences could be high and the risk is uncertain.

In deciding whether risks have been reduced to a level which is ALARP HSE has stated ‘our experience suggests that in most cases adopting good practice ensures that the risks are effectively controlled’ (HSE, 1999). Authoritative sources of relevant good practice would include:

- those given in prescriptive legislation, Approved Codes of Practice, and Government Guidance;
- standards produced by standards making organisations (for example, British Standards and the International Organization for Standardization); and
- guidance agreed by a body representing an industrial or occupational sector such as a trade federation, provided it has gained general acceptance.

It is relatively rare that processes or activities are banned (i.e. deemed intolerable). One example was the banning in 1967 of the manufacture and use of 2-naphthylamine and its salts. This was because its combination of physical, chemical and toxicological (potent carcinogenic) properties meant that control of exposure was very difficult and the potential ill-health effects severe.

### 3.2.2 Risk assessment duties under the Management of Health and Safety at Work Regulations

The specific requirement on industry to assess risks arising from work activities is a provision of the Management of Health and Safety at Work Regulations, 1999 (MHSWR). The regulations were first introduced in 1992 and came into force in 1993. They require employers and self-employed people to make a `suitable and sufficient’ assessment of the risks created by their undertaking so as to identify the measures they need to have in place to comply with their duties under health and safety law. The regulations implement the EC Framework Directive (89/391/EEC). (European Commission guidance for Member States sets out how to fulfill the risk assessment duties in the directive (European Commission, 1996a).) The assessment provisions of the MHSWR are comprehensive and superimposed over all other workplace health and safety legislation.

Further regulations and guidance deal with risk assessment provisions for specific risks. The Control of Substances Hazardous to Health Regulations, 1994 (COSHH), which cover the assessment of the risks to human health from chemicals, are outlined below.
HSC sets out the general principles that should be followed in carrying out a risk assessment under the MHSWR in an Advisory Code of Practice (HSC, 2000). These principles are broader than setting out the need to identify hazards and evaluate risks but also cover the approach to adopt. For example:

- the risk assessment should ‘take account of the views of employees and their safety representatives who will have practical knowledge to contribute’;
- it is necessary to ‘observe the actual [workplace] practice’; and
- it is necessary to ‘address what actually happens in the workplace or during the work activity’.

Where an employer has five or more employees a written record of the significant findings of the risk assessment should be made including a record of the preventive and protective methods in place to control the risks, and what further action, if any, needs to be taken to reduce risk sufficiently.

### 3.2.3 Risk assessment duties under COSHH

The Control of Substances Hazardous to Health Regulations, 1994 (COSHH) are goal setting regulations which provide a framework for the control of substances hazardous to health arising from work activities. The substances covered under COSHH include veterinary medicines and pesticides such as those to which farmers may be exposed. The regulations were first introduced in 1988. They include duties on employers to carry out risk assessments; prevent or control exposure; and provide employees with an appropriate level of information, instruction and training.

The regulations and associated Approved Codes of Practice are given in (HSC, 1999). A brief guide is given in (HSE, 1999a) and fuller guidance in ‘COSHH Essentials’ (HSE, 1999c). These are supplemented by a range of other publications including a leaflet on COSHH in agriculture which contains notes on good practice (HSE, 1997). For the specific case of dipping sheep, the leaflet (HSE, 1998) sets out ‘the steps necessary under....COSHH.. to assess the risks and decide what precautions are needed’.

Fundamental to COSHH is giving priority to preventing exposure to hazardous substances. Where possible this should be achieved by changing the method of work so that the operation giving rise to the exposure is no longer necessary, or by substituting with another substance or a different form of the same substance in order to eliminate or reduce the risk. When deciding whether to use substitution, it is necessary to consider not just risks to health but also to safety and the environment. Further guidance on substitution is given in (HSE, 1994). After substitution, achieving adequate risk control by process or engineering means, such as ventilation systems, may be considered. Finally, if adequate control cannot be achieved by substitution or engineering measures, the use of PPE may be considered. Hence, under COSHH, PPE should effectively a last resort.

‘COSHH Essentials’ (HSE, 1999c) describes how to carry out a ‘generic’ health risk assessment. Further guidance is given in (HSE, 1999a; HSE, 1999b). The broad approach mirrors
that under the MHSWR as outlined above. It is worth noting that, in specifying that it is necessary to consider what actually happens in the workplace, one example given is that ‘agricultural employees may well be tempted to discard protective coveralls and other PPE during hot weather and strenuous activity.’

Prior to issuing the guidance in 'COSHH Essentials' (HSE, 1999c), HSE commissioned underpinning market research (Topping, 1998; Topping, 2000) into the understanding of COSHH by small and medium enterprises. Whilst most respondents reported that steps were taken to protect employees, awareness of COSHH was limited with 53% of those using chemicals daily being unaware of any legal requirements for establishments manufacturing or working with chemicals. The approach taken to controlling exposure was the opposite to that required under COSHH. Substitution was rarely considered, and use of PPE was as likely as the use of engineering or process controls. Respondents were also found to rely heavily on information from suppliers, product labels, and personal experience rather than sources such as Trade Associations and HSE.

3.2.4 Occupational Exposure Limits under COSHH

For the case of airborne substances only, Occupational Exposure Limits (OELs) are used to define adequacy of control under COSHH. These legal limits are expressed as a concentration of the hazardous substance in the air averaged over a specified period of time. OELs have been set for about 600 chemicals and are listed in (HSE, 2000). Some additional information is also given. This includes a ‘skin notation’ if a substance can be absorbed into the body through unbroken skin.

There are two types of OEL: Occupational Exposure Standards (OESs) and Maximum Exposure Limits (MELs). Their relationship to the tolerability of risk framework described above is set out in (HSE, 1999) and (Topping, 2000). An OES corresponds to a level of exposure at which there is minimal risk to the health of workers. It represents a level of risk which can be classed as close to or below that which is considered broadly acceptable (‘insignificant’). Employers are required to meet the standard, they do not have to reduce exposures below it, and they can have exposures above it provided that they take appropriate action to meet the standard as soon as is reasonably practicable. MELs, by contrast, are set for substances which have serious health implications and for which an OES cannot be set (HSE, 2000). MELs are set as the outcome of a decision making process involving not only the protection of the health of the employee but also socio-economic considerations. Under COSHH exposure should be reduced as far below a MEL as is reasonably practical; it is not simply compliance with the MEL level.

OELs are set by HSC on the recommendation of the Advisory Committee of Toxic Substances and following assessment of the chemical by the Working Group on the Assessment of Toxic Chemicals. This process is described in (HSE, 2000). Three important facets are:

- publication of the assessment approach used;
- public consultation on any proposed new OELs; and
• publication in (HSE, 1999d) of the scientific and technical basis upon which the OELs have been set for all individual chemicals which have been recently reviewed.

3.3 Regulatory assessments of risks to human health from chemicals

In this section we outline the approach which has been developed over many years in a regulatory context to assess the risks to people from exposure to potentially toxic chemicals. The approach has been used in setting health-based standards for exposure to chemicals, (for example environmental air quality standards, acceptable daily intakes for food additives, and occupational exposure limits), and in product licensing (for example, pesticides and medicines). For a detailed description see, for example, (Royal Society, 1992; National Research Council, 1983; National Research Council, 1994; European Commission, 1996b).

Very broadly, the current approach is to consider whether the toxicity of the chemical under consideration is such that a threshold dose can be defined, below which humans do not experience adverse health effects. (The main exceptions to this are ‘genotoxic carcinogens’ - chemicals which can damage genetic material potentially leading to cancer, and ‘respiratory sensitisers’ - those chemicals which can cause asthma.) If such a threshold dose can be defined, it is then either:

• used in the context of product licensing by comparing it with the dose it is estimated people will receive, based on their likely patterns of exposure from use of the product (i.e. will peoples’ estimated, real-life exposure be such that they will absorb less than the threshold dose?), or

• used in the context of setting exposure standards, by deriving from the threshold dose and the nature of the exposure what corresponding exposure concentrations could be allowed (i.e. to what concentrations could people be exposed such that exposure was less than the threshold dose?).

The elements of this approach are as follows:

1. From the available toxicological database identify the dose defining a ‘no-observable-adverse-effect-level’ (NOAEL) for the appropriate critical adverse biological or health effect. The toxicological database will be very largely comprised of animal studies and may be of variable quality.

2. Apply to this NOAEL ‘uncertainty’ ‘assessment’ or ‘safety’ factor(s), which will depend largely on the nature of the toxicological database, to set a lower acceptable threshold dose to protect humans and which meets the stipulated health protection criteria for the particular standard. The application of ‘uncertainty factors’ also depend on the regulatory context.

3. If being used within a licensing/approving process (e.g. pesticides) then estimate the likely exposure of appropriate populations such as operators, bystanders etc. when the product is being used.
4. Compare this exposure dose with the threshold defined in (2) after application of the uncertainty or assessment factor(s) to the NOAEL. An estimated exposure lower than the threshold will signify meeting the approval/licensing criteria.

5. For exposure standard setting the threshold dose defined in (2) is rolled out into an appropriate standard, such as an 8 hour time weighted average atmospheric exposure standard (OEL) or 15 minute short-term exposure limit (STEL). These standards can then be used as part of health-based risk management.

The general scheme outlined above encompasses the expert judgment of the toxicologist in appraising the toxicological database, establishing the most suitable NOAEL and applying the appropriate uncertainty factor(s). Exposure assessment, as defined in (3) above, in many contexts involves both simulation from generic computer models of exposure [i.e. for pesticides the use of POEM, EUROPOEM] and also the expert input of the occupational hygienist in how users’ should and will handle the product in practice.

There is a difference in the practical application of uncertainty factors depending on the regulatory context. Fairhurst (Fairhurst, 1995) highlighted that in establishing an OEL within the occupational setting, the influence of technical and socio-economic as well as health considerations are important when considering the level of uncertainty factor to apply to the NOAEL. In contrast, for pesticides being approved in the UK as plant protection products and complying with the appropriate EU directive 91/414/EEC the regulator would have to meet the directive’s definition of the threshold dose as ‘the maximum amount of active ingredient to which the operator may be exposed without any adverse health effect’. In this context the threshold derived from the NOAEL adjusted by uncertainty factor(s) is termed the Acceptable Operator Exposure Level (AOEL) and the uncertainty factor must be large enough to give a fully protective health-based limit. Thus pesticide approval has been noted as far more precautionary than OEL setting in the occupational field (RATSC, Risk Assessment & Toxicology Steering Committee, 1999a & 1999b; ICPS, 2000). The rational behind this difference has been defended on grounds of likely differences in the extent of heterogeneity in exposed populations (healthy workers versus the population including susceptible groups) and the controlled nature of occupational exposure associated with OEL limits (Fairhurst, 1995). Also highlighted is that pesticide approval process is defined as solely health-based and takes no account of technical or economic feasibility.

It should again be noted that an OEL is an exposure limit which may be monitored against as part of risk management, whereas the AOEL is part of an approval process rather than a risk management tool.

### 3.3.1 The use of uncertainty/safety/assessment factors in regulatory assessments for chemicals

The use of ‘uncertainty factors’ are an important element in the regulatory assessment process.

Extrapolation by means of ‘uncertainty factors’ is made necessary because of the lack of chemical-specific toxicological knowledge for humans that remains after extensive evaluation.
of the available data. Essentially a largely animal toxicology database has to be used to substantiate a dose in humans which will define the likelihood of an adverse health effect. In many contexts the overall ‘uncertainty’ factor is separated into a number of specific factors which are applied multipicatively to take account of various uncertainties in the toxicology database. These extrapolation factors include;

- applying the largely animal toxicology data to the human situation- ‘inter-species factor’,
- considering the likely variability in response within a human population to any given exposure- ‘intra-species factor’,
- taking account of ‘route-to-route factors’ in dosing. The majority of active ingredient toxicological studies are performed by the oral route whereas occupational exposure is usually by the inhalation and dermal route, and for pesticides the dermal route is of major importance,
- taking account of the significance of the critical adverse toxicological effect in terms of the severity and frequency of actual health consequence ‘outcome severity’,
- taking account of some uncertainties in the extent and depth of the toxicological database- ‘confidence in the database’.

These factors may be found in the various literature describing chemical risk assessment as ‘safety factors’, ‘uncertainty factors’, ‘extrapolation factors’, ‘adjustment factors’, ‘assessment factors’ etc. After establishing a NOAEL from the available toxicology database, the appropriate assessment/safety factors are applied in a multiplicative fashion to the NOAEL to give the adjusted dose figure which is compared with the exposure (estimated) that workers using the product appropriately are likely to experience.

In general terms there is active and ongoing debate amongst those involved in regulatory approval processes for chemicals about whether the uncertainty or assessment factors are over-conservative or being applied mechanistically without regard to a fundamental understanding of their basis (Fairhurst, 1995; Dourson, 1996; Risk Assessment & Toxicology Steering Committee, 1999f; Vermeire, 1999). A predefined overall uncertainty factor has been historically applied for the establishment of a number of ‘limits. This 100-fold “safety factor” had originally been proposed as an “adequate margin of safety” for the derivation of food additive standards by the US Food and Drug Administration (Lehman, 1954). This 100-fold factor is often explained as the product of the two assessment/uncertainty factors with default values of 10, one for the intra- and one for the inter-species variability. Currently these default values are still used by many international regulatory bodies for these two factors, but largely with default values of 1 for the other uncertainty factors. A recent review by experts from a number of EU countries discussed in depth the use and combination of the separate assessment factors involved in carrying out pesticide (plant protection product) approval (ICPS, TNO, MRC IEH, GSF & FIOH, 2000). This adds to continuing discussions concerning the use of assessment factors in regulatory frameworks (Stevenson, 1995; ECETOC, 1995; Renwick, 1993; Vermeire, 1999) in not only worker safety, but also in protecting bystanders, susceptible groups and those exposed via dietary residues etc.
3.4 Approval processes

The criteria and methodology used for assessing worker safety as part of granting marketing authorisation for veterinary medicines (sheep ectoparasiticides are classed as veterinary medicines for marketing and authorisation purposes) were neither closely specified in law nor published by the relevant authorities at the time of this report. Therefore, it was not possible to use them in this report in a manner that allowed scrutiny and informed critical review. However discussions with those involved in approvals for veterinary medicines (VMD) and pesticides (PSD & HSE) indicate the processes are in principle very similar and follow the general model described in section 3.3. Approval processes are used to establish whether the regulatory authorities are satisfied that a specific product or active ingredient can be marketed/approved. Depending on the nature and use of the product or active ingredient different UK regulatory authorities will be involved in this process. For the type and class of chemical that are used to control ectoparasites, these authorities could be HSE, VMD and PSD. It should be noted that some countries (e.g. National Registration Authority for Agricultural and Veterinary Chemicals Australia) operate single regulatory authorities that combine functions carried out by separate authorities (VMD, PSD, HSE) in the UK.

OP products, which include those used in agricultural and sheep ectoparasite treatments, have come under scrutiny for re-review on an international and UK basis. OP products have approval/marketing authorisation as veterinary medicines for the treatment of ectoparasites in a number of animals. One OP compound is licensed as a human medicine (malathion which is used to treat lice and scabies). OP products are also widely used as insecticides for plant protection products in agriculture and for non-agricultural purposes such as cockroach and moth control in the home. Products used in this way are classed as pesticides for marketing authorisation.

Whether an OP product is being authorised as a human or veterinary medicine, or as a plant protection product, the three criteria considered are safety, quality, and efficacy. The report by OGOP (OGOP, 1998) notes that the licensing systems are similar for human and veterinary medicines but slightly different for pesticides. It finds that the systems are compatible with a statement of the precautionary principle. (The report was prepared before the European Commission communication on the precautionary principle described in Appendix A and the meaning of the precautionary principle is part of the OGOP considerations.) The report also notes that the way in which uncertainties in risk estimation are handled in the licensing systems is a precautionary approach. For example, this includes the use of conservative ‘safety factors’ or ‘uncertainty factors’ in relation to pesticides.

3.4.1 Marketing authorisation for chemicals as veterinary medicines

UK governmental decisions on the approval and licensing of veterinary medicines are taken on the basis of advice from the Veterinary Products Committee (VPC). The three criteria considered in the approval process are the quality, safety and efficacy of the product. (The safety criterion relates to users, consumers and the environment.) The ‘burden of proof’ lies with the manufacturer - in other words they must demonstrate that their product meets the criteria (European Commission, 1998a-c). The manufacturer submits an Application Dossier to the authorising body which is either a National Authority or the European Medicines Evaluation Agency (EMEA). The UK National Authority is the Veterinary Medicines
Directorate (VMD). This Application Dossier includes a demonstration of the potential risks to user safety and a report by an expert commenting on the applicant’s user risk assessment. Some aspects of the user safety information required are specified in European Commission guidance (European Commission, 1998a-c). However, the way in which the user risk assessment should be carried out is not specified. The authorising body then carries out an evaluation of the manufacturer’s application. Again, the way in which this evaluation should be carried out in relation to the user risk assessment is not prescribed. Our understanding is that there is no formal setting on an AOEL within the user/worker risk assessment. The marketing authorisation for a product may be suspended or revoked if new information indicates that an approval is no longer appropriate.

To date, all sheep ectoparasiticides used in the UK have been granted marketing authorisation under the National Procedure whereby the evaluation of the application is by the VMD.

Appendix B gives further details on: the role of the VPC; the legislation, procedures and authorising bodies involved in marketing authorisation; the safety, quality and efficacy criteria; and the aspects of the user safety information which are specified in the European Commission guidance.

**3.4.2 VPC/VMD Evaluation of user-safety risk assessments**

The VPC/VMD does not have a publication specifically aimed at setting out the way in which Application Dossiers are evaluated. (The same applies to the EMEA.) However, some information with regard to user safety is given in (VPC, 1999b):

> ‘A precautionary approach is built into the authorisation process ...... The risk to operators is addressed by taking a worst case scenario for exposure and calculating the margin of safety in comparison with the dose at which no adverse effects were found. A minimum 10-fold safety margin is usually required: the precise margin would depend on the severity of the adverse effect and other factors such as the likelihood of the occurrence of the worst case scenario. In our 1993 review of OP sheep dips a 100-fold safety margin was used, based on a dose which had produced no adverse effects in a human volunteer study.’

What the worst case scenario refers to is not stated. However, we note that the outcome of the 1996 VPC review of OP sheep dips was that ‘there continued to be no scientific justification for advising the withdrawal of organophosphorus sheep dips provided that they are used in accordance with current recommendations’ (VPC, 1997).

**3.4.3 Consideration of the merits of publishing details of the VPC/VMD evaluation of user-safety risk assessments**

The need for greater openness about the way user safety is evaluated for any product was considered in our report. In addition the need for greater openness about the way user safety is evaluated for specific products was addressed. The VPC/VMD does not publish the evaluation of Application Dossiers for specific products because much of the relevant information cannot legally be disclosed. This applies particularly to much of the information pertaining to
the quality and efficacy of products. The legal position and general issues relating to disclosure have been considered by OGOP. In (OGOP, 1998) it is noted that:

‘the VPC is unable to publish a certain amount of detailed documentation, including evaluation papers, whereas the corresponding papers on pesticides are published. This attracts attention and no doubt creates an impression of secrecy, perhaps out of proportion to the amount of information withheld’.

It is also noted that disclosure of information to the public would require a change in primary legislation and it is recommended that further consideration should be given to doing so.

Whilst supporting this recommendation, it is unclear as to whether the legal restrictions are such as to wholly preclude publication of details of the user-safety risk assessments. For example diazinon could readily undergo approval review by both VMD/VPC for its use as a veterinary medicine and also by PSD/ACP as a plant protection product. There would be large areas of commonality within the risk assessment. An evaluation report with certain caveats concerning commercial confidentiality would be produced ultimately by PSD, whereas little would be in the public domain from VMD.

In an increasingly globalised market for veterinary medicines and pesticides, it has been interesting to have almost complete access to the recent comprehensive risk assessment for diazinon (NRA, 2000) from the National Registration Authority (Australia). This is a ‘unitary’ regulatory authority covering veterinary products, pesticides and all agrochemicals, albeit operating under different primary national legislation but dealing largely with the same multinational manufacturers of products that may seek approval in the UK.

However, in line with other government bodies, the VPC has in the last couple of years taken a number of additional actions to promote openness in regard to their work generally. For example, minutes of VPC minutes are now published and in September 2000 a forum was held to give an opportunity for interested members of the public to meet members of the VPC and discuss their work.

3.4.4 Information requested from the VMD regarding user risk assessments for sheep ectoparasiticides

For the purposes of the quantified risk assessment stage of this project, information was sought from the VMD on toxicity, worker exposure and user risk assessments for: OP dips; pyrethroid dips and pour-ons; and injectables. In addition to useful information on sources of toxicity and worker exposure data in the public domain, the following information was helpfully provided:

- Worker exposure information from studies into OP dipping which were carried out by applicants some years ago. However, the VMD considers that these studies are less comprehensive than recent studies which are in the public domain.

- An example of an assessment of risks to operators associated with the use of injectables. The VMD does not hold information on worker exposures to injectables - as indicated by
the example assessment, this information is not needed because a simple worst-case estimation of worker exposure is an appropriate approach.

- Various VPC deliberations and submissions to the VPC concerning OP sheep dips.

The VMD were unable to provide any further details on user risk assessments within the necessary timescale for this project. We should emphasise that the VMD proved helpful and informative in many other areas associated with licensing/approving veterinary products.

3.4.5 Information on the VPC reviews of worker safety aspects of OP sheep dips

The VPC has undertaken four wide ranging reviews related to worker safety aspects of OP sheep dips. For example, issues taken into account have included: reported cases of ill-health, the prevalence of sheep scab, the sales of sheep dips, resistance of ectoparasites to pyrethroids, the provision of protective equipment, and the application to sheep dipping of COSHH. The outcomes and resulting advice have been published and this information is assessed in the qualitative consideration of the adequacy of risk control measures in the workplace in relation to OP dipping in this report.

The first general review was completed in 1993 (VPC, 1993), and this was followed by reviews which, in addition to other issues, considered the findings of research by the Institute of Occupational Hygiene (VPC, 1995), the effectiveness of the Certificate of Competence Scheme for purchasing sheep dips (VPC, 1997) and the findings of research by the Institute of Occupational Medicine (VPC, 1999a & 1999b).

3.4.6 Marketing authorisation and approvals for chemicals as plant protection products (pesticides)

Registration of pesticides, such as OPs & SPs, in the context of plant protection products within member states of the EU is carried out by regulatory organisations within individual member states. However registration is increasingly carried out under a number of EU directives, flowing from an overarching directive (91/414/EEC), which attempts to harmonise procedures within the EU on the principles of efficacy, risks to plants, human and animal health and the environment. The approval process for plant protection products in terms of the EU-defined directives is described in detail in Appendix C.

Within the UK decisions on pesticide approval and licensing is carried out on the advice of the Advisory Committee of Pesticides (ACP). Recommendations of the ACP are based on evaluation reviews carried out by either PSD or the Biocide and Pesticide approval unit (BPAU) of HSE on the submissions made for specific products or a.i. by the manufacturers. Whether PSD or HSE are involved in the review process depends on the agricultural or non-agricultural use of the product.

The evaluation reviews carried out by PSD or HSE are available, subject to a valid reason for access being cited and with the proviso that recipients cannot make commercial use of the contents of such publications as described in the Control of Pesticides Regulations 1986 and Control of Pesticides (Ammendment) Regulations 1997. Therefore it is transparent concerning
the basis of how the safety of individual pesticides have been assessed. Both PSD & HSE also indicate that public access to underlying raw data used in the evaluations can be arranged. Within the UK the transparency of the pesticide approval process has been further improved in 2000 by the ACP producing a document intended for the lay-person to describe its function and by holding ‘open’ meetings.

The general process whereby pesticides are evaluated in terms of workers safety has been described in section 3.3. The figure in Appendix C maps out the tasks again, using the terminology that developed from the EU attempt at harmonising pesticide registration. ‘Hazard identification and dose-response evaluation’ is that activity associated with review of the available toxicological database (supplied by the manufacturer in the case of an actual approval) for the specific chemical of interest. This is to identify (a) the appropriate adverse effect endpoint and (b) the NOAEL. Subsequently there is extrapolation from the NOAEL to an AOEL which is a level to ensure protection of human health. This is carried out by applying uncertainty or assessment factors to the NOAEL depending on the data within the toxicology database. ‘Exposure assessment’ relies on the combination of expert judgment on the working practices associated with the likely use of the chemical, evaluation of experimental/field studies and increasingly sophisticated computer model of exposure. For the purpose of carrying out these steps in this report this study relied on reviews of published evaluations by international or UK regulatory bodies of those specific chemicals registered in the UK for sheep ectoparasite treatment. However, we would highlight recent evaluation reviews from international regulatory bodies on three of the OPs which have been associated with sheep-dipping in the UK, diazinon which is still registered and chlorfenvinphos and propetamphos, neither of which is currently registered for use, but which were used extensively in the late 1980s-early 1990s when concerns about health problems were being raised. These recent reviews are:

- **Diazinon Review (2000)** by the National Registration Authority (NRA) for Agricultural and Veterinary Chemicals, Canberra Australia. The NRA is the independent statutory authority for the regulation of agricultural and veterinary chemicals and as such combines many of the functions of the VMD and PSD/HSE pesticide registration section. The diazinon review was carried out as part of the systematic review of existing registered chemicals;

- **Diazinon Review** by United States Environmental Protection Agency (US EPA) preliminary evaluation carried out in 2000 with completion in early 2001;

- **Propetamphos review** by US EPA undertaken in 1999/2000;

- **Chlorfenvinphos review** carried out by the NRA, Australia in 1999. (Chlorfenvinphos is currently registered in Australia for treating sheep and cattle against various ectoparasites.)
Risk assessments for the same a.i. as either pesticide or veterinary medicine are carried out as part of the approval process for placing products containing the a.i. on the market. These approval processes are driven by the respective EU directives and national legislation. For example for diazinon or cypermethrin considered as constituents of plant protection products (pesticides), the aspects of worker safety considered at the EU and member state level are clearly laid down as previously described and Appendix C. Similarly for the same a.i. used as part of veterinary medicines worker safety is one element of the approval process that allows the particular product containing the a.i. to be used for the designated purpose. Therefore either as a plant protection product or a veterinary medicine, a risk evaluation for worker safety should have been performed for the particular product for the stipulated use. These approval procedures are risk assessment processes. They assume that post-approval the products will be used in the appropriate way described for their use and with the designated exposure control measures. They are not part of risk management.

We have carried out quantified risk assessments for sheep ectoparasite treatments in an analogous manner to that for a pesticide under review or as a new approval within the current EU regulatory framework for plant protection products. We used this approach because the methodology and uncertainties in the process are well documented, it is not an unfamiliar approach to members of the study team and, as previously noted, we are advised that it is similar to the procedure that is carried out for veterinary medicines (see section 3.4.1). In the time available and given that our brief was not to carry out a formal regulatory approval process, we have relied heavily on data within published reviews by various national and international bodies (PSD UK, BPAU HSE UK, US EPA, NRA Australia, WHO, FAO etc.) rather than carry out in-depth critiques of source material. Where appropriate, we highlight the key reviews on which we have relied.

Our principal health risk assessment was the use of the OP pesticide diazinon in sheep dip, where it is an effective, broad spectrum treatment for a wide range of ectoparasites. Diazinon remains the only OP with approval subsequent to the recent UK moratorium on sheep-dipping and for future use with appropriate removal of concentrate handling. We recognise that other OPs have been historically used in sheep-dipping during the 1980s & 1990s, principally propetamphos and chlorfenvinphos, and which, with diazinon, have been associated with health concerns. Our reason for focusing on the particular OP diazinon is driven more by its likely future use in the context of sheep ectoparasite treatment rather than an a priori assumption concerning any health risks associated with this particular OP. Our other attempts at risk characterisations for operator safety have centered on the use of SPs in dips and as pour-ons, and also the injectable treatments.

In the following sections related to quantified risk assessments, we first discuss and characterise the toxic hazards related to the individual a.i.s, we then go on to undertake ‘risk estimations’ for these chemicals. Risk estimations involve the establishment of the critical toxicological end-points and associated NOAELs. For OPs associated with sheep-dipping which has been the cause of ongoing, contentious debate we discuss current issues around definition of an appropriate NOAEL. We then go on to describe the ‘exposure assessments’ for the a.i. as used in the particular work practices for treating sheep ectoparasites. The ‘risk
evaluation’ process then compares the data from the ‘risk estimations’ with the worker exposure assessments for each a.i.. We have attempted to show this ‘risk evaluation’ data in a readily understandable diagrammatic form. Two approaches are used in this report, firstly the process of establishing of a “safe” exposure level, an AOEL, from the NOAEL and investigating whether the likely occupational exposure levels meet this dose. Secondly, we quote the NOAEL: exposure ratio which are frequently defined as TER (toxicology exposure ratios) or MOE (margins of exposure) among various regulatory bodies. Finally, we discuss the outcome of these quantified risk assessments with the recent history of sheep-ectoparasite treatments, the reporting of ill-health to the VMD principally associated with OP sheep dips and our estimate of the likely incidence of symptoms associated with those so have undertaken sheep-dipping.
4. TOXICITY - THE HAZARD

The brief of this report is to focus on possible acute health effects caused by exposure to the active ingredients used in sheep-ectoparasite treatment. This section largely deals with the acute adverse effects in humans but where relevant also highlights environmental toxicology concerns.

4.1 Organophosphorus compounds

The acute or short-term health effects of an excessive OP exposure are well-documented and agreed as related to the short-term, anti-cholinergic effects of OPs. Other effects such as delayed neuropathy and the intermediate syndrome are reported to be caused by high doses of some specific OPs and occur later than the immediate short-term effects. Their biological mechanisms are not completely understood. Delayed neuropathy is an established phenomena such that standardised animal tests to establish whether specific OPs may cause it are part of routine toxicity testing that are required now for product approval. Intermediate syndrome as a distinct clinical entity still remains controversial among some experts. The ability of single or multiple doses at levels below where there is any evidence of an anticholinergic effect to cause chronic ill-health remains unsubstantiated, controversial and outside the scope of this report. Research is currently being carried out in this area.

4.1.1 General description of mode of action of OPs.

Organophosphorus pesticides poison humans and insects through their effects on a key enzyme, acetylcholinesterase, found at junctions in the nervous system. They combine chemically with the enzyme acetylcholinesterase and inactivate it, forming the basis of the ‘anticholinergic effect’. Acetylcholinesterase is an enzyme essential for the normal control of transmission of nerve impulses. Loss of acetylcholinesterase activity allows the accumulation of acetylcholine which in normal transmission of signals across gaps (synapses) between nerve cells has to be very rapidly broken down. Effectively excess acetylcholine at the synapse stops the nerve signal being turned “off”. This substance is secreted by nerve endings that activate muscles, glands, and other nerves. Accumulation of sufficiently high levels of acetylcholine at junctions between nerves and muscles will cause muscle contractions or twitching. Accumulation of acetylcholine at junctions between nerves and glands results in gland secretion; and accumulation between nerves in the brain causes sensory and behavioural disturbances.

4.1.2 Symptoms of acute OP poisoning

The main symptoms of acute OP poisoning include headache, nausea, dizziness, pin-point pupils, blurred vision, tightness in the chest, difficulty in breathing, muscle weakness or twitching, difficulty in walking, vomiting, abdominal cramps, and diarrhoea. Effects on the central nervous system may include confusion, anxiety, drowsiness, depression, difficulty in concentrating, slurred speech, poor recall, insomnia, nightmares, and a form of toxic psychosis resulting in bizarre behavior. The type, range and severity of these symptoms that are presented probably depend on a number of factors including the dose of OP absorbed, the route of OP exposure, the specific OP involved and the time between absorption of the OP
and presentation to the doctor. It should be noted that many of the symptoms are relatively non-specific.

4.1.3 Diagnosis

Diagnosis can be made by correctly associating the presentation of some of the symptoms noted in 4.1.2 with excessive exposure to an OP or other anticholinergic chemical structure. Diagnosis is aided by the laboratory measurement of acetylcholinesterase activity found in red blood cells (erythrocyte AChE) and a similar enzyme, butyrylcholinesterase, found in plasma (pChE). Such measurements are surrogates of the effect of the OP on AChE activity at critical sites in the nervous system. Importantly there are differences in the rates of recovery of inhibited AChE in target sites, erythrocyte AChE and the plasma enzyme, which means that the timing of the blood samples with regard to exposure influences the relationship found between symptoms and any depression in blood surrogate enzymes (Heath, 1992; Mason, 2000). Both enzymes, but especially pChE, show wide normal variation between individuals so that in only severe cases can a diagnosis be made without reference to the normal level of enzyme activity in that individual (Mason, 1989; Coye, 1986; Midtling, 1985). A more detailed description of the use of erythrocyte AChE and pChE measurements to monitor OP absorption in the occupational setting is given elsewhere in this document. However in cases of short term, high OP exposure where the patient is presenting with significant symptoms and is examined temporally close to the exposure, both erythrocyte AChE and pChE may be obviously depressed when compared against a population reference range (Heath, 1992).

In cases of subclinical poisoning the diagnosis may be missed due to the clinician not recognising the cause of the symptoms, which may be mild and non-specific. Subjects may complain of “flu-like” symptoms, and unless the doctor takes a detailed recent history of possible chemical exposure or is experienced in the presentation of OP toxicity, an incorrect diagnosis may be made. Given the relative non-specific symptoms found in OP poisoning, there have been concerns that individual cases of sub-acute OP toxicity have been missed and delays have meant that appropriate biological samples have not been taken to help confirm or exclude the symptoms as OP-related.

There have been isolated reports that suggest significant symptoms of acute OP toxicity may possibly be present without any depression in pChE or erythrocyte AChE, but this may be explained by blood samples being taken at the wrong time, use of inappropriately wide population reference ranges rather than the individual’s baseline values or imprecise analytical technique (Mason, 1989). We would suggest that there is general consensus that for blood samples taken at an appropriate time close to exposure, depressions in an individual’s erythrocyte AChE would correlate reasonably with the extent of anticholinergic symptoms whereas plasma ChE tends to be more sensitive to OP exposure without necessarily reflecting symptoms. Increasing delay between exposure and blood sampling weakens such relationships.

4.2 Pyrethroid compounds.

Synthetic pyrethroids (SPs) were developed in the light of the insecticidal properties of pyrethrum flowers (Chrysanthemum cinerariaefolium) which have been known from early times in Persia and exploited in Europe from the beginning of the nineteenth century. The
developed SPs combine high toxicity to insects with low mammalian toxicity. For example, comparison of the ratios of \( \frac{LD_{50} \text{ (rat)}}{LD_{50} \text{ (insect)}} \) for SPs and OPs show approximately a 100-150 relative safety factor for pyrethroids (Elliott, 1978). SPs have been used for many years with relatively few serious problems reported, this is attributed to their relatively low toxicity, low skin penetration and rapid metabolism to non-toxic chemicals in mammals. However, above certain internal doses SPs can cause neurotoxicological problems. There are two general classes of SPs; those such as permethrin which do not have an alpha-cyano group in their structure and those which do (cypermethrin, deltamethrin & fenvalerate). The presence of this cyano group and the spatial conformation of the compound at a specific part of the chemical influence the level of their activity and toxicity.

4.2.1 General mode of toxicity of SPs

Pyrethroids stimulate nerves by causing pronounced repetitive activity, similar to the effects noted for DDT. Such effects of excessive SP absorption can be found in the central nervous system, sensory organs, nerves involved in motor actions and neuromuscular junctions. Non alpha-cyano SPs, such as permethrin, cause nerve triggering of short duration while those such as cypermethrin that contain an alpha-cyano group can induce intense repetitive nerve impulse activity that can finally lead to a depression of the nerve impulse (Perger, 1994). There is evidence that an excess of alpha-cyano containing SPs can also influence the release of neurotransmitters such as gamma-aminobutyric acid and catecholamines.

4.2.2 Symptoms of acute SP exposure

All SPs induce skin sensation to varying degrees - numbness, itching, burning, tingling and warmth have been reported in those exposed to SPs (Kolmodin-Hedman, 1982; Knox, 1984; Shuje, 1988). Effects appear most frequently with the cyano containing SPs such as cypermethrin and deltamethrin. Such symptoms are thought to relate to skin contact with the SP. Some of these dermal effects have been ascribed to acidic metabolites produced by esterase-activity found in the skin, alternatively an SP-induced lowering of the threshold of sensory nerve fibres or nerve endings has been suggested (Le Quesne, 1980).

Whilst most cases of SP exposure are thought to lead to mild symptoms, such as numbness tingling and irritation, in a few cases where exposure has been very high serious toxicity can occur. In a review of 573 cases of acute pyrethroid poisoning (334 accidental exposure and 229 cases of occupational exposure) in China, two subjects died of convulsions and one subject died of pulmonary oedema (He, 1989). Under occupational conditions where the exposure was mainly dermal, first the skin was affected followed by any systemic symptoms as late as 48 hours after exposure. Mild acute symptoms include skin effects, dizziness, headache, nausea, anorexia and fatigue. Additionally in moderate poisoning mild disturbances of consciousness and muscular fasciculation in limbs were seen. Symptoms of severe poisoning were convulsive attacks, transient changes in EEG and repetitive discharges in EMG, coma or pulmonary oedema. The vast majority of patients recovered within 1-6 days, but in those who suffered severe poisoning and convulsions, the duration of recovery took up to 55 days. The authors reported no long-standing or residual symptoms. Similarly, Chen (Chen, 1991) reported no long-term health effects in a study of over 2000 cotton growers. Whilst it is wholly inappropriate to compare the absolute incidence rates of symptoms in Chinese cotton growers with UK-usage of SPs for sheep treatments, Chen found
approximately a quarter suffered mild dermal symptoms but only 0.3% developed systemic symptoms. This reflects the general consensus view about the relatively low toxicity of SPs to humans. However it should be noted that there is also a view held by a minority opinion that relatively limited SP exposure can produce a wide variety of chronic complaints (Muller-Mohnssen, 1999). In a study of 144 subjects Muller-Mohnssen reported evidence of changes in personality, intellectual performance, sensory/polyneuropathy, central nervous disorders, autoimmune and other immunological abnormalities including sensitivity to other chemical exposure. Such a presentation shows similarities with the effects put forward by those groups who voice concerns about the chronic effects of OP exposure. However, Muller-Mohnssen’s study has been criticised as largely reliant on telephone and questionnaire investigation of subjects.

### 4.2.3 Environmental toxicity of SPs

Whilst the mammalian toxicity of SPs is relatively low, their toxicity towards fish and other aquatic life is very high. This is obviously relevant to SPs used in sheep-ectoparasite treatment where contamination of water-courses from spent sheep-dip or inadvertent access of recently SP-treated sheep to streams and rivers can cause serious environmental harm. For example, the 96 hour LC$_{50}$ for brown trout and carp are between 1-3 µg/l of active SP, whilst the concentration of active a.i. in sheep-dip may be 44-250 mg/l which is a 20,000-100,000-fold concentration difference. SPs in sheep-dip can however be neutralised by chemical treatment. Some idea of the likely environmental risk of SPs from spent sheep-dip can be gained from Environment Agency reports on Sheep Dip studies in Wales (Environment Agency 2000, 1999 & 1998). These found between 6% and 33% of samplings from streams were positive for cypermethrin and flumethrin (SPs used in sheep-ectoparasite treatment) and 7-20% of these water samples had cypermethrin levels greater than the protective Environmental Quality Standards Maximum Allowable Concentration of 1 ng/l. Three substantiated pollution incidents involving SPs were recorded in the 1999 study, while eleven SP pollution incidents were noted in the 1998 study.

Figure 4.2.3a shows quoted LC$_{50}$ for various fish species and the concentration of active ingredients (diazinon, propetamphos and cypermethrin) used in plunge dips. This comparative data suggest that whilst spillage of either OP or SP at dip strength may potentially have serious effects on fish life, SP represent a very more serious relative threat from leakage of dilute dip into rivers or other water courses.
Figure 4.2.3a Lethal concentrations (LC50) for diazinon (diaz), propetamphos (prop) and cypermethrin (cyper) in comparison with concentrations of these three chemicals at the recommended dipping levels. The concentrations on the y-axis are shown on a logarithmic scale.

4.3 Macrocyclic lactones (Avermectins, Ivermectin, Doramectin, Moxidectin).

Avermectin and related compounds have relatively low toxicity. Avermectins are the generic name given to a group of lactones produced from microbial fermentation of the actinomycete *Steptomyces avermitilis*. Ivermectin is a mixture of two closely similar avermectin structures. Doramectin has close structural similarities with ivermectin, produced by fermentation of the same microbial strain. Moxidectin is produced by chemical modification of nemadectin, a natural fermentation product from *Streptomyces Cyaneogriseus*. It is also a macrocyclic lactone, again structurally similar to ivermectin.
4.3.1 General mode of toxic action of macrocyclic lactones

The data suggest that avermectins are of low toxicity to humans. The toxic mode of action of this class of agents is by modulation of the chloride channel in the nerve and muscle cells of the parasites. These chloride channels are largely controlled by GABA receptors. In mammals, including humans, the neural GABA receptors are restricted to the central nervous system, which is protected by the blood-brain barrier. As avermectins exhibit poor penetration of the blood-brain barrier, this explains the wide safety margin in humans exhibited by these compounds.

4.3.2 Symptoms from acute macrocyclic lactone exposure

Avermectins remain a class of drugs which have made substantial contributions to both human and animal health. Ivermectin has been used on millions of people worldwide for the treatment of parasites such as Onchocera volvulus which causes “river blindness”. Any symptoms from ivermectin are relatively mild in treated subjects (up to 0.2mg/kg) and have largely been ascribed to immunological reactions to the treated dead parasites in tissues rather than the ivermectin treatment itself. Other data on volunteer studies and adverse reaction data have been made available from the pharmaceutical manufacturer. Some mild symptoms, such as headache, have been reported in healthy volunteers given 0.1 mg/kg. Forty reports of self-injection with ivermectin solutions designed for animal use have been collated. Pain at injection site, but also nausea, general numbness, variable blood pressure, urticaria and cellulitis were noted. Dermatitis has been found after dermal exposure and accidental oral ivermectin exposure lead to mydriasis, vomiting, tachycardia and somnolence.

In two recorded incidents of accidental self-injection with an unknown volume of 1% moxidectin, no local or general reactions were observed.

4.3.3 Environmental toxicity of macrocyclic lactones

Concerns have been raised about the excretion of macrocyclic lactones in the faeces from animals treated with these chemicals for parasites and the possible detrimental effect on those beetles and other insects where dung play an important role in their life-cycle. Many dung-using insects have a beneficial influence by not only spreading the nutrients contained in dung into the ecosystem, but also by reducing host facilities for various insect pest species. Unfortunately, macrocyclic lactones are almost entirely excreted in the faeces of treated sheep. These concerns have been raised in the UK and other countries in both the Northern and Southern hemisphere, given the wide spread registered use of macrocyclic lactones around the world for controlling ecto- and endo-parasites. There has tended to be a lack of consensus in the scientific community on the risk of macrocyclic lactone residues in this respect. This was largely due to the complex interactions under consideration including temperature, rainfall, animal management, pasture quality and climate. However, it has been pointed out that dung size is correlated with its lifespan as a microhabitat for pests. Sheep droppings are small and tend to dry out quickly, except in winter, losing their attraction for insects. Also most UK dung-seeking insects will utilise whichever dung is available.
The NRA carried out a special review of this concern in the context of the Australian geography, ecology and treatment regimes. This review found no clear evidence of any long term detrimental effects (National Registration Authority, 1998).

4.4 Amitraz

Amitraz has been noted to cause changes in blood pressure, heart rate, and mental alertness. Poisoning leads to impaired consciousness, hypotension, hypothermia and possibly hypoglycemia. Nausea, vomiting, diarrhea, headache, dizziness and incoordination may also occur. There is an isolated case report of a man being fully immersed in cattle dip of diluted amitraz for only a few seconds, but subsequent decontamination at the site was not thorough. After 36 hours he suffered a throbbing headache and vomiting, although the possibility of a concomitant viral infection has been questioned in this case.

4.5 Cyromazine

Cyromazine is an insect growth regulator widely used in controlling fly larvae around cattle pig and poultry units as well as in control of sheep ectoparasites. The exact mode of insectacidal action of cyromazine is unknown but causes severe developmental disruption during the larval stage. We can find no relevant data on adverse effects in humans for cyromazine or the major metabolite melamine. It appears to have low environmental toxicity, although bees may be at risk.
5. RISK ESTIMATION

This section deals with the establishment of NOAELs concerning the appropriate adverse or critical toxicological effects for the specific a.i. used in various sheep ectoparasite treatments. This invariably involves a review of the largely animal toxicological database, not just in terms of defining dose-response relationships for critical effects of relevance to humans but also with regard to those studies which may be most appropriate for the sort of work exposure pattern that would be encountered using the a.i. We have not undertaken a review of the original toxicological datasets for each a.i., but have compiled and reviewed those NOAELs defined by a number of regulatory and international bodies.

In selecting appropriate NOAELs for sheep-dipping and other sheep ectoparasite treatments we have borne in mind that for sheep-farmers and their workers these are short-term activities (1 to 2 days and certainly less than 7 days), possibly carried out 2-3 times a year (short-term, intermittent exposure). Thus a NOAEL derived from an acute or short-term repeated dose is more appropriate than that derived from chronic studies. Whilst this exposure pattern is appropriate for farmers, there is an increase in the use of contractors for sheep-dipping. For this activity/worker cohort, although seasonal, a NOAEL derived from longer subchronic repeated dose studies is more appropriate. Therefore in our opinion it may be entirely appropriate to have different NOAELs for a specific a.i. when considering sheep treatment carried out by owner farmers and their workers as opposed to contractors who may be carrying out the work activity over a period of several months. Exposure assessment of contractors is discussed in the relevant section of the report.

5.1 OP risk estimation

5.1.1 Definition of the adverse effect for organophosphate chemicals

For OPs which have anticholinergic activity, there is an ongoing debate about the nature of the “adverse” effect chosen for establishing an NOAEL. For many regulatory authorities the adverse effect for these class of chemicals has centered on the inhibition of brain or red blood cell acetylcholinesterase (AChE) in the appropriate animal toxicology model. Inhibition of AChE enzyme activity in nervous tissue and associated with neuro-muscular junctions is clearly associated with overt, acute toxicity. The same enzyme is also found in readily accessible red blood cells as well as nervous tissue and has been recognised as a useful surrogate of OP action at the target site, although toxicodynamic considerations mean that the time courses of enzyme inhibition may not run in parallel. In practice, depressions in blood AChE activity by OP can be monitored at serial time points throughout an animal experimental toxicology study, whereas activity in the central nervous tissue can only be performed after the final sacrifice of the animal.

A distinctly different enzyme found in blood plasma, (butyrylcholinesterase, plasma cholinesterase, pseudocholinesterase, pChE) is also inhibited by OPs and is widely used as evidence of human or animal over-exposure. A further complication may be that blood plasma from various animal species, such as dogs and rats which are widely used for regulatory purposes, contains both AChE and pChE, unlike human plasma which is overwhelmingly pChE. Given that adverse anticholinergic effects also occur in the peripheral nervous system as well as the
central system, there is currently considerable interest in whether a test for peripheral nervous tissue acetylcholinesterase inhibition could provide an alternative or addition to blood measurements (SAP, 1997; Mileson, 1999).

It has been suggested that a divergence of opinion exists between some regulatory bodies and the agrochemical industry on the toxicological significance for establishing an NOAEL that can be ascribed to the “cholinesterases” i.e.- AChE in nervous tissue, AChE in red blood cells and plasma ChE (Carlock, Chen et al. 1999; Padilla 1995; Chen, Sheets et al. 1999). The industry position is generally that plasma ChE should not be used as an adverse effect in risk assessment, that erythrocyte AChE inhibition from human data should take precedence over animal data for determining NOAELS and, where available, brain AChE data should take precedence over erythrocyte AChE data (Carlock, Chen et al. 1999). Documentation on the use of data on cholinesterase inhibitions has been recently produced by several regulatory bodies- EPA(US) (Office of Pesticide Programs, 2000) and PSD (UK) (Samuels, 2000) to clarify their individual positions.

While historically regulatory risk assessment procedures for OPs in the UK, EU and Canada have tended to use animal erythrocyte or brain AChE as the adverse effect or toxic endpoint for establishing a NOAEL, there are some regulatory agencies, such as the NRA (Australia) and EPA (US) which seem to have put increasing emphasis on inhibition of plasma ChE as an endpoint in the absence of erythrocyte or brain AChE inhibition. In fact both the EPA (US) and the NRA (Australia) have very recently carried out reviews of diazinon as part of a regulatory re-approval processes (US EPA, 2000; National Registration Authority, 2000b) and have apparently used inhibition of plasma ChE as the appropriate toxicological endpoints in these updated assessments.

The current UK position on the interpretative use of the various cholinesterase measurements has been further clarified through an internal PSD document (Samuels, 2000) and recent discussions by the ACP. ACP document 281 (277/00) notes that:-

‘when setting NOAELs for cholinesterase effects, the normal practice should be to use the more sensitive of erythrocyte and brain cholinesterase in each study. However, data on erythrocyte cholinesterase could be overridden if satisfactory data were available on cholinesterase in peripheral nerve tissue. The rationale for not basing risk assessment solely on brain cholinesterase (as is the practice of some other regulatory bodies) is that because of the blood-brain barrier, it is possible that the peripheral nervous system could be more sensitive than the central nervous system. Erythrocyte cholinesterase provides a surrogate for cholinesterase in the peripheral nervous system. However, it is recognised that it may often be over-sensitive as a marker. For example, in studies based on repeat doses, there is less scope for regeneration of cholinesterase in erythrocytes than in peripheral nerve tissues. Changes in plasma cholinesterase are not an appropriate basis on which to set reference doses because they do not represent an adverse effect. In determining NOAELs in studies based on cholinesterase, a reduction of 20% or more should be considered toxicologically relevant, and the pattern of effect at all dose levels should be taken into account as well as the statistical significance of findings at each individual dose level.’

This differs subtly from the Office of Pesticide Programs 2000 report which states that ‘acetylcholinesterase inhibition in the nervous system is viewed as key event... critical effect in the hazard assessment.....the OPP, however, may use plasma cholinesterase inhibition data under certain circumstances, such as if the red cell data are insufficient or poor quality or unavailable.............’
The ACP position would agree with our practical experience of over twenty years of routine monitoring using both erythrocyte AChE and plasma pChE measurements of workers in a range of industries where there is a risk of potential OP exposure. We have noted depressions in pChE in monitored workers without any complaint of subjective symptoms, but where the worker has complained of recent subclinical symptoms, such as runny nose, wheeziness or mild “flu-like” symptoms, we have invariably found some significant depression in erythrocyte AChE. In *in-vitro* experiments we have also found pChE enzyme to be more sensitive than erythrocyte AChE to inhibition, needing a ten-fold increase in the concentration of the activated amount of diazinon (diazoxon) in blood to inhibit erythrocyte AChE by 15% compared to the same level of inhibition in the plasma enzyme.

Therefore, given adequate quality of the published data, we have defined NOAELs for short-term exposure to OPs based on significant inhibition of red blood cell or brain AChE inhibition (>20%) from largely single dose, sub-acute studies or short-term repeated dose studies.

### 5.1.2 Use of human OP exposure data

Given the availability of human data on OP exposure, including diazinon, from field studies and ethically-approved human volunteer studies, we have used these data to try and confirm the extrapolation from animal-based NOAELs to the target species (humans) and to substantially strengthen the worker exposure assessment for diazinon used in sheep-dipping.

The use of human volunteer data within the framework for pesticide registration has remained a contentious issue, particularly in the USA and especially with regard to human NOAEL setting studies. Various pressure groups have suggested that the agrochemical industry are interested in human volunteer studies in an attempt to circumvent the application of a more protective inter-species uncertainty factor from animal studies, and that such pesticide studies are invariably unethical. Other opinion has pointed out that it is inappropriate to consider pesticides as a special case with regard to general chemical toxicity and that modern human volunteer studies are universally governed by independent ethical committee review using guidance on biomedical research (Helsinki Declaration, 1964). Human studies have also been suggested as being more appropriate and reliable in assessing human health than using animal studies, albeit such studies are usually of small cohort size and do not cover susceptible groups such as children.

This debate has caused the US EPA some concerns. Prior to 1998 they consistently accepted human volunteer pesticide safety data, although some staff had suggested that they should not encourage such studies. In 1998 the US EPA adopted an interim policy that human studies would not be used to establish regulatory levels such as NOAELs, but by late 2001 the agency admitted it was again reviewing data for human pesticide volunteer studies, although a formal policy statement had not been issued. The issue of human volunteer studies in this context has been referred to the US National Academy of Sciences. It should be noted that human volunteer studies involving potentially toxic substances are conducted and supported by both commercial and regulatory bodies. For example, phase 1 clinical studies investigating new drugs, food and colour additives are probably the most prominent examples of human volunteer studies for toxicity.
The study team’s experience of human data collected from field studies together with appropriate and ethically-obtained human volunteer studies is that they can be a substantial help in both risk assessment and risk management issues. HSL has recently carried out low-level human volunteer studies on chlorpyrifos, propetamphos and diazinon. As these were single, low dose experiments they were not set-up to define a NOAEL or help substantiate a NOAEL derived from animal studies. Rather they were carried out to gain information such as the dermal penetration of specific pesticides in humans and the relationship between dose, and those urinary metabolites which can be routinely monitored in field studies, and any evidence of blood cholinesterase inhibition. As will be shown, they are invaluable in helping to define the relationship between exposure and internal dose. We understand that Novartis/Syngenta (holder of diazinon license) may have in the last two years also carried out some human volunteer studies on diazinon which may be more directly relevant to defining the NOAEL for cholinesterase inhibition. Currently we have not gained access to these studies.

5.1.3 Key reviews used to establish NOAELs for OPs

In establishing the NOAELs we have used the following published regulatory reviews among other data sources;

1. PSD evaluation on diazinon no 113 (Pesticide Safety Directorate, 1991)
2. NRA (Australia) review of diazinon (National Registration Authority, 2000b)
3. EPA (US) revised human health risk assessment for diazinon (US EPA, 2000)
4. EPA (US) updated and revised health risk assessment for propetamphos (US EPA, 1999)
5. PSD evaluation on chlorfenvinphos (Pesticide Safety Directorate, 1994)
6. NRA (Australia) review of chlorfenvinphos (National Registration Authority, 1999)

5.1.4 Defined NOAELs for OPs currently or previously used extensively in sheep-dipping

The systemic NOAELs that we defined from our review of available material are as follows.
5.2 Defined NOAELs for other sheep ectoparasite treatments

<table>
<thead>
<tr>
<th>Active ingredient (use)</th>
<th>NOAEL (mg/kg/day)</th>
<th>Lead study</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazinon (currently approved as dip)</td>
<td>2.5</td>
<td>acute rat oral neurotoxicology. (Chow, 1994) Quoted in (US EPA, 2000; National Registration Authority, 2000)</td>
<td>Based on rbc AChE inhibition. NOAEL appropriate for farmer/worker undertaking dipping not contractors.</td>
</tr>
<tr>
<td>Diazinon for contract use</td>
<td>0.02</td>
<td>(Pettersen, 1994) Quoted in US EPA 2000 &amp; National Registration Authority 2000.</td>
<td>Based on rbc AChE inhibition. NOAEL appropriate for contractors. Significant inhibition noted at 4,8 &amp;13 weeks.</td>
</tr>
<tr>
<td>Propetamphos (no longer approved as dip)</td>
<td>0.08</td>
<td>4 week data from 6 month repeat oral dose in dogs. Quoted in (US EPA, 1999)</td>
<td>Based on rbc AChE inhibition. This NOAEL is supported by NOAEL of 0.05 mg/kg/day established for brain AChE in mouse 4 week study also quoted in (US EPA, 1999)</td>
</tr>
<tr>
<td>Chlorfenvinphos (no longer approved as dip)</td>
<td>0.15</td>
<td>4 week repeat oral dose study in rats. Quoted in (National Regulatory Authority, 1999)</td>
<td>note likely large inter-species differences (dog=3.9mg/kg/d; mice=2 mg/kg/d in similar studies). Note single dose, volunteer human study showed 40% rbc AChE inhibition at 1mg/kg.</td>
</tr>
</tbody>
</table>
6. WORKER EXPOSURE ASSESSMENT

A literature search was conducted in order to find references which contained:

   a) quantitative or qualitative assessments of dermal or inhalation exposure i.e.
      occupational hygiene information;
   b) biological monitoring data;

during the use of OPs or SPs for the treatment of animal ectoparasites by dipping, using
pour-ons or injectable macrocyclic lactones.

The purpose for this was two fold; firstly to obtain a picture of potential exposures and
secondly to find data which could be used as surrogate measures of exposure in the risk
estimation process.

Attempts were also made to find unpublished data by approaching various commercial,
regulatory and scientific organisations who we thought may have such data. This proved to be
largely unsuccessful.

6.1 Published Exposure Data

6.1.1 Dips

We found five studies with useful quantitative estimates of dermal exposure and or biological
monitoring data;

These studies are listed below and summarised in Appendix D;


   of Welsh sheep farmers’. (Rees, 1996)

cides and the Effectiveness of Protective Clothing During Sheep Dipping Operations’
   (Niven, 1994)

   Practices', Institute of Medicine Report (IOM) TM/93/03 (Niven, 1993)


6.1.2 Pour Ons

We found only one paper containing exposure information relevant for pour-ons. This was an
American study using pour-on insecticides to treat hogs (Stewart, 1999).
6.1.3 Injectables

We found no exposure assessment data on the use of injectables.

Consultation with MAFF supported our finding on the limited, relevant published data available for pour-ons and injectables.

6.1.4 Off-label uses

We have found a worker exposure study carried out in Australia on a common showering dip system (Buzacott 60R) (Apthorpe, 1998). This was a study commissioned for the National Registration Authority. This two-man system is capable of dipping 60 sheep at once using spray nozzles at the bottom and top of the enclosure. It used 0.01% diazinon which was pumped from the holding sump to the spray heads and then recirculated back to the sump. This was a field study monitored over eight days, using a blue dye added to the dip. The operators wore overalls, wellington boots and hats. PVC gloves were worn while dispensing the concentrate, cleaning the sump and sometimes when handling the dipped sheep. The study noted that measured hand exposure was comparatively low because of the use of gloves, but highlighted splashing to the lower body due to the engineering set-up of this showering system. The measurement data and using the assumption of a dermal penetration rate of 4%, the study suggested a median systemic dose of approximately 0.4 mg/day (0.006 mg/kg/day). The worst case suggested a systemic dose of about 2.4 mg/day (0.034 mg/kg/day).

6.2 Exposure Predictions

In order to assess the risk to health presented by use of sheep ectoparasite control products it is necessary to firstly predict or estimate the likely operator exposure. Three approaches have been used in this report:

1. The use of published biological monitoring data (alkyl phosphate urinary metabolites) from field studies on sheep farms combined with human volunteer studies carried out by HSL (Griffin 1998, Garfitt 2002a,b). This allows the urine metabolites levels found in the field studies to be converted into the workers’ likely exposure (systemic dose). Data in Garfitt 2002(a) has been used to predict systemic dose from dipping activities containing diazinon and is more fully described in section 6.2.1. It should be stressed that this is an estimation of exposure from “real life” monitoring data, not a prediction.

2. The approach used by the UK Pesticides Registration Authorities. This has been used to predict systemic exposure to dips containing the currently registered OP diazinon, OPs which were widely used (propetamphos and chlorfenvinphos) and synthetic pyrethroids. The approach is described in section 6.2.2.

3. Worst case predictions. We consider that neither the literature or available models for prediction of exposure (i.e. DEFRA’s (formerly MAFF) operator exposure model (POEM) or the indicative distributions of exposure contained in HSE’s
Dermal Exposure to Non Agricultural Pesticides document) can provide data that could be meaningfully used for prediction of exposure to pour-ons and injectables. Therefore we have made predictions of systemic dose based only on worst case exposures for injectables containing macrocyclic lactones. We have no prediction of systemic dose for pour-ons because we considered that there are so many variables and unknowns it would be meaningless to assign a quantitative value. This is further described in sections 6.2.3 and 6.2.4.

6.2.1 Approach using biological monitoring for assessing exposure to diazinon during dipping and other ectoparasitic treatments

Biological monitoring is the measurement of a substance or its metabolites in blood, urine or breath and can be used as an aid to the assessment of exposure by all routes (ingestion, through the skin and inhalation). It is an established technique used routinely by occupational health professionals to assess the likely internal dose for a wide variety of chemicals (Lauwerys, 1993; Health & Safety Laboratory, 1999).

For OP pesticides the measurement of six dialkyl phosphate metabolites in an individual’s urine allows exposure to be assessed for about 80% of any of the OPs that have been approved for use over the last decade (Nutley, 1993). In the case of OP-based sheep dips this method had allowed exposure to chlorpyrifos, chlorfenvinphos and diazinon to be measured but not propetamphos. Biological monitoring has been used for routine monitoring in a number of the field studies where there is exposure to OPs, including a limited number related to sheep dipping. A urinary biological method has been recently published for assessing propetamphos exposure (Jones et al 1999, Garfitt 2002b) but has not been used in field studies of sheep dipping. However this newly developed biological monitoring method for propetamphos is currently being used in conjunction with dialkyl phosphate metabolites to investigate exposure in workers handling fleeces and hides from sheep treated for ectoparasites.

There is the question whether biological monitoring techniques could be, or have been used for other sheep ectoparasitic treatments. In the case of SPs, although validated analytical methods have been available for the metabolites of cypermethrin (Woollen, 1992; Kuhn, 1996; Health & Safety Laboratory, 1999), there appears no published data on their use to study occupational exposure in those undertaking sheep dipping or using pour-ons containing cypermethrin.

There are no reported biological monitoring methods for the macrocyclic lactones used for sheep ectoparasite treatment.

Estimation of systemic dose from biological monitoring data and human volunteer studies

The metabolites of OPs excreted in urine are proportional to a systemic (internal) dose which could have arisen by oral, dermal or inhalation routes. If the toxicokinetics and quantity of metabolites arising from a known systemic dose are known then the urine metabolite levels found in field studies could be converted into systemic doses. The Health & Safety Laboratory has completed a human volunteer study for diazinon on behalf of HSE (Garfitt 2002a),
having done similar studies for chlorpyrifos (Griffin, 1999) and propetamphos (Garfitt 2002b). These studies look at the excretion of urinary metabolites after exposure by either the oral or dermal route to defined single doses of the respective OP. Differences in the toxicokinetics of urinary dialkyl phosphate excretion between the dermal and oral routes were seen. Given the agreed view that the dermal route of exposure is of key importance in sheep-dipping, the dermal volunteer experiment data were used in this report to generate estimations of systemic dose.

Using the data on diazinon (Garfitt 2002), a 100 mg (328 μmoles) dermal dose of diazinon, occluded and left on the skin for 8 hours, gave rise to a mean cumulative excretion of 1550 nmoles ± 579 nmoles (standard deviation) total diethyl metabolites (diethylphosphorothioate & diethylphosphate) over 4 days. This is equivalent to a systemic dose of 0.47 mg of diazinon and therefore approximately 0.5% of the applied dermal dose was explained by urinary excretion. The concentration found in volunteers’ urine at the 22 hour sampling time-point after dosing was 61.8 μmol total diethyl phosphate metabolites/mol creatinine. This urine sample at this specific sampling time would be an equivalent time-frame to a urine sample taken ‘pre-work next day’ in sheep dipping field studies.

Taking the median urine metabolite level (17 μmol/mol) in ‘pre-work next day’ samples from those workers using diazinon in three of the published sheep dip studies (section 6.1.1) and comparing it to the mean value found in volunteers (61.8 μmol/mol) suggests a median systemic dose in sheep dippers of 426 nmoles of diethyl metabolites (17/61.8 x 1550) or 0.13 mg diazinon. The same calculation for the 95 percentile urine metabolite levels found in sheep dippers gives a systemic dose of 0.98 mg and for the maximum urine metabolite level seen in the field studies (227 nmol/mol creatinine) the calculated systemic dose is 1.7mg.

The above calculations assume that where there is 100% bioavailability of diazinon, i.e. the total urinary diethyl metabolites (diethylphosphorothioate & diethylphosphate) represent the systemic diazinon dose on an equi-molar basis. If diazinon was metabolised to substances not detected by the urine method or if there was significant excretion by another route (i.e. faecal) then the estimated systemic dose would need to be adjusted to account for the internal dose not reflected in urine. Such data would be derived from intravenous dosing where 100% bioavailability is assumed. No human volunteer studies of intravenous diazinon exposure have been undertaken, although such studies for other pesticides have been undertaken by TNO (Netherlands). An intravenous experiment in rhesus monkeys (Wester, 1993) suggested 56% of the internal dose was excreted in urine, but this experiment monitored the 14C labelled pyrimidinyl ring of diazinon, where biliary excretion of ring metabolites may be important and not reflect the excretion of water-soluble dialkyl phosphates. The HSL human volunteer study also used an oral diazinon dose of approximately 1mg and found 66 ± 12% of the dose as total diethyl phosphate metabolites. This figure is in agreement with animal studies using radiolabelled diazinon; 70% radioactivity in urine as diethyl phosphates using oral 32P- diazinon in a lactating cow (Robbins, 1957) and 65% of label in urine using oral ethoxy-labelled diazinon in rats (Mucke, 1970). Mucke (Mucke, 1970) also noted that in rats only a small proportion (approximately 6%) of the diethyl phosphates (diethylphosphorothioate & diethylphosphate) produced after esterase activity was further metabolised to carbon dioxide.
We cannot distinguish between two alternative explanations of urinary dialkyl phosphates reflecting only 66% of the oral diazinon dose. Either the urinary dialkyl phosphates reflect 66% of the systemic dose of diazinon (and the balance of the dose is in other metabolites which were not measured (i.e. the oral dose is approximately 100% bioavailable but more extensively metabolised), or that urinary dialkyl phosphates do reflect 100% of systemic diazinon dose on an almost equivalent molar basis and the oral studies just reflect the lower gut absorption of the pesticide. In the former case of oral diazinon being 100% bioavailable then the median, 95% and maximum systemic doses calculated above from sheep dipping studies should be increased (by 100/66) to 0.2mg, 1.48mg and 2.6 mg respectively. Interestingly, a previous HSL oral human volunteer study with chlorpyrifos, which is another diethoxy phosphoryl-aromatic ring structure OP, suggested approximately 90% of the oral dose were recovered as urinary dialkyl phosphates (Griffin, 1999), implying an almost equivalence between urinary metabolites and systemic dose.

*Estimation and investigation of exposure routes using biological monitoring data*

The human volunteer study can also be used to look at exposure in the field studies. The metabolite levels in urine samples collected in four field studies the day after exposure are summarized in table 6.2.1a below together with occupational hygiene measurements and estimates of the levels of skin contamination during the dipping. The table also includes our calculations of expected levels of metabolites from these field-observed levels of skin contamination based on data from the HSL volunteer study.

In the volunteer study all urine was collected at timed intervals for several days. The values used in the calculations below are for the samples collected the morning after the 8h exposure and are equivalent to the samples collected ‘pre-work next day’ in field studies.

**Table 6.2.1a**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>mean measured metabolite (sd) umol/mol</th>
<th>maximum measured metabolite umol/mol</th>
<th>Mean diazinon on skin Occ. Hyg. mg</th>
<th>maximum diazinon on skin Occ.Hyg. mg</th>
<th>calculated* metabolite from mean diazinon on skin umol/mol</th>
<th>calculated* metabolite from max diazinon on skin umol/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blatchford &amp; Davison 1991</td>
<td>7</td>
<td>23.9 (18.1)</td>
<td>59</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Niven et al 1993</td>
<td>35</td>
<td>25.3 (33)</td>
<td>154</td>
<td>0.19</td>
<td>0.72</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Niven et al 1994</td>
<td>18</td>
<td>40.4 (56.4)</td>
<td>227</td>
<td>0.6</td>
<td>6</td>
<td>0.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Sewell et al 1999</td>
<td>52</td>
<td>29.3 (32)</td>
<td>128</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

* calculated from a 100 mg dermal dose applied to 78cm² which produces 61.8 umol total ethyl phosphate metabolites/mol creatinine in ‘pre-work next day’ urine samples

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The observed levels of skin contamination in the Niven studies (Niven, 1993 and 1994) appears to account for less than 2% of the measured levels of metabolites in the same studies. The calculations above assume that diazinon in either concentrate or diluted dip would behave in the same way as pure diazinon applied to the arms of the volunteers. If diazinon in sheep dips were absorbed more efficiently e.g. due to the presence of penetration enhancers in the formulation or greater surface area of contact or higher skin temperature due to physical work, then more of the observed levels of metabolites could be explained. It seems unlikely that such an influence could explain the size of the discrepancy.

However, it seems more likely that there could be other sources of contamination not measured in the field studies. Foremost among these is likely to be contamination by concentrate as noted in the Niven (Niven, 1993) and Sewell (Sewell, 1999) studies. The Niven (Niven, 1993) study used a fluorescent marker in the diluted dip and for technical reasons, did not measure concentrate exposure at all. This study also noted that it may underestimate exposure to dilute dip because of interference from dirt and faeces. The second IOM study (Niven, 1994) using sampling suits and pads did not measure exposure to the hands or face, although the first study had shown this to be significant. Support for the involvement of dip concentrate comes from the last IOM study (Sewell, 1999) which, although no measurements were taken of skin contamination, did pay attention to concentrate handling events and found an association between measured urinary metabolite levels and the number of concentrate handling events. Thus the difference between urinary metabolite levels measured in the workers and the predictions from the noted levels of skin contaminated with dilute dip reflect the importance of handling dip concentrate in defining the total dose absorbed by the worker.

Another possible explanation may be ingestion, which is very difficult to assess in field studies. The volunteer studies using an approximate 1mg (0.011 mg/kg) oral dose showed urinary metabolite levels of 460 to 870 µmol/mol 2-3 hours after dosing, decreasing in ‘pre-shift next day’ samples (24h after oral dosing) to less than 30 µmol/mol. Ingestion of 1mg of concentrate (2-6 µl depending on diazinon concentrate strength) or dilute dip (2.5ml) at the beginning of dipping would give urinary metabolites similar to those found in the sheep dip field studies. It would seem unlikely that ingestion of 2.5ml of dip would go unnoticed but ingestion of 2-6 µl of concentrate may be possible, particularly if hand-mouth activity is considered in the context of sheep-dipping as a work activity. (This could involve simple wiping of the lips with contaminated hands and subsequent licking of the lips.) If ingestion was largely responsible and occurred more than one hour before the end of dipping then the ‘end of dipping’ urine sample would probably have higher metabolite levels than those collected ‘pre-shift next day’ due to the difference in toxicokinetics in oral and dermal exposure. Although this is found in a few of the samples collected in the IOM studies it cannot prove ingestion is an important route of exposure.

6.2.2 Using UK pesticides registration authorities approach for assessing exposure during dipping

The following sections describe the general approach in carrying out an exposure assessment that would be followed by those in UK authorities responsible for pesticide registration.
Description of the approach and derivation of values used in prediction of systemic dose

This approach uses values derived from occupational hygiene or experimental data to provide a value(s) for potential dermal exposure to the skin or clothing and potential inhalation exposure. These values are then used to estimate a systemic dose of a.i. during a particular work activity.

In the case of the skin exposure, penetration values as percentages of total skin dose are used to estimate how much active ingredient goes through clothing or skin. These penetration values may be gained from published data or by use of generic default values. The potential skin exposures are expressed as volume (mls) of formulation, in this way they can be used generically for any a.i. in a range of formulations providing the concentration of the a.i. in the formulation is known. The derivation of values for potential dermal exposure to various parts of the body are described in this section and summarised in table 6.2.2a. The values used for skin penetration are shown in table 6.2.2b. In the case of inhalation exposure it is assumed that all of the a.i. potentially available (i.e. the estimated or measured inhalation exposure) is absorbed and adds to the total systemic dose. The values for inhalation are discussed below. This approach does not account for any exposure via ingestion.

In this approach applied to sheep dipping the contribution of exposure to the systemic dose during concentrate handling, usually during ‘mixing and loading’, and the contribution during the activity, in this case dipping with the diluted a.i., are considered separately. This is also discussed later in this section.

Potential whole body dermal exposure

We consulted with HSE’s Biocides and Pesticides Assessment Unit (BPAU) who provided us with the data that they would use if they were to do a risk estimation for registration purposes for sheep dip. This data was derived from the Niven report (Niven, 1994) and can be used to estimate exposure during dipping with any active ingredient. As described earlier this study collected dermal exposure data using whole-suit and patches worn both outside and underneath protective clothing. BPAU used the ‘whole suit worn outside protective clothing’ and ‘whole suit worn beneath the protective clothing’ data to provide median and 95th percentile values for potential dermal exposure to the body for workers wearing no PPE or wearing appropriate PPE. The derived values are shown in table 6.2.2a.

Potential exposure via the hands

Gloves were not used as sampling devices in the Niven 1994 study (Niven, 1994) and therefore hand exposure is not accounted for in the derived figures for whole body dermal exposure above. However in the study by Niven et al 1993, (Niven, 1993) an early version of the Health and Safety Laboratory’s fluorescence monitoring technique was used to assess skin exposure. The fluorescence technique estimated that 0.7mg of diazinon was retained on the skin of sheep dippers, the concentrations used meant that the dippers retained the equivalent of up to 8ml of diluted dip on their skin per sheep dipping session. The fluorescence monitoring part of the Niven 1993 study was reported separately (Roff 1993). Further work has subsequently been carried out on this technique and in a personal communication the author
estimated that this result could vary by as much as a factor of 3, ie a worst case could be 24ml of the dilute formulation. Roff in 1993 found that 75% of the total contamination was on the hands i.e. 18ml formulation could be used for exposure prediction purposes. Exposure to the hands is a particularly important route of exposure route due to concentrate handling. Unfortunately the fluorescence method was not able to distinguish which contamination on the hands was due to concentrate handling and that which was due to deposition from exposure to dilute formulation.

Where no data is available for hand contamination Registration Authorities will tend to use a default known as the ‘6ml spill’. This has been a widely accepted default value for around the last decade, originally derived by the US EPA.

**Potential exposure via the feet and face**

The skin on the face is likely to get contaminated during dipping. Contaminant could be absorbed by the skin or be ingested. The skin on the feet can also be an important route of contamination due to ‘reservoirs’ of contaminant forming in contaminated footwear and socks/skin possibly being effectively occluded in impervious wellington boots. It is unlikely that, unless contamination is gross, socks will be changed and feet decontaminated with the frequency that may be employed for hands and gloves. However we have no data on exposure via these routes and it is not considered in the prediction.

**Inhalation exposure**

Niven (Niven, 1993) measured exposure via the inhalation route for six workers during dipping. They found exposure to be below the analytical detection limit for the volume of sample and time of sampling (i.e. for 4hr <0.01mg.m⁻³) and stated that if it were assumed that the exposure of operators was at the level of analytical detection, then the maximum 8hr time weighted average (TWA) exposure concentration would be approximately 0.01mg.m⁻³. This can be compared with the current inhalation-based for diazinon of 0.1mg.m⁻³ (Health & Safety Executive, 2000).

**Exposure via ingestion**

The ingestion route could contribute significantly to the dose particularly if any concentrate splashes got directly into the mouth or hand-mouth activity after concentrate handling. This is not taken into account in this approach.

**Exposure to concentrate**

In order to both assess exposure or to implement appropriate control measures it is important to know the contribution of concentrate and dilute dip to the systemic dose. The data from the 1994 Niven report (Niven, 1994) on whole body dermal exposure data represents

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5 HSE could find no records on the history of the current OES for diazinon, suggesting that the its historical basis lies with the similar ACGIH TLV value for diazinon. The ACGIH TLV committee is currently reviewing its exposure limits for organophosphates (communication-M. Meldrum, HSE.)
exposure to both concentrate and dilute dip. However no hand exposure is included and as this is the most likely route of exposure during concentrate handling i.e. mixing & loading we decided to add this to our prediction. We have no data for mixing and loading of concentrate during dipping so have used a nominal value for mixing and loading from POEM. We have reservations about using this because the data is derived from laboratory experiments of pouring concentrate into a vessel like a tractor sprayer. This is a different exposure scenario to that of pouring concentrate into a dip and mostly measures exposure from splashes which is only one of the contributory routes. The systemic doses derived from using a nominal value for mixing and loading are shown in tables 6.2.2a and 6.2.2 b.
Table 6.2.2a  Summary Of Values For Prediction Of  Systemic Exposure During Dipping

<table>
<thead>
<tr>
<th>Activity &amp; Route</th>
<th>Value used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mixing &amp; Loading</strong></td>
<td></td>
</tr>
<tr>
<td>whole body</td>
<td>nil</td>
</tr>
<tr>
<td>hands</td>
<td>0.2ml concentrate per operation (from POEM)</td>
</tr>
<tr>
<td>inhalation</td>
<td>nil</td>
</tr>
<tr>
<td><strong>Dipping</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Potential dermal exposure to whole body **no PPE** | i. median; 0.6ml/min formulation/4hr dipping  
ii. 95th percentile; 2.91ml/min formulation/4hr dipping  
(derived from Niven et al 1994) |
| Potential dermal exposure to whole body **with PPE** | i. median; 0.005ml/min formulation/4hr dipping  
ii. 95th percentile; 0.043ml/min formulation/4hr dipping  
(derived from Niven et al 1994) |
| hands during dipping | i. 18ml/4hr dipping (from Roff et al 1993) |
| inhalation       | nil        |

Table 6.2.2b Skin and clothing penetration values used

<table>
<thead>
<tr>
<th>barrier</th>
<th>penetration value</th>
</tr>
</thead>
<tbody>
<tr>
<td>clothing</td>
<td>5% (from POEM)</td>
</tr>
<tr>
<td>skin - diazinon</td>
<td>4% (from Australian National Registration Authority Review of Diazinon 2000)</td>
</tr>
<tr>
<td>skin - synthetic pyrethroids</td>
<td>3% (from Prinsen &amp; Van Sittert, (Prinsen, 1979))</td>
</tr>
</tbody>
</table>

**Prediction of systemic exposure to dips containing diazinon and SPs use the derived values.**

The values described in tables 6.2.2a and 6.2.2b were used to predict systemic doses during likely dipping scenarios using OP and synthetic pyrethroid containing products. The derived doses are shown in tables 6.2.2c-h and examples of the calculations are shown in Appendix E.

The scenarios for which doses were calculated are as follows:

1. dipping using the manufacturer’s recommended dip strength, with and without concentrate handling; wearing PPE during dipping and gloves during concentrate handling

2. dipping using the manufacturer’s recommended dip strength, with and without concentrate handling; wearing **no** PPE during dipping but gloves during concentrate handling.
3. double strength dip; dipping using twice the manufacturer’s recommended dip strength, with concentrate handling; wearing no PPE during dipping but gloves during concentrate handling

4. dipping using manufacturers recommended dip strength, with concentrate handling; wearing no PPE during dipping and no gloves during concentrate handling i.e. a worst case scenario

The resulting values using median and 95th percentile values for body exposure are shown in table 6.2.2c for diazinon and table 6.2.2d for cypermethrin. For propetamphos, flumethrin and chlorfenvinfos, (see tables 6.2.2e, f, g) only the 95th percentile values were used because as can be seen in tables 6.2.2c and 6.2.2d, using the median and 95th percentile gives similar values.

Doses for the worst case scenario (as defined in the fourth exposure scenario above) for all active ingredients are summarised in table 6.2.2h
### Table 6.2.2c Predicted systemic dose during dipping with diazinon

<table>
<thead>
<tr>
<th></th>
<th>total systemic dose (mg)</th>
<th>dip strength (%)</th>
<th>concentrate strength (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>median</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPE</td>
<td>1.73</td>
<td>0.04</td>
<td>60</td>
</tr>
<tr>
<td>noPPE</td>
<td>1.84</td>
<td>0.04</td>
<td>60</td>
</tr>
<tr>
<td>PPE</td>
<td>0.29</td>
<td>0.04</td>
<td>no conc handling</td>
</tr>
<tr>
<td>noPPE</td>
<td>0.4</td>
<td>0.04</td>
<td>no conc handling</td>
</tr>
<tr>
<td><strong>95%ile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPE</td>
<td>1.74</td>
<td>0.04</td>
<td>60</td>
</tr>
<tr>
<td>noPPE</td>
<td>2.29</td>
<td>0.04</td>
<td>60</td>
</tr>
<tr>
<td>PPE</td>
<td>0.3</td>
<td>0.04</td>
<td>no conc handling</td>
</tr>
<tr>
<td>noPPE</td>
<td>0.85</td>
<td>0.04</td>
<td>no conc handling</td>
</tr>
<tr>
<td><strong>twice strength dip &amp; 95%ile</strong></td>
<td>3.56</td>
<td>0.1</td>
<td>60</td>
</tr>
</tbody>
</table>

key;  PPE = wearing PPE for dipping, plus gloves for concentrate handling
no PPE = wearing no PPE for dipping but gloves for concentrate handling
twice strength dip & 95%ile = wearing PPE for dipping, plus gloves for concentrate handling

Diazinon dip notes:
i. median/95th percentile indicates value used for dermal exposure to body
ii. 18ml used as value for in-use dip on hands (Roff 1993)
iii. 0.2ml/operation (nominal value from POEM) used for hand contamination during mixing & loading, assume 3 events - protective gloves worn with 90% protection
iv. 4% skin penetration
v. twice strength dip & 95precentile; dip at twice recommended strength, 95th percentile whole body contamination

### Table 6.2.2d Predicted Systemic Dose During Dipping with cypermethrin

<table>
<thead>
<tr>
<th></th>
<th>total systemic dose (mg)</th>
<th>dip strength (%)</th>
<th>concentrate strength (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>median</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPE</td>
<td>0.29</td>
<td>0.02</td>
<td>10</td>
</tr>
<tr>
<td>noPPE</td>
<td>0.33</td>
<td>0.02</td>
<td>10</td>
</tr>
<tr>
<td>PPE</td>
<td>0.11</td>
<td>0.02</td>
<td>no conc handling</td>
</tr>
<tr>
<td>noPPE</td>
<td>0.15</td>
<td>0.02</td>
<td>no conc handling</td>
</tr>
<tr>
<td><strong>95%ile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPE</td>
<td>0.29</td>
<td>0.02</td>
<td>10</td>
</tr>
<tr>
<td>noPPE</td>
<td>0.5</td>
<td>0.02</td>
<td>10</td>
</tr>
<tr>
<td>PPE</td>
<td>0.11</td>
<td>0.02</td>
<td>no conc handling</td>
</tr>
<tr>
<td>noPPE</td>
<td>0.32</td>
<td>0.02</td>
<td>no conc handling</td>
</tr>
<tr>
<td><strong>twice strength dip &amp; 95%ile</strong></td>
<td>0.97</td>
<td>0.05</td>
<td>10</td>
</tr>
</tbody>
</table>

key;  PPE = wearing PPE for dipping, plus gloves for concentrate handling
no PPE = wearing no PPE for dipping but gloves for concentrate handling
twice strength dip & 95%ile = wearing no PPE for dipping, plus gloves for concentrate handling
Cypermethrin Dip

notes;

i. median/95th %ile indicates value used for dermal exposure to body,
ii. 18ml used as value for in-use dip on hands (Roff 1993),
iii. 0.2ml/operation (nominal value from POEM) used for hand contamination with
    concentrate during mixing & loading, assume 3 events - protective gloves worn with
    90% protection
iv. 3% skin penetration
v. twicestrength dip & 95%ile; dip at twice recommended strength, 95th % ile
    whole body contamination

Table 6.2.2e dipping with propetamphos during dipping as recommended by label i.e.
correct strength dip, wearing PPE and wearing gloves concentrate handling

<table>
<thead>
<tr>
<th></th>
<th>total systemic dose (mg/4hr dip)</th>
<th>dip strength (%)</th>
<th>concentrate strength (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%ile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPE</td>
<td>1.2</td>
<td>0.032</td>
<td>40</td>
</tr>
<tr>
<td>PPE</td>
<td>0.24</td>
<td>0.032</td>
<td>no conc handling</td>
</tr>
</tbody>
</table>

Table 6.2.2f dipping with flumethrin during dipping as recommended by label i.e.
correct strength dip, wearing PPE and wearing gloves concentrate handling

<table>
<thead>
<tr>
<th></th>
<th>total systemic dose (mg/4hr dip)</th>
<th>dip strength (%)</th>
<th>concentrate strength (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%ile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPE</td>
<td>0.15</td>
<td>0.007</td>
<td>6</td>
</tr>
<tr>
<td>PPE</td>
<td>0.04</td>
<td>0.007</td>
<td>no conc handling</td>
</tr>
</tbody>
</table>

Table 6.2.2g dipping with chlorfenvinfos during dipping as recommended by label i.e.
correct strength dip, wearing PPE and wearing gloves concentrate handling

<table>
<thead>
<tr>
<th></th>
<th>total systemic dose (mg/4hr dip)</th>
<th>dip strength (%)</th>
<th>conc strength (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%ile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPE</td>
<td>0.6</td>
<td>0.050</td>
<td>10</td>
</tr>
<tr>
<td>PPE</td>
<td>0.37</td>
<td>0.050</td>
<td>no conc handling</td>
</tr>
</tbody>
</table>
Table 6.2.2h - Worst case; dipping wearing no PPE for dipping and no gloves for concentrate handling, uses the 95th percentile values for body exposure.

<table>
<thead>
<tr>
<th></th>
<th>total systemic dose (mg/4hr dip)</th>
<th>dip strength (%)</th>
<th>concentrate strength (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazinon</td>
<td>15.3</td>
<td>0.04</td>
<td>60</td>
</tr>
<tr>
<td>Cypermethrin</td>
<td>2.1</td>
<td>0.02</td>
<td>10</td>
</tr>
<tr>
<td>Propetamphos</td>
<td>10.3</td>
<td>0.032</td>
<td>40</td>
</tr>
<tr>
<td>Flumethrin</td>
<td>1.2</td>
<td>0.007</td>
<td>6</td>
</tr>
<tr>
<td>Chlorfenvinphos</td>
<td>3.5</td>
<td>0.050</td>
<td>10</td>
</tr>
</tbody>
</table>

6.2.3 Exposure assessment for pour-on treatments

Published data on pour-on treatments by Stewart (Stewart 1999), was noted in section 6.1.2. Unfortunately even this study cannot be readily used as the basis for dose prediction using pour-ons as it only contains very limited data and the concentration of a.i. in the products used is not given. We considered doing a worst-case estimate based on an operator receiving a whole dose i.e. one sheep’s worth to the hands of the most concentrated product on the market (6% cyromazine, other a.i. at approximately 1%). On further consideration we concluded that there were so many other variables that would compound any estimate (e.g. number of sheep treated, contribution from rubbing against treated sheep/fences) that any prediction would be given more credence than it deserved. Consultation with BPAU (HSE) and PSD confirmed that field study exposure data applicable for ‘pour-ons’ was not available. The National Registration Authority’s review of diazinon (National Registration Authority, 2000) also highlighted the lack of measurement data and problems with using POEM to estimate applicator exposure for this particular work activity.

6.2.4 Exposure assessment for Injectable treatments

There are three injectable products currently listed in the Veterinary Products Compendium 2000-2001. Two of the products recommend that the maximum size syringe used is 2.5ml, used to inject the product subcutaneously in the neck. The worst case would be to self-inject with the whole syringe full i.e. 2.5ml of a 1% solution (i.e. 25 mg) of moxidectin, doramectin or ivermectin.

6.2.5 Summary of estimated systemic doses using the registration authority approach and comparison with the biological monitoring approach

It is interesting to note that the estimate of exposure using the registration authority approach is largely driven from the estimate of concentrate handling and the protection afforded by wearing gloves. For the median estimation, the registration approach over-estimates the likely dose when compared with the dose calculation from biological monitoring data obtained in observed dipping studies. However, there is a considerable degree of agreement between the
two approaches when estimating the 95th percentile. The registration approval approach considerably over-estimates exposure as a worst-case scenario compared to the biological monitoring data. This over-estimation in worst case situations was discussed with staff at BPAU and PSD, who acknowledged that such over-estimation is not unknown using such approaches to exposure assessment.

<table>
<thead>
<tr>
<th></th>
<th>Systemic body dose using biological monitoring approach (mg)</th>
<th>Systemic body dose using occupational hygiene approach* (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>95th % ile</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>worst case</td>
<td>1.7</td>
</tr>
<tr>
<td>Diazinon Dip</td>
<td>median</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>95th % ile</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>worst case</td>
<td>-</td>
</tr>
<tr>
<td>Cypermethrin Dip</td>
<td>median</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>95th % ile</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>worst case</td>
<td>-</td>
</tr>
<tr>
<td>Flumethrin dip</td>
<td>95th % ile</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>worst case</td>
<td>-</td>
</tr>
<tr>
<td>Propetamphos</td>
<td>95th % ile</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>worst case</td>
<td>-</td>
</tr>
<tr>
<td>Chlorfenvinphos</td>
<td>95th % ile</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>worst case</td>
<td>-</td>
</tr>
<tr>
<td>Ivermectin, doramectin &amp;</td>
<td>worst case</td>
<td>-</td>
</tr>
<tr>
<td>moxidectin injectable</td>
<td>worst case</td>
<td>-</td>
</tr>
<tr>
<td>Doramectin injectable</td>
<td>worst case</td>
<td>-</td>
</tr>
</tbody>
</table>

* median and 95th percentile values from scenario of handling concentrate and wearing PPE (for dipping) and gloves for conc. handling). Worst case is no PPE and concentrate handling wearing no gloves
# reflects systemic doses adjusted by factor discussed in 6.2.1.
7. RISK EVALUATIONS

7.1 Risk evaluations for a.i. used in dipping.

We have attempted to pull together diagrammatically data on published LD$_{50}$, NOAEL, exposure predictions (median, 95th percentile) and other dose data related to human ill-health or occupational exposures. These diagrams (figures 7.1a-d) show an AOEL dose, applying an overall 100-fold uncertainty or assessment factor derived from inter- and intra-species uncertainty factors of 10-fold to appropriate animal experimental data.

In table 7.1a we have calculated MOE (TER) ratios using the 95th percentile exposure predictions for a number of scenarios where appropriate PPE is or is not used and handling of the concentrate chemical is or is not part of the worker exposure. For diazinon we can also use the calculations from the biological monitoring approach which uses measurement data from normal dipping activity.

Table 7.1a Margins of exposure (MOE) or Toxicity-exposure ratios (TER) for active ingredients used for dipping. 95th %tiles from exposure assessment predictions or biological monitoring data* have been used for the calculations.

<table>
<thead>
<tr>
<th>a.i</th>
<th>PPE &amp; conc. handling</th>
<th>PPE &amp; no conc. handling</th>
<th>no PPE &amp; conc. handling</th>
<th>no PPE &amp; no conc. handling</th>
<th>Biolog. mon. approach</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MOE (TER) ratios</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazinon</td>
<td>100</td>
<td>581</td>
<td>11 &amp; 76*</td>
<td>207</td>
<td>118*</td>
</tr>
<tr>
<td>Propetamphos</td>
<td>5</td>
<td>23</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chlorfenvinphos</td>
<td>18</td>
<td>28</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cypermethrin (HC)</td>
<td>549</td>
<td>1,433</td>
<td>315</td>
<td>492</td>
<td>-</td>
</tr>
<tr>
<td>Flumethrin</td>
<td>327</td>
<td>1,226</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Using criteria that would likely be applied in the context of pesticide approval (plant protection product) the data presented suggest that neither propetamphos or chlorfenvinphos would meet approval criteria (MOE<100; exposure >AOEL) for sheep dipping, even without any handling of the OP concentrate. Diazinon would meet approval criteria; both the exposure prediction and the biological monitoring data from field studies suggesting that a MOE of 100 could be achieved even with concentrate handling as long as PPE was worn whilst dipping and appropriate gloves during concentrate handling. The biological monitoring approach, which uses data from monitored sheep dipping activities involving concentrate handling, suggests that the worst case measured indicates an MOE (TER) of 76 while 95% of all monitored sheep-dippers achieved an MOE (TER) of 118 or greater.

We note the relative closeness between the defined NOAEL (2.5mg/kg) for diazinon and data which suggests clinical ill-health at systemic doses of 15 mg/kg. Removal of workers from any handling of diazinon concentrate (closed concentrate systems) gives MOE (TER) greater than 200 whether appropriate PPE or not was worn. We feel that given that an MOE of 200
gives additional safety to cover the apparent closeness of NOAEL and frank human toxicity
this strengthens the decision to remove concentrate handling. However from this analysis it
seems appropriate that diazinon is registered for use as sheep-dip, whereas propetamphos and
chlorfenvinphos are no longer approved for this purpose.

Both SPs investigated meet approval criteria whether or not concentrate handling is involved
in the worker’s activities.

We would highlight the agreement between the exposure estimation and biological monitoring
approaches for the 95th percentile data when investigating diazinon. The worst case exposure
predictions, where it is assumed that gloves are not worn when handling concentrate, gives a
significantly higher dose prediction than the worst case derived from field study biological
monitoring data. This needs some further investigation as to whether the model is over
predicting the dose absorbed through hand contamination with concentrate or whether gloves
were worn in the monitored field studies. The data for OPs strengthen the opinion that
concentrate handling is the major element in defining exposure.

We would also highlight that these analyses are based on farmers or their workers carrying
out dipping at most 2-3 times a year. They are not appropriate for the case of dipping
contractors, where different NOAELs may be necessary to reflect the more chronic exposure
and there is currently a paucity of exposure data (or biological monitoring data) to make
adequate worker exposure assessment.
Dose-response relationship for diazinon

Systemic dose mg/kg

AOEL

Likely lethal
Serious clinical
Other occ. stud.
Human NOAEL
Animal NOAEL
Median Dipping
95% Dipping
Worst case dip

0.0001
0.001
0.01
0.1
1
10
100
1000

0.01
0.1
1
10
100
1000

6a* 6b* 6c*
7,8 9 10
7 8 3
31 14 15 16 4
17 18 9 10 2
Figure 7.1b

Dose-response relationship for cypermethrin/high cis cypermethrin/flumethrin

- LD50 oral
- Likely lethal
- Serious clinical
- Human NOAEL
- Animal NOAEL
- Median dipping
- 95% dipping
- Worst case dip

10⁻³
10⁻²
10⁻¹
10⁰
10¹
10²
10³

Systemic dose mg/kg

AOEL

AOEL

11
12
13
10
9
8
7
6
5
4
3
2
1

high cis cypermethrin

Flumethrin
Figure 7.1c

Dose-response relationship for chlorfenvinphos
Figure 7.1d

Dose-response relationship for propetamphos

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Explanatory notes for figure 7.1a

1. Human exposure (Rao, 1965) by subcutaneous injection of approximately 14mg/kg diazinon. Whole blood ChE 14% of normal on admission - vomiting, muscular twitching, pyrexia, increased pulse, pupils equal and normal. No salivation or sweating. Treated with atropine. ChE recovery in 20 days.

2. Values quoted from internal EPA review document.

3. Calculations based on HSL human volunteer study (2000) and urinary biological monitoring data from IOM field studies.


5. Human exposure (Halle, 1987) by application to genitalia of approximately 15 mg/kg. Comatose on admission to hospital, excessive salivation, pupils unequal and small, extremities flaccid and without tendon reflexes. High blood pressure and shallow respiration. Subjects 30 minute after exposure was feeling sick with blurred vision.

6a Human overdose (Klemmer, 1978) oral - within 30 minutes semi-stuporous profuse diaphoresis, fixed pinpoint pupils muscle weakness, twitching.

6b Human overdose (Klemmer, 1978) oral - within 30 minutes semi-stuporous profuse diaphoresis, fixed pinpoint pupils muscle weakness, twitching and jerking of all extremities.

6c Human overdose (Klemmer, 1978) oral 15gm - Immediate vomiting, developing diaphoresis, progressive muscle weakness, abdominal cramps and diarrhea.

7. BPAU Exposure assessment assuming no PPE, using 0.04% dilute dip and handling 60% concentrate

8. BPAU Exposure assessment assuming appropriate PPE, using 0.04% dilute dip and handling 60% concentrate

9. BPAU Exposure assessment assuming no PPE and using 0.04% dilute dip, but with no concentrate handling.

10. BPAU Exposure assessment assuming appropriate PPE and using 0.04% dilute dip, but with no concentrate handling.


12. Noted in US EPA risk assessment documentation for diazinon. 0.25 mg/kg/day oral (short-term, pChE endpoint)
13. 2.5 mg/kg single dose study using RBC AChE or brain AChE as endpoint (Chow, 1994). Acute neurotoxicity studies (MRID 43132201 & 44219301 in US EPA documentation) in rats noted as relevant study for defining acute NOAEL.


15. Based on HSE's OES for inhalation of diazinon, assuming 10,000 liters respired volume & 100% uptake. The background data for this limit is not obvious and the adverse effect not defined, whether inhibition of pChE or erythrocyte AChE


17. Novartis study submitted to US EPA (2000) describing homeowner volunteers using lawn products containing diazinon- biological monitoring data used to calculate systemic dose

**Explanatory notes for figure 7.1b**

1. BPAU approach no PPE and including concentrate handling of high cis cypermethrin
2. BPAU approach with PPE and including concentrate handling of high cis cypermethrin
3. BPAU approach with no PPE and no concentrate handling of high cis cypermethrin
4. BPAU approach with PPE, but no concentrate handling of high cis cypermethrin
5. BPAU worst case for high cis cypermethrin
6. Animal NOAEL taken from WHO task group documentation on cypermethrin -chronic study 1989
7. Animal NOAEL taken from WHO task group documentation on alpha-cypermethrin chronic- 13 week dog oral study 1992
9. Animal NOAEL quoted for deltamethrin
10. BPAU approach with PPE and concentrate handling for flumethrin
11. BPAU approach with PPE, no concentrate handling. flumethrin
12. BPAU worst case scenario for flumethrin
13. Oral ingestion suicide attempt, note SP in this case is deltamethrin

**Explanatory notes for figure 7.1c**

1. LD$_{50}$ oral dog noted in PSD or NRA documentation
2. LD$_{50}$ oral/dermal rabbit noted in PSD or NRA documentation
3. LD$_{50}$ oral mouse noted in PSD or NRA documentation
4. LD$_{50}$ i.v. dog noted in PSD or NRA documentation
5. LD$_{50}$ oral rat noted in PSD or NRA documentation
6. LD$_{50}$ i.v rat noted in PSD or NRA documentation

7. Calculated from human volunteer dermal studies (Hunter, 1969) assuming that external dose not recovered from skin & skin-cover relates to absorbed dose. Used 80% emulsifiable concentrate & 24% emulsifiable concentrate & a.i. in trimethyl benzenes applied to skin areas from 40-800 cm$^2$ for around 4 hours. No inhibition in erythrocyte AChE and plasma ChE greater than 20%.

8. Calculated from human dermal studies (Hunter, 1969) assuming that external dose not recovered from skin & skin-cover relates to absorbed dose. Used 80% emulsifiable concentrate & 24% emulsifiable concentrate & a.i. in trimethyl benzenes applied to skin areas from 40-800 cm$^2$ for around 4 hours. No inhibition in erythrocyte AChE but plasma ChE depression greater than 20%, 24 hours post exposure.

9. Calculated from human dermal study assuming that external dose not recovered from skin & skin-cover relates to absorbed dose. (Brown V. 1966). Single volunteer applied occluded to forearm for 6 hours. No inhibition in erythrocyte AChE or clinical signs but plasma ChE inhibited 45% at 96 hours.

10. Single human volunteer, oral single dose study at 1mg/kg bw (Brown V. 1966). Note 94% of an oral radiolabelled dose had been reported to be excreted in 27 hours after dosing (Hutson D 1969). Plasma ChE inhibited >50%; erythrocyte AChE inhibited >40% 6 hours after dosing.

11. (a) 4 week dog oral study- 3.9 mg/kg/day, (b) 2 & 4 week mice oral study- 2mg/kg/day, (c) 4 week rat oral study- 0.15 mg/kg/day. Taken from NRA review of chlorfenvinphos using erythrocyte AChE inhibition. Species differences in metabolism may account for species sensitivity. Approximately 90% of administered oral dose excreted in urine in all species.

12. BPAU approach with PPE and concentrate handling

13. BPAU approach with PPE and no concentrate handling
14. BPAU approach worst case scenario.

**Explanatory notes for figure 7.1d**

1. Acute oral study in rat submitted to USA EPA for review (MRID 41607417). Doses 116.1 mg/kg males, 94.4 mg/kg females

2. Acute dermal study in rabbits submitted to US EPA review (MRID 41607418). Dose 486 mg/kg

3. Acute 14 day inhalation study in rat (MRID 41529301 261 mg/kg males, 120 mg/kg females submitted to US EPA review

4. BPAU approach with PPE and concentrate handling

5. BPAU approach with PPE but no concentrate handling

6. Worst case scenario

7. Animal NOAEL taken from 4 week time point in a 6 month repeat oral study in dogs

**7.2 Risk evaluations for pour-ons.**

Our opinion is that there is not enough data to undertake an exposure prediction and precludes doing a risk evaluation, even though NOAELs were established. We could find no biological monitoring data that would allow a similar approach to that undertaken for diazinon.

**7.3 Risk evaluations for injectables**

Occupational hygiene assessment was that, unless accidental self-injection was involved, exposure to these chemicals would be so low as to make a quantifiable exposure assessment difficult. Figure 7.3a represents the available data. Reports of self-injection appear to suggest it is a very rare incidence. In the worst case of self-injection with the full syringe of chemical, the systemic dose would be around the defined NOAEL levels and also the therapeutic dose of ivermectin used worldwide to treat onchocerciasis in humans. Therefore we consider that the avermectin injectables meet safety criteria, as long as syringe sizes for multiple animal dosing are not substantially increased and appropriate needle guard and syringe assemblies continue to be used.
Explanatory notes for figure 7.3a

1. Worst case for worker assuming self-injection of 25mg of a.i.

2. Oral administration LD₅₀ of doramectin 100mg/kg male rat & 500 mg/kg male mouse.

3. NOAEL for moxidectin from 90 day study in dogs (JECFA 45th committee).

4. NOAEL of 0.1mg/kg for ivermectin, mouse teratogenicity study.

5. Oral doses of up to 0.2mg/kg ivermectin given to humans as antiparasite treatment.

6. NOAEL for doramectin oral 3 month dog study

7. Doramectin intramuscular dose of 7.5mg/kg caused ataxia and depression noted in pigs.

8. Doramectin intramuscular no systemic toxicity or at injection site noted in sheep.
9. Doramectin oral repeated dosing in dogs (more sensitive species) of 2mg/kg - anorexia, tremor and ataxia.

10. oral moxidectin LD\textsubscript{50} in mice/rats 200mg/kg

11. acute oral ivermectin dose (24 mg/kg) in rhesus monkeys caused mydiasis and sedation

12. calculation for self injection of moxidectin submitted to VMD

8. INCIDENT OF SHORT-TERM ILL-HEALTH ASSOCIATED WITH OP DIPPING

A continuing level of concern about ill-health caused by sheep ectoparasite treatment has been raised by an number of individuals and pressure groups. Concerns centre largely on the possibility of the OPs used in sheep dipping causing both short-term and chronic ill-health. This project focuses on acute ill-health. A number of investigations have looked at chronic ill-health (COT, 1999) or the clinical aspects of long-term low-dose exposure (Royal College of Physicians and Royal College of Psychiatrists, 1998). ‘Sheep dipper flu’ has been referred to by many sources as a common, short-term consequence of the particular work activity, but what ‘sheep dippers flu’ is and whether caused as an acute toxic effect of OPs or other complex pathological and physiological mechanisms such as reaction to endotoxin exposure and physical stress remains unanswered. Research into the incidence and cause of ‘dippers flu’ was a recommendation for further research from the report on organophosphates by the Committee of Toxicity (COT, 1999).

There are a number of approaches that we can carry out on available data in investigating the relationship between exposure to OP sheep dips and short-term ill-health effects;

1. Analysis of the data collected from the reporting system used for ill-health from exposure to veterinary medicines,

2. Investigation of the data presented in the risk evaluation section of this report (section 7) on the likelihood of exposure(s) to OPs during sheep dipping to give systemic doses above the NOAELs and towards doses associated with clinical effects.

3. Analysis and comparison of any biological monitoring (urinary analytes) or biological effect monitoring (blood cholinesterase measurements) data on sheep dippers and other occupational cohorts where OP exposure is found.

8.1 Reporting schemes for ill-health from OPs

OPs are classified as veterinary medicines when used in sheep dipping for the purpose of ectoparasitic control. Incidents involving peoples’ health as a result of exposure involving veterinary medicines should be reported to the Veterinary Medicines Directorate (VMD)
who have a Suspect Adverse Reactions Surveillance Scheme (SARSS) dealing with such problems. Essentially in this context SARSS is a pharmacovigilance scheme with similarities to that used to identify adverse reactions to human clinical drugs. However SARSS attempts to collect information on adverse reactions in not only the treated animal species, but also those applying the treatment e.g. farmers, vets etc. A different scheme run by HSE (Pesticide Incidents Appraisal Panel -PIAP) deals with ill-health problems from OPs defined as pesticides. PIAP is a post-approval monitoring scheme for pesticides, and works by drawing together reports on incidents investigated by HSE and local authorities in order to detect unforeseen toxic effects or exposure routes. Its conclusions are fed back into the approval process so that conditions of approval can be amended if necessary. Incidents are not reported directly to PIAP but are referred to it by the investigating authority. Therefore an adverse reaction to some OPs and SPs would follow different reporting and investigative routes depending on the usage of the OP or SP.

HSE guidance informs that where people have been affected by exposure to veterinary medicines, they should initially seek medical advice, taking the product label or data sheet with them to the doctor or hospital. Affected persons are advised to then make a report of the incident and to contact the relevant authority with that report. The current reporting form MLA 252A is available from the VMD, HSE offices, veterinary practices, veterinary investigation centres and animal health offices. In addition all licence holders for veterinary products are required to maintain and make available to the VMD registers of any adverse reactions involving their products. In practice, suspect adverse reaction (SAR) reports received between 1985 and 1999 were from members of the public (6%), farmers (16%), doctors (7%), veterinary surgeons (6%), via the appropriate marketing authorisation/licence holder of the product involved (52%), the HSE and the National Poisons Information Service (NPIS)(6%). A small number of reports (7%) were also received from other bodies such as pharmacists, agricultural merchants and trading standards officers.

An Appraisal Panel for Human Suspected Adverse Reactions was set up by the VPC in 1991 to consider such adverse reports gathered by VMD. The Panel members come from various relevant sectors including medicine (human and veterinary), epidemiology, toxicology and occupational health and safety. Specialists from the Department of Health, the VMD and the HSE give support to Panel members in assessing cases and reaching decisions. The terms of reference of the Appraisal Panel are to evaluate all suspected adverse reaction reports, identify any trends of emergent problems with veterinary medicinal products in humans, to generate hypotheses as to the possible cause of these trends and monitor the consequences of recommendations for change in working practices or use. The Appraisal panel reports its findings to the VPC and produces an annual report.

Injuries caused by chemicals at work, such as acute poisonings, scalds and gassings are reportable under HSE’s Reporting of Injuries, Diseases and Dangerous Occurrences Regulations (RIDDOR) as industrial injuries. Employers of affected persons and self-employed people are duty-bound to report acute illnesses caused by exposure to organophosphorus substances under the RIDDOR.
A number of pamphlets have been produced that publicise the SARSS scheme, RIDDOR or PIAP.

1. Sheep dipping AS29 rev2 1998, HSE- issued free to all farms and gives contact details for SARSS.

2. Reporting of Incidents of Exposure to Pesticides and Veterinary Medicines INDG141 rev1 1999, HSE- free publication attempts to explain differences between pesticides & veterinary medicines and to whom should adverse reactions be reported.

3. Veterinary Medicines. Safe use by farmers and other animal handlers AS31 1998 HSE- free leaflet on farmers’ duties under COSHH refering to RIDDOR and SARSS.

4. Agriculture: Your Health Carry Card IAC(L) 102 1998, HSE- issued to workers in the agriculture sector with advice to take the card with them to GP or hospital if necessary. Sheep dip is specifically mentioned.

5. Farmwise. Your Essential Guide to Health & Safety in Agriculture MISC 165 1999, HSE.- free publication, RIDDOR is briefly mentioned but not SARSS, suggesting using form F2508A for notification of symptoms to HSE.

6. Sheep Scab. A Farmers Guide 1999. MAFF- free publication that stipulates adverse reactions must be reported to SARSS

7. Use Sheep dips Carefully! 1993. MAFF/VMD - free publication that was distributed to all sheep farmers


8.2 Limitations of the ill-health reporting schemes

The COT report on OPs (COT, 1999) noted the minimal data on symptoms and signs collected in the PIAP scheme. This report has not reviewed the value of PIAP in the investigation of OP exposure and acute ill-health.

From 1991 to 1996 inclusive, all human SARs associated with OP sheep dips were assigned a category (acute or chronic reaction) and a categorical conclusion depending on the conclusiveness of evidence linking the given symptoms to the known effects of the active ingredient to which the person(s) was/were exposed. The appraisal panel bases the assessment of each case along a similar procedure to that used by the PIAP. In 1993 the Panel made some changes to the definition of the categories used for classification. Following a review of procedures (Lawson, 1996), the appraisal panel no longer classifies individual cases according to
causation. Also their reports suggest that they focus on different product groups each year. For example, in 1991/1992, the Panel focused totally on OP sheep dip reports. From 1993 to 1997, OP sheep dip reports were considered with reports of SARs associated with other products and in 1998 reported OP sheep dip SARs were not considered, with the exception of those deemed to be “serious” in nature. This changing nature of the published reports from the appraisal panel make it difficult for any independent investigation on trends in reported acute effects from OP sheep dips and likely causation in terms of work-practices.

Other limitations of the SARSS scheme with respect to OPs and sheep-dipping have been raised previously in the context of the OP sheep dip debate and reiterated during this project by a number of contacts. They include:

- The lack of laboratory evidence to support suspected ill-health case reports in the majority of cases. This is even though for OPs well established and interpretable diagnostic strategies are available based primarily on blood cholinesterase measurements and urinary metabolite monitoring, if samples are collected at an appropriate time to the exposure. A number of possible collection and analysis routes are available via the primary health care (GPs), NPIS, regional NHS toxicology centres or HSE;

- People reporting adverse reactions are almost never seen in a clinically relevant time scale by someone with expertise in toxicology;

- The time lag between a suspected ill-health event occurring and consideration by the appraisal panel;

- The lack of a proactive approach in following up initial reports, this is of particular importance if reliance is to be made solely on subjects’ recall of their symptoms and work-practices. This leads to insufficient data for the appraisal panel to make an appropriate conclusion;

- The quality and nature of the data received, which is highly variable, means that the database is of little real use in making observations regarding trends.

Unfortunately we were unable to arrange a meeting with the SARRS section at the VMD to discuss these comments.

We note that two pilot research schemes on adverse reaction reporting have been funded around the initiation of the appraisal panel for human adverse reactions.

Dr V Murray (National Poisons Unit, Guy’s and Lewisham NHS Trust) set up an adjunct to the VMD reporting system during the compulsory dipping season of autumn 1991 and a period in 1992. The aims were to identify all reaction enquiries to NPIS (London) related to sheep dip, follow-up all cases using a specifically designed questionnaire and proactive collection of blood samples for cholinesterase measurements. This scheme reported 34 cases of sheep dip exposure during 6 weeks of compulsory autumn dipping, 29 of which were occupational. Blood cholinesterase results were available on 19 cases of which 10 were considered ‘confirmed cases of OP exposure’ (Murray, 1992). Dr Murray highlighted the
value of any appropriately collected biochemical evidence and follow-up by specific questioning as soon as possible of those reporting adverse effects.

The second pilot scheme derived from the British Medical Association’s working party on pesticides. It recommended that a ‘green card’ reporting system be established, to run parallel to the existing SARSS reporting schemes with the purpose of obtaining data on exposure to pesticides and suspected adverse effects on health. The ‘green card’ scheme was conceptualised as being analogous to the ‘yellow card’ scheme, already operational for GPs for the purpose of reporting adverse reactions to human prescribed drugs. It was intended as an early warning system, enabling better monitoring of exposure to pesticides.

The pilot scheme was funded for three years by HSE to operate in the West Midlands and Trent regions. The coordinating body was the West Midlands Poisons Unit lead by Dr A Vale based in Birmingham. The three year scheme ran from October 1990 to September 1993 with the specific main aim of assessing the frequency and severity of acute pesticide poisoning in the UK. Principal objectives of the scheme were to introduce a surveillance and monitoring scheme, in the West Midlands and Trent Regions using free-post “Green Cards” for the reporting of pesticide incidents, to establish appropriate follow-up and clinical audit of patients referred for expert advice and also special outpatient referral facilities for rapid assessment of suspected cases. These objectives were designed so that a better distinction could be made between suspected and definite cases of acute pesticide poisoning.

HSE reviewed the success of the Green Card pilot scheme after three years and decided not to continue with it. Dr Vale stressed that for any successful adverse reaction scheme concerning pesticides immediate notification and rapid follow-up of evidence is necessary, including fuller investigation of the symptoms reported and, if possible, biochemical evidence.

8.3 Number of reported cases and estimation of incidence of ill-health from SARSS data.

An analysis was undertaken of available published reports on acute adverse human health effects on SARSS investigated by the Appraisal Panel of the VPC. This covers the period 1993-1996 when a differentiation of acute and chronic reactions was made. Distinction between SARSS reports considered by the Appraisal Panel and those adverse reports defined as ‘confirmed’ or ‘likely’ by the Appraisal Panel was attempted. There was largely agreement between our analysis of the combined category ‘likely and confirmed’ cases and figure 8.3a on acute cases presented in the COT report on organophosphates (COT, 1999). The data in figure 8.3a shows a substantial increase in acute SARSS in 1991 which is not related to the extent of OP sheep dip use but possibly increased publicity given to the possible health effects of OP sheep dips. However, in general terms the number of acute SARSS between 1984 and 1990 was higher than between 1994 and 1998, and this reflects the general levels of OP sheep dip sales during these periods.
Figure 8.3a taken from COT report (COT, 1999). Shows the trend in sales of OP sheep dips in thousand kg of active ingredients and annual numbers of acute human SARSS by year of onset of adverse reaction

Whilst SARSS is a reporting scheme which has been actively publicised in terms of OP sheep dip, it is a voluntary scheme and there is evidence that all schemes dealing with the reporting of occupational ill-health suffer from considerable under-reporting. Studies by HSE’s Field Operations Division suggest that only 3-10% of those who perceived that they had suffered some symptoms related to OP sheep dips had reported to the VMD or HSE. Similar levels of under-reporting are found in the Health and Safety Statistics 1998/1999 (HSC) where self-employed people in agriculture under-report any injury or illness by about 95%. Data from the questionnaire-based Labour Force Survey (1990) on ‘reportable injury’, undertaken on behalf of HSE, and comparison with ‘reported injury’ via RIDDOR strongly suggests that agriculture is an industry sector with a high level of under-reporting and that ‘self-employment’, such as farmers, may have reporting rates less than 5%.

Therefore to estimate a true incidence of acute health effects OP sheep dip we have used the acute case data derived from the SARSS scheme and applied an under-reporting factor of 95%. The SARS Appraisal Panel data for the period 1993-1996 inclusive have been used for this estimation as post-1996 there had been no division between acute and chronic effects. The number of both ‘confirmed’ and ‘likely’ cases of acute OP adverse effects for the 1993-1996 period are given as 52 by the Appraisal Panel published data. However, an upper estimate of 102 cases in the same category can be assumed with the addition of those SARSS reports originally defined in SARSS reports as ‘insufficient evidence’ but which possibly contained a similar proportion of occult ‘real cases’. MAFF census data were used for the number of UK sheep holdings (approximately 113,000). Two-man dipping operations being
carried out twice a year were assumed and that between 40% -70% of UK sheep farms were estimated as using OP dips during the period under consideration (1993-1996).

This prevalence of OP plunge dipping on UK sheep farms largely derived from the published analysis carried out by Liddel (Liddel, 2000), shown in section 2.6 and based on audited sales of ectoparasite treatments. However, it has been suggested that unpublished field data collected by HSE suggested a lower prevalence of OP use at around 20-25% within the last 2-3 years. This data may suggest that Liddel’s analysis based on UK ingredient sales may be over-estimating the prevalence of OP plunge dipping, in turn this may imply ‘off-label’ use of OP product. Alternatively, geographical influences on the need for differing sheep ectoparasite treatments may distort limited field survey data as being representative of UK as a whole. The differences may simply reflect a reduction in the use of OP plunge dipping from the first half of the 1990s in the later years of this decade. Further enquiries from FOD, HSE doubted whether their surveys on sheep dipping could give an accurate figure on the UK prevalence of OP dipping activities.

Using our estimates of between 40-70% for the prevalence of plunge dipping during 1993-1996, the likely incidence of some adverse acute health effects from OP sheep dipping as around 0.8-1.5 cases per 1000 ‘man-dips’ in this period. i.e. noticeable short-term symptoms would have occurred in 0.1% of dipping occasions during this period. Obviously any overestimation of the extent of OP plunge dipping would lead to an appropriately increased incidence of acute adverse health effects. We would highlight the number of suppositions and extrapolations that have been made to gain this incidence of acute symptoms.

Such an estimate assumes that during 1993-1996 the SARSS scheme collected representative data on the ‘true acute symptomology’ found during OP sheep dipping and that the 95% under-reporting figure is still a valid estimate given the media attention on OP sheep dip amongst the farming community during the early 1990s. More recent data from SARSS would suggest that the incidence may now be much lower than 1 per 1000 man-dips. Of concern using this analysis is that there is little concrete explanation, by way of changes in workpractice or OPs used, for the induced peak of reported acute adverse reaction in 1991. If this peak is explained, as has been anecdotally suggested, as an altered perception to OP dips through media interest, then the analysis on incidence undertaken above must be treated with caution.

We have considered subjectively whether in 1/1000 ‘man-dips’ it would be surprising for an accidental and considerably higher exposure to occur. In 1993-1996 those undertaking plunge dipping on sheep farms were potentially handling OP concentrates between 40-60%. Most other occupational scenarios using OP concentrates, largely manufacturing and formulation of pesticide products, should be strictly controlled by appropriate application of engineering controls and possibly PPE in the factory. However, we do still find isolated cases of blood cholinesterase depression during routine surveillance of such workers. (Workers would very likely be undergoing routine health surveillance according to MS17 (HSE, 1987; HSE, 2000a) in this sector). Therefore in the relatively uncontrolled situation of sheep dipping where there has been evidence of poor use of PPE, we find it feasible that incidents of high skin contamination (spills & splashes) with concentrate could happen at an incidence rate of 1/1000 when concentrate handling is allowed. This analysis does not answer the question whether these
incidental ‘high exposures’ would be ‘high enough’ to cause significant acute adverse anticholinergic health effects.

8.4 Estimation of acute, adverse health effects from toxicology data.

Figure 7.1a and the associated notes suggest that acute, serious clinical poisoning has been defined in two cases where the systemic dose of diazinon was around 15 mg/kg. The NOAEL has been defined as 2.5mg/kg from short-term animal studies based on the inhibition of erythrocyte acetylcholinesterase. The relatively narrow margin (6-fold in dose) between the defined NOAEL and the dose causing very serious clinical ill-health has been noted earlier. We also note that we can find no case reports of any sheep-dipper having been immediately hospitalised and treated for acute OP poisoning.

We have calculated the likely level of skin contamination from diazinon concentrate (60%) that would present three chosen systemic levels of diazinon. Dermal penetration was based on the 4% predictive figure used in the BPAU approach detailed in section 6.2.2. This penetration figure is in agreement with that defined by Wester (Wester, 1993), but eight-fold higher than that found in the human volunteer diazinon study at HSL (Garfitt 200a). It should be noted that there are differential rates of absorption of pesticides depending on skin site. Forearm, abdomen and head are likely to have similar dermal penetration rates for diazinon and close to the figure used in this report (Maibach, 1971; Wester, 1989; Wester, 1993; Halle, 1987). It is likely that some areas of skin or contaminated, damaged skin or mucous membranes could have significantly higher absorption.

Table 8.4a. Predictions of dermal and ingestion volumes reflecting the NOAEL and above to frank anticholinergic poisoning.

<table>
<thead>
<tr>
<th>Systemic dose (mg/kg)</th>
<th>Likely effect</th>
<th>Likely level of skin contamination with 60% diazinon concentrate</th>
<th>Likely ingestion level of 60% diazinon concentrate +/- adjustment for likely oral bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>Defined NOAEL based on erythrocyte acetylcholinesterase inhibition</td>
<td>7 mls</td>
<td>0.29-0.44 mls</td>
</tr>
<tr>
<td>7</td>
<td>Estimated dose likely to cause significant acute symptoms</td>
<td>20 mls</td>
<td>0.82-1.24 mls</td>
</tr>
<tr>
<td>15</td>
<td>Serious clinical, frank toxicity needing immediate hospitalisation and antidote therapy.</td>
<td>44 mls</td>
<td>1.75-2.65 mls</td>
</tr>
</tbody>
</table>

The BPAU approach computes that continuous contamination with very large volumes of dilute dip would be necessary to give such systemic doses (e.g. for a systemic dose of 7 mg/kg would need to absorb the OP from the equivalent of being contaminated with 240 litres (53 gallons) of dilute dip for over 4 hours. The data may suggest that it would be unlikely to achieve systemic levels this high from simple exposure to dilute dip.
The data in table 8.4a suggests that in practice a sheep-dipper needs to get approximately 7-20 mls or more of diazinon concentrate on their skin and not take appropriate decontamination of washing with copious amounts of water in order to precipitate some acute adverse anticholinergic effects. Exactly how long the 7mls or more of concentrate would need to be in contact with the skin is not easily definable. Seven mls of skin contamination with a liquid is in practice a large volume which should be readily noticeable to the subject if on the hands or face. However, the exposure to concentrate may be an additional, but smaller spill of concentrate on the skin if the work practices of the subject are already poor (see figure 7.1a and associated section on ‘worst case scenarios’). It may be possible for dippers to have volumes of concentrate underneath or inside protective equipment, such as gloves, rubber boots etc., leading to occluded contaminated skin which would lead to an absorption period for the duration of dipping.

When concentrate handling was part of sheep dipping the rare events of relatively large volumes of concentrate in contact with the skin and not adequately decontaminated could have led to noticeable adverse effects. However, we can find no evidence of any sheep dipper having been admitted to hospital with the sort of serious, acute anticholinergic effects where antidotes and supportive therapy are necessary.

8.5 Analysis and comparison of biological monitoring or biological effect monitoring data on sheep dippers and other occupational cohorts with OP exposure.

The following sections deal with biological monitoring and biological effect monitoring data undertaken by HSL for OP exposure. We have limited the review to this source of data as we know both the quality and limitations of the data-set.

In comparison with other work activities, sheep dipping forms only a small proportion of the OP monitoring that HSL has carried out over the last 10-20 years. Monitoring sheep-dippers has been mostly confined to research field-studies rather than routine monitoring or investigation of incidents concerning alleged over-exposure. The data suggest that the level of OP exposure to individuals undertaking sheep-dipping is largely no different to other work activities/industry sectors that we have monitored. There is insufficient data in isolation to make a quantitative estimate of the incidence of exposure likely to be associated with subclinical, anticholinergic symptoms of OPs. However, our experience of other industry sectors where concentrated solutions of OPs are used and potential dermal and hand-mouth contact is possible, suggest that blood cholinesterase depressions and minor symptoms may occur. Minor symptoms may include mild flu-like symptoms such as headaches, runny noses, tiredness. Out of approximately 130 blood samples from sheep-dippers taken at the appropriate time after dipping for cholinesterase monitoring, only one sample shows a depression in erythrocyte acetylcholinesterase that could possibly be associated with minor anticholinergic symptoms, but the pattern of plasma cholinesterase inhibition in this subject does not appear consistent. Four other samples (4/128) show some minor evidence of a depression in plasma cholinesterase alone that could be related to OP exposure, but is unlikely to be associated with symptoms of an anticholinergic nature.
The data suggest that sheep-dipping is not an activity that generally leads to OP exposure greater than firms formulating OP products and using OP concentrates. Also a substantial proportion of sheep-dippers who have undergone monitoring had urinary alkyl phosphate levels within the distribution for the non-occupationally exposed control group, suggesting relatively little occupational exposure.

The estimate in section 8.3 suggests that the incidence of short-term, subclinical symptoms suffered by sheep-dippers handling both OP concentrate and using the diluted dip may have been about one case per thousand man-dipping activities (i.e. 0.1%). It should be noted that we only have 130 appropriate blood cholinesterase measurements and around 400 urine measurements for sheep-dippers, some of which may have not been collected at the appropriate time in order to investigate the suggestion of an excessive exposure in 1/1000 ‘man-dips’. However, our experience from biological and biological effect monitoring data collected at HSL from various industrial sectors which also handle OP concentrates, would not be at odds with such an estimate.

8.5.1 Comparison of blood cholinesterase measurement in sheep-dippers and other occupational cohorts exposed to OPs.

HSL has undertaken routine monitoring of blood cholinesterase (both plasma ChE & erythrocyte AChE) in workers exposed to OP pesticides for over twenty years. The majority of the samples received by the laboratory are from occupational health professionals who are providing health surveillance for workers in a number of industry sectors at risk of OP exposure. This activity has largely been in accordance with HSE guidance (HSE, 1987). Almost all the samples we have received from hospitals are taken for this reason rather than hospital attendance due to possible poisoning. This is reflecting hospital income generation activity. However, a number of investigative field studies, including some on sheep-dips, have undergone the same routine cholinesterase measurement technique. We have also measured blood cholinesterases on a much smaller number of samples from subjects who have complained to their GPs or HSE about possible over-exposure to OPs. Thus the general level of monitoring activity has not to any real extent been directed by HSL/HSE, but reflects the activity of occupational and primary health-care professionals.

The activity on blood cholinesterase measurements has been undertaken with the aim of maintaining an assay with good, defined precision that allows detection of significant changes in plasma ChE and erythrocyte AChE activity in an individual below levels where symptoms from may be expected. A number of research and development studies have also been carried out within HSL to support this service in terms of interpretation of the results (Lewis, 1981; Mason, 1989; Mason, 1993; Mason, 1997; Mason, 2000; Sams, 1999). Our current interpretation of cholinesterase measurements is based on published literature, our research and experience of twenty years of monitoring activity. The basis of the monitoring has been:

- that wide inter-individual variation, particularly for plasma ChE, has meant that interpretation of a single sample after possible exposure needs to be compared against results for that individual when they have not been exposed. (i.e. minimum consists of exposed & baseline samples). However, recent investigations on the use of specific activity measurements for plasma ChE has suggested that interpretation may be possibly be made on a
single post-exposure blood sample. However, this method has not as yet been used in any study of OP exposure in sheep dippers;

- that when the sample is taken close to exposure, plasma ChE is invariably more sensitive to OP exposure, but depressions in erythrocyte AChE are more related to likely anticholinergic symptoms;

- that in chronic, repeated exposures it is possible to decrease substantially an individual’s level of plasma ChE and, to a lesser extent, erythrocyte AChE without any anticholinergic symptoms, whereas in an acute exposure symptoms may appear at smaller decreases from unexposed levels;

- that interpretation of plasma ChE and erythrocyte AChE is more complex, but not impossible, when blood samples are taken several days after the end of exposure;

- that urinary measurements of alkyl phosphates are much more sensitive measures of OP exposure than blood cholinesterase measurement, but may not necessarily reflect likely toxicity as well as blood cholinesterase measurements.

Ideally excessive OP absorption should be identified by a decrease in the level of plasma ChE or erythrocyte AChE activity in an individual from the activity levels found in the same individual when they have not been exposed to OPs for at least 60 days (baseline value) (HSE, 1987; Mason, 2000). In some cases the practical definition of a "baseline" or unexposed measurement level in an individual is difficult to obtain. This minimum of 60 days without exposure is often difficult to reconcile with many occupations where OPs are used. It is also possible to interpret the changes between serial ChE or AChE measurements rather than against a "baseline" value in order to identify abnormal changes in enzyme activity in an individual (Mason, 1989). Our current long-term analytical precision defines "trigger levels" of 15% for differences between serial measurements for both blood enzymes. A percentage change greater than the 15% “trigger level” between two measurements is statistically greater than would be expected from a normal, unexposed population using our method, and in a potentially exposed subject reflects likely OP absorption (Mason, 1989). We would not expect that subjects who show some depressions in enzyme activity greater than our “trigger levels” to necessarily show any anticholinergic symptoms.

HSL has maintained a database of all blood cholinesterase measurements for at least the last twenty years. Records are indexed by individual and workplace or referral centre. Over this period approximately 2,800 individuals have been monitored for both pChE and erythrocyte AChE; a number of the firms and individuals have been monitored on a routine basis for over ten years.
Table 8.5.1a. Numbers of individuals monitored by HSL up to 1998 as a result of potential OP pesticide exposure (routine monitoring & research studies)

<table>
<thead>
<tr>
<th>Industry type or source of samples</th>
<th>No. of individuals monitored</th>
<th>Percentage of total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers, formulators</td>
<td>554</td>
<td>20.0</td>
</tr>
<tr>
<td>Hospital referrals, not sheep dippers</td>
<td>122</td>
<td>4.4</td>
</tr>
<tr>
<td>Seed merchants/dressing</td>
<td>34</td>
<td>1.2</td>
</tr>
<tr>
<td>Agricultural contractors</td>
<td>460</td>
<td>16.6</td>
</tr>
<tr>
<td>Sheep dip surveys, plus other sheep dip referrals</td>
<td>168</td>
<td>6.1</td>
</tr>
<tr>
<td>Individuals (various, worktype unspecified, but not sheep-dippers)</td>
<td>295</td>
<td>10.6</td>
</tr>
<tr>
<td>Agricultural/Horticultural Research Institutes</td>
<td>626</td>
<td>22.6</td>
</tr>
<tr>
<td>Pest control (LA &amp; commercial)</td>
<td>148</td>
<td>5.3</td>
</tr>
<tr>
<td>Farm workers (not sheepdippers)</td>
<td>208</td>
<td>7.5</td>
</tr>
<tr>
<td>Forestry commission</td>
<td>154</td>
<td>5.6</td>
</tr>
</tbody>
</table>

The table 8.5.1a shows that only a relatively small number of sheep-dippers have had blood samples analysed at HSL for possible OP-induced depression of blood cholinesterases. This must be compared against the apparent level of reported ill-health and symptoms for this work-sector in comparison our experience of the other sectors shown. Our particular perspective is that since about 1989 onwards, the level of raised concerns and reported ill-health about OP exposure and sheep-dipping is in contrast to the general lack of concerns raised in the other sectors. This could have been due to the relatively high level of OP exposure in farmers carrying out sheep-dipping or the specific OP used in dipping. These possibilities are discussed later.

A few specific firms within the group classified as ‘manufacturers/formulators’ weight the level of monitoring activity, this is due to the occurrence of depressed blood cholinesterase levels at intervals within their workforces (Mason, 2000). Likewise one agricultural contractor has extensive long-term monitoring due to a history of problems during periods of maintenance on their spray equipment. Isolated individuals in various sectors have had a significant blood cholinesterase depression. Thus we have monitored a number of workers who have had a least one depression of blood cholinesterases above our defined trigger levels. Where we have any information on the nature of symptoms suffered by these workers with a depression in blood cholinesterase, they are mostly of minor flu-like or respiratory nature and invariably occur with erythrocyte AChE depressions at levels somewhat greater than our “trigger levels”. Most incidents of blood cholinesterase depression where we have data on the work activity relate to exposure to concentrated OP solutions or their residues contaminating equipment and the inappropriate use of PPE or poor hygiene.

Of the 168 individuals in the table above defined as related to sheep-dipping, 128 meet the criteria of (a) having a baseline measurement as well as the index sample, (b) the blood sample was taken within an appropriate time related to exposure (<36 hours after exposure) and (c) the plasma was without haemolysis. Of these only one shows a level of depression in erythrocyte AChE (figure 8.5.1a) which may have been associated with some subclinical symptoms, but without the expected depression in plasma ChE given the ideal time of
sampling. Four other individuals show plasma ChE depression above our trigger level suggesting some OP exposure, but without depression in erythrocyte AChE. We would not expect any obvious symptoms in these subjects. As a group the sheep-dippers show no evidence of a statistically significant mean depression in post-dipping samples compared to baseline measurements for either plasma ChE or erythrocyte AChE, although the mean plasma ChE does appear lower in the post-dipping samples (figure 8.5.1b).

The incidence of cholinesterase depression in sheep-dippers with other work activities shown in the above table is easiest made with ‘farmworkers- not dippers’, ‘individuals- unspecified but not sheep-dippers’ and ‘hospital referrals’. These are categories where invariably there are only two measurements per individual (index and baseline measurement) which is also the case for almost all the sheep-dippers. The sheep-dippers do not show any statistically significant difference in prevalence of depressions in plasma ChE or erythrocyte AChE compared to these other groups.

We would highlight that there are ongoing developments in the use of blood cholinesterase measurements as a biological effect monitoring strategy to identify OP absorption. The current use of cholinesterase enzyme activity measurements is based on the comparison of activity levels in samples taken as soon as possible after potential exposure with an unexposed, baseline level of activity in that individual. In cases of accidental exposures that invariably means that a subsequent blood sample for baseline activity measurements must be collected some period (60 days) after the index sample. This is often leads to practical difficulties in ensuring that two appropriate blood samples are collected and some concern in the subject under investigation, who expects some interpretation from the first blood sample rather than waiting two months. Based on the early work of Brock (Brock, 1990a &1990b), HSL has been investigating the use of specific activity measurements ([enzyme activity]/[enzyme protein concentration]) in the index blood sample, rather than needing baseline samples, to interpret likely over-exposure. Currently this technique has not been applied to sheep-dipping activities, but figure 8.5.1c shows cholinesterase specific activity data from controls and two cohorts where the standard serial activity measurements had shown evidence of depressions in enzyme activity after comparison with baseline activities. However, the specific activity technique does not show any increased sensitivity over the standard serial enzyme activity measurements in detecting low-level OP absorption. There have also been discussions about the possibility of using the specific immunochemical detection of aged plasma cholinesterase or erythrocyte acetylcholinesterase (Mason 1993; Mason 2000b) as more sensitive biomarker of OP absorption than standard enzyme activity measurements. Such phosphorylated enzyme entities may be detectable for a longer period in blood samples than any depression in enzyme activity.
Figure 8.5.1a showing the percentage change from baseline blood cholinesterase activities in those from the HSL database noted as sheep-dipping. Our “trigger level” of 15% depression of enzyme activity is identified on the graphs.

Figure 8.5.1b showing the relationship between percentage changes in plasma ChE and erythrocyte AChE (index/baseline) in the sheep-dippers.
Specific Activity levels for plasma ChE (kU/mg protein) in two groups of OP exposed workers and controls

8.5.2 Comparison of urinary alkyl phosphate measurements in sheep-dippers and other occupational cohorts exposed to OPs.

HSL has used a method for the measurement of urinary alkyl phosphates since about 1990. This method measures six urinary metabolites that would detect exposure to all OPs used for sheep-dipping, except propetamphos (Nutley, 1993). In the last two years a method to detect propetamphos has been developed and validated (Jones 1999). The measurement of urinary alkyl phosphates can discriminate between exposure to diethoxy and dimethoxy OP structures. The two major OPs used for sheep-dipping, besides propetamphos, in the last ten years are the diethoxy OPs- chlorfenvinphos and diazinon.

Human volunteer studies carried out at HSL on oral and dermal exposure to chlorpyrifos, propetamphos and diazinon have confirmed that the urine measurements of alkyl phosphates can detect OP absorption at levels considerably less than that necessary to cause an inhibition in plasma ChE or erythrocyte AChE.

A number of studies of workpractices where there is potential OP exposure have been carried out using urinary alkyl phosphate measurements. The data is shown in figure 8.5.2a. Largely...
these have been planned research, field studies rather than monitoring initiated by an occupational physician for health surveillance reasons or in response to likely OP-induced problems. However, urinary data from one formulator firm (formulator 1) was collected in response to earlier problems in a factory where there had been very significant depressions in blood cholinesterase levels and some mild flu-like symptoms suggestive of excessive OP absorption (Mason, 2000). Workpractices were considered to have been improved at the time of the urine sampling in this factory. It should be noted that urine samples in some of these studies shown in figure 8.5.2a may not have been collected at exactly the same time post-exposure or at the optimum time for interpretation. HSL has approximately 400 urinary alkyl phosphate measurements associated with sheep dipping. These include some of the data which formed some of the UK research studies noted earlier in this report, but also other monitoring exercises. Data on the urinary excretion of urinary alkyl phosphates in UK subjects without any occupational or home/garden exposure to OPs are also available using the same method and are noted as ‘controls’. The levels of urine metabolites in this group probably reflects dietary exposure, but it is unclear whether this is gut absorption of the parent OP or the non-toxic alkyl phosphate residues found in food or water.

This data suggest that sheep-dipping is not an activity that generally leads to OP exposure greater than two firms formulating OP products where the work involves handling OP concentrates. Also a substantial proportion of sheep-dippers have urinary alkyl phosphate levels within the distribution of the non-occupationally exposed control group, suggesting very little or no occupational exposure. We note that 400 urine samples from sheep-dippers collected over a 10 year period represents a very small fraction of the number of ‘man-dips’ performed in this period (see section 8.3) and perhaps not representative if trying to substantiate our suggested incidence rate of 1/1000 accidental high exposures during sheep-dipping activities which included handling of OP concentrate.

Therefore these urine measurements suggest that generally sheep-dipping has not been an activity where exposure to OPs is substantially higher than other industry sectors handling such products and for a proportion of sheep dippers it is impossible to prove any exposure. However the data does not prove that incidental, high exposures did not occur with the frequency we have calculated.
Figure 8.5.2a showing total urinary alkyl phosphate levels measured by HSL in a number of discrete workplaces or work activities involving exposure to various OPs.
9. DISCUSSION OF QUANTITATIVE RISK ASSESSMENTS

We would re-emphasise that we have largely undertaken a pesticide approval/marketing authorisation approach to investigate worker safety. We have investigated diazinon, registered for sheep dipping by VMD as a veterinary medicine, and also propetamphos and chlorfenvinphos which are no longer registered but were widely used in sheep dip during the 1980s and early 1990s.

In the last two years a general review of all anticholinergic compounds (including OPs) used as pesticides was instituted in the UK by PSD. A decision has recently been made by the approval/license holders not to pursue the re-registration of diazinon through this procedure. Similarly chlorfenvinphos was not supported by the approval/license holder during the early stage of this new review. Propetamphos was never registered in the UK as a plant protection product. However, it should not be assumed that the decisions not to re-register chlorfenvinphos and diazinon as plant protection products were due to toxicological problems with these chemicals. Such decisions were the commercial responsibility of the approval/license holders. Therefore currently diazinon, propetamphos and chlorfenvinphos are not approved in the UK as plant product pesticides.

The main outcomes of our quantitative risk assessments are that:

1. Diazinon would meet an approval process for worker safety as used by farmers for sheep dipping. A much wider margin of safety is given by a recent decision to remove concentrate handling from the process of sheep dipping and may be relevant given the apparent closeness of the defined NOAEL and doses suggested to cause significant health-effect;

2. The revoked registration of propetamphos and chlorfenvinphos by VMD for sheep-dipping is supported by our analysis;

3. SPs used for sheep dipping would meet an approval process;

4. There is a lack of exposure data to fully investigate the worker safety of pour-ons;

5. The a.i.s of injectables pose no worker safety problems as currently used, even in the rare case of self-injection. However, further review should be made of the possible health risk from the formulates used in the injection solution;

6. Biological monitoring data from field sheep dipping studies with diazinon combined with low-level human volunteer studies produced valuable “real world” exposure data that can be used to critically explore underlying assumptions of predictive exposure calculations based on models such as POEM;

7. We could not investigate workers safety for sheep-dip contractors, largely due to the lack of information on worker exposure from use of the diverse types of mobile facility used. Similar concerns on worker exposure data arise for the increasing ‘off-label’ use (jetting/showering) of active ingredients. However, a
lower NOAEL and associated AOEL would be appropriate for contract dippers using diazinon. Our preliminary review (5.1.4) would suggest an acute NOAEL for contractors using diazinon at possibly a 1/100 of that defined for farmers undertaking their own dipping. A single report (Apthorpe, 1998) on a jetting/showering system suggested comparable levels of daily systemic dose to those we have suggested for plunge dipping (table 6.2.5).

8. An estimated incidence for adverse symptoms was calculated of 1 in 1000 ‘man-OP dips’ where concentrate handling was involved. This is based on SARSS data for 1993-1996 and a number of suppositions and extrapolations. This may reflect believable scenarios based around spillage of sizeable volumes of concentrate on skin without appropriate decontamination. Available biological measurements suggest that sheep-dipping using OPs has not led to OP doses significantly different to other occupational sectors using OPs and many monitored sheep dippers’ exposure were indistinguishable from the normal population.

Our recommendations are that:

1. Exposure data on pour-ons is needed so that exposure assessments can be carried out. This deficiency has been recognised by UK and international regulatory authorities;

2. Given the likely increased use of contractors, more information on their exposure is needed. Many of the contractors may use ‘off-label (no-approved)’ techniques for treating sheep, such as jetting and showering. Not only is the efficacy of these treatments needed in terms of approval, but the level of ‘off-label’ activity and the likely worker exposure needs to be considered. We have not been able to consider whether diverse, off-label sheep treatments or standard mobi-plunge dips show adequate levels of safety to contractors. However we point out that recent reports from the Environment Agency suggest that ‘off-label’ use is increasing in certain geographical areas (Environment Agency 1999; Environment Agency 2000).

3. Concerns about the health effects from sheep-dipping with OPs remain a high profile and sensitive issue. The OP diazinon remains registered for sheep dipping with the proviso that concentrate handling should not be undertaken. Our analysis substantiates this position. But we suggest that consideration should be given to some means of substantiating that exposure will be below levels of concern, where PPE is properly used and enclosed concentrate systems are in operation. Such a suggestion is in agreement with discussions at an international, EU-sponsored workshop for regulators of pesticides (plant protection product) (Orta Italy, March 2000) and a recent research report (ICPS, 2000) which highlighted the potential value of ‘post-registration human monitoring studies’ in openly confirming AOELs and allaying concerns among key elements of public and political opinion. It is interesting that at this meeting the representative from the appropriate EU Directorate expressed his concern about
the apparent increasing lack of trust of the general public in the pesticide regulatory process as protecting human health.
PART 2 QUALITATIVE ASSESSMENT OF WORKPLACE RISK CONTROLS

10. QUALITATIVE ASSESSMENT OF WORKPLACE RISK CONTROLS

This section deals with qualitative issues in risk assessment and risk management concerning the use of OPs to combat sheep ectoparasites, and the feasibility of substituting less hazardous chemicals.

10.1 Reducing the use of chemicals for ectoparasite control

Farm workers use OP sheep dips and other chemical ectoparasite controls in two ways:

- to prevent ectoparasitic outbreak - the proactive approach; and
- to address specific problems that arise - the reactive approach.

The proactive approach of prevention and protection is strategic. In the case of host specific parasites (scab, lice), the goal is to stop parasites entering the flock. For parasites that are not host specific (blowfly, ticks, headfly, keds) the aim is to prevent them getting onto the sheep or, if they do, to prevent their development (e.g. by the use of insect growth regulators (IGR)). This approach can be adopted for vulnerable sheep in secure situations if a persistent product is used (Taylor, 2000).

The other, tactical, approach involves waiting until evidence of infestation arises before using any form of chemical treatment. When evidence of infestation does occur, the whole flock may be treated with the appropriate chemical for the parasite, thus ensuring that infestation in unaffected animals is prevented. Taylor (Taylor, 2000) points out that this approach relies on being able to effectively detect the parasite, recognise its type and react quickly.

The most effective animal husbandry is based on preventative methods and strategies must be geared towards a flock approach, rather than an individual animal approach. The ultimate goal of good flock management is to prevent ectoparasitic infestation.

Different categories of management system are characterised by differences in the prevalence and priorities of the various ectoparasites, largely due to geographic factors. The four categories of flock categories and management systems in the UK are: ‘hill’, ‘upland’, ‘lowland’ and ‘store finisher’.

<table>
<thead>
<tr>
<th>System</th>
<th>Parasite Priorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill</td>
<td>Ticks top priority in some areas.</td>
</tr>
<tr>
<td></td>
<td>Blowfly, scab and lice.</td>
</tr>
<tr>
<td></td>
<td>Headfly in some areas only.</td>
</tr>
<tr>
<td>Upland</td>
<td>Ticks top priority in some areas.</td>
</tr>
<tr>
<td></td>
<td>Blowfly, scab and lice.</td>
</tr>
<tr>
<td>Lowland</td>
<td>Blowfly top priority.</td>
</tr>
<tr>
<td></td>
<td>Scab and lice.</td>
</tr>
<tr>
<td>Store</td>
<td>Scab and lice.</td>
</tr>
</tbody>
</table>
The parasite priorities will determine other management factors and product/strategy choices for ectoparasite treatments.

Factors that influence product/application method choices are:

- timing of applications;
- cost of product;
- facilities available to carry out the treatment, pollution risks from chemical disposal,
- target parasites;
- target sheep;
- number of animals that need to be treated;
- the availability of necessary labour;
- human health considerations

The main objective of the study commissioned by the Environment Agency (Liddel, 2000) was to investigate the potential use of flock management with the optimal use of chemical treatment employing a variety of application methods as a means of providing effective ectoparasitic control.

The study produced several key findings, summarised below, which are of major relevance to attempts to reduce the use of chemicals in the control of ectoparasites.

- Eradication of ectoparasites is a desirable, but not a realistic, objective.
- Any practice bringing sheep together encourages the spread of ectoparasites.
- Plunge dipping using OPs is widely believed to be still the best form of control.
- Efficacy is often not maximised because of; misdiagnosis of the ectoparasite; not using the correct chemical for the target parasite; or through use at inappropriate times.
- There is greater use of contract dippers, often using mobile equipment. These contract dippers often use showers or jetters to apply chemicals as they allow a higher throughput of sheep and create less waste. These methods of application, however, may be ‘off-label’ and their efficacy has not been measured. Importantly less consideration of worker safety seems to have been applied to this activity.
- Few farmers have a cohesive strategy for ectoparasite control.
- There is much confusion about the various products, their uses and limitations.
- There is a need to reduce the use of sheep dip compounds, particularly SPs which may pose significant environmental risk.
- The optimum control strategy will vary between region and system.
- Feral sheep pose a particular problem.
- Better co-ordination between graziers of common land is called for.
- “Treated only” markets are not leading to reductions in chemical usage.
- No products are currently licensed to de-infest sheep-transporters of ectoparasites and the recent foot-and-mouth outbreak has re-emphasised the distances that sheep may be transported.
- The Groundwater Regulations and concern over human health are influencing farmers’ choice of chemical treatment.
- Hobby and part-time farmers may contribute to ectoparasite survival and spread through their lack of knowledge and inadequate facilities.

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These findings led to recommendations being made at three levels: (1) national; (2) system/geographic; and (3) flock level. Listed below are some of the recommendations which have relevance to reducing chemical use in controlling ectoparasites.

National Level:

- Success on areas of common grazing requires the co-operation of all graziers involved.
- The issue of feral or wild sheep should be addressed. Fences should be properly maintained and these animals should be removed to prevent them from mingling with maintained flocks.
- “Treated only” markets should be discontinued. This would leave responsibility for control with the purchaser, and would potentially lead to a significant reduction in the use of dips in sensitive areas in the autumn.
- A “register” of contractors should be established to facilitate the provision of rapid and consistent guidance to contractors and provide a focus for the effective exchange of ideas and evaluation of treatment systems with regulatory authorities such as VMD, Environment Agency and HSE.
- A product (or products) needs to be developed and authorised for use in treating vehicles and sheep pens at market against scab, lice etc.
- Continued research into alternative and new methods for the control of ectoparasites is essential.
- A priority area for research should be to establish the efficiency, product requirements, benefits and environmental risks of jetting and showering equipment. Farmers should be made explicitly aware of the limitations of such techniques, including that such use of ectoparasiticides is “off-label” (not licensed).

We note that there is a trade body for agricultural contractors which may be used as a conduit for the provision of guidance and may also be useful to gain information on the level and effectiveness of treatments which currently may be considered “off-label”.

System/Geographic Level:

- Those in control of ‘secure’ enclosed flocks should concentrate on maintaining security and controlling blowfly. Dipping is not essential unless security is badly breached.
- Security against parasites from sheep arriving into the flock must be ensured. This can be achieved with endectocides/injectables for scab and cypermethrin pour-on for lice. Only replacement stock need be involved in these treatments. Blowfly control should be based on insect growth regulators or cypermethrin products. Jetting with OPs could also prove to be a practical alternative in the future.
- It is estimated that a significant proportion of the sheep population could be in the category of secure flocks for ectoparasitic control. It is anticipated that the approach described above will result in a medium to long-term (5 to 10 years) reduction in the need to dip. A secure “fire-wall” in lowland flocks will reduce the pressure on hill flocks to dip prior to movement.
Flock Level:

- In the light of the confusion among sheep farmers, the literature/advice available to them should contain simple guidance on products, their activity/limitations and how they might be used as part of a strategy for ectoparasite control. In particular, the timing of the use of various products relative to their maximum efficacy should be emphasised.

- Farmers need a means of assessing their own particular level of risk from the various ectoparasites, this risk assessment can then be used to choose the most appropriate strategy.

- There is potential for considerable benefits through cost savings to farmers from using an ectoparasite control strategy that is based on optimal use of chemical control agents.

The above seems an appropriate strategy that if applied would lead to less use of chemical treatments. However, several contacts within our study (NFU, academics in agricultural colleges, veterinarians working with agrochemical industry) suggested that current practice was largely founded on a pragmatic, precautionary method of regular treatment with an anti-ectoparasite treatment of broad spectrum activity as possible. Cost of treatment is probably a strong influence on farmers current choice.

10.2 Improving exposure control during OP dipping

Many of the studies which have monitored sheep dipping activities have highlighted both the need for improvements to be made to engineering control measures, and the lack of (or poor use of) PPE. Reviews by the VPC on sheep dipping also note that PPE and engineering controls need improving. The influence of training and other means, such as publishing guidance, on improving work practices has also been highlighted.

10.2.1 Engineering controls

A field survey carried out as part of HSE's Field Operations Directorate (FOD) Key National Objective Report 2000/2001 focused on sheep dipping. It found that 36.2% of facilities had inadequate engineering controls to protect operators from exposure to diluted dip. These inadequacies consisted of; no waist high splash screens between the plunger and the dip bath; lack of splash and droplet screens at the entrances and exits to the dip baths; and the use of wooden, rather than metal, handled dipping crooks. In 21.1% of these cases, an Improvement or Prohibition Notice was served by HSE because of these inadequacies. Comment from FOD was made that these outcomes were still an improvement on those found in earlier field studies of sheep dipping.

Anecdotal evidence suggests that splash boards and screens may impede the flow of sheep into the dipping system as sheep avoid moving towards solid objects. It is possible, therefore, that a safety/efficacy trade-off with respect to these types of controls is taking place.
10.2.2 Use of Personal Protective Equipment (PPE)

There are two main sources of guidance relating to the need for, and specification of, adequate PPE for workers using OP sheep dips. These are:

- information provided by Governmental bodies such as the HSE and MAFF; and
- information provided by the manufacturers of OP sheep dips in the form of safety labels on the products, safety data sheets and guidance sheets/leaflets on correct use of the product.

The current recommended specification for PPE is detailed in HSE Leaflet AS29 (rev) Sheep Dipping. These recommendations are replicated on product labels and in manufacturers’ guidance leaflets. The original leaflet was produced in 1991 and revised in 1994, 1995 and 1998 and a video of the same name has also been produced. AS29 gives advice on various aspects of sheep dipping and was produced in conjunction with the Scottish Environment Protection Agency, the Veterinary Medicines Directorate and the Environment Agency. It contains a comprehensive section specifying the use and care of PPE, including a diagram of a worker dressed in the recommended clothing. Since 2000, manufacturers of OP sheep dips must supply a laminated advice sheet and two pairs of gloves with every sale of their product. The laminated sheet, which should be displayed near the dipping facilities, also depicts a worker clothed in the recommended PPE.

A number of studies on sheep dipping over the last decade give some idea of the actual use of protective clothing which can be compared against the guidance in AS29. These studies are detailed in Appendix G. As part of this project we have talked to various parties with an interest in sheep dipping. A number of common and salient findings, listed below, can be drawn from these studies and discussions.

- When used correctly, the recommended protective clothing minimises worker exposure to sheep dips.
- The use of exposure control measures is highly variable, both between and within farming establishments.
- There is a high level of non-compliance with the recommended protective clothing.
- A significant proportion of ill-health reports to SARSS appeared associated with use of inadequate or no PPE.
- Where protective clothing was used, it often seemed to be inadequate either in type or condition.
- Poor maintenance of PPE is frequently encountered, for example clothing may be in a poor state of repair and/or not washed between dipping sessions.
- Handling of the dip concentrate was the procedure most likely to result in high exposure levels, but there appeared to be widespread poor working practice associated with this activity. Many workers did not use gloves when handling the dip concentrate and where gloves were worn it was not clear whether they provided adequate protection.
- There appears to be a wide divergence of opinion on the practicability and physical burdens associated with the recommended PPE. Some opinion (among end-users and farming representatives) considered it to be impractical to be worn for extended periods.
when undertaking large scale dipping, whereas others (including regulators, agricultural inspectors and veterinarians) could see no real problem with its use.

- The 2000/2001 survey by HSE’s Field Operations Directorate suggests that although there has been a substantial improvement in this area since the early 1990s, there is still room for further improvement on the use of PPE.

As noted above, there remains a body of opinion that questions the practicability of wearing the recommended PPE during heavy, physical labour, often in warm temperatures. This may, in part, reflect the influence of poorly sited and ergonomically organised dip structures, rather than be entirely related to the problems associated with PPE. The non-specific symptoms of ‘dippers flu’ have been linked to anticholinergic effects of OPs, but some of the symptoms could be equally linked to physical overexertion, heat stress and dehydration caused by working with inappropriate dipping systems. Endotoxin exposure from sheep fleeces has also been suggested as a potential cause for the symptoms. It may be pertinent to consider whether enough is known about the interrelationships between the recommended PPE, the engineering and ergonomics of dipping and physiological effects of the activity. Such issues may have been addressed by new research prompted by the 1999 COT report (COT, 1999).

### 10.2.3 Training

The Certificate of Competence in the Safe Use of Sheep Dips, introduced in 1995, is issued by the National Proficiency Test Council (NPTC). The law requires that all purchasers of sheep dips hold this Certificate, which meets the requirements of HSE under the Health and Safety at Work Act and the COSHH Regulations. The scheme originally applied only to dipping using OPs, although from the end of 1998 all sheep dips were included.

In 1995 HSE FOD carried out a survey which examined compliance with the COSHH Regulations at sheep dipping facilities. In almost all measures observed, standards at farms where someone held the Certificate of Competence (48.5% of the 660 premises surveyed) were better than at those without. Measures looked at included use of PPE, engineering control implementation and the correct use of products. It is impossible to be definite that the Certificate of Competence had some causal influence on dipping standards, rather than a simple association between better farms being more likely obtain the certificate. The influence of training via the Certificate of Competence would be gained through further follow-up surveys.

The VPC and NOAH have suggested extending the Certificate of Competence to cover all workers involved with sheep dips and in disposing of waste dip. However, the HSE/HSC have equivocally opposed extending the current certification process to all users, fearing that this may compromise the requirements of current legislation; duty holders may focus unduly on the acquisition of a once-and-for-all qualification in the belief that their obligations are then fully discharged. Duty holders are subject to the requirements of the Health and Safety and Work Act and the COSHH Regulations, these already include adequate training, instruction, competence and supervision of any work activity. It is argued that merely obtaining a certificate could never fulfill all of these requirements all of the time. HSE is also concerned that resources would be used to fund the formalities of the scheme rather than on reducing actual risk. Furthermore, enforcement and subsequent prosecution may be adversely affected by any extension since such action might be made more difficult if the duty holder held a
certificate. The HSE view is that risk reduction is more appropriately tackled through advice, guidance, publicity and enforcement (OGOP, 1999). However, field study evidence suggests that the weight of guidance, publicity and advice produced has still not eliminated poor work practices. Our recent contact with NOAH suggest that they still support wider certification, notwithstanding HSE’s reservations.

Comment from the recent field study by FOD (2000/2001 HSE) suggests that the training system is working well in practice.

10.3 Substituting for OP dipping by other means of ectoparasite control

Efforts to reduce OP-related risks have resulted in the widespread use of alternative chemicals and methods of treatment for ectoparasites. It should be reiterated that SP-dips potentially pose higher environmental hazards. Non-chemical and vaccine treatments for ectoparasite control may also be future options but they remain at the research level at the current time. It was pointed out during discussions with NOAH that animal health is not a growth area within the general pharmaceutical industry and that this may hamper bringing new products through the licensing process to commercial use.

Any efforts to substitute OP sheep dips with other chemicals must consider not only the health risks to workers associated with the substitute chemical, but also its efficacy, ease of use, persistence and environmental impact. As Gray and Hammitt (Gray, 2000) pointed out:

“The effect of countervailing risks may partially or completely offset the reduction in the target risk.”

Consideration of substitute chemicals must therefore involve careful weighing up of the pros and cons of the chemical under consideration, along with those of all other potential substitutes.

10.3.1 Farming perspective on substitution of OP dipping

This section examines the relative advantages and disadvantages associated with:

- OP dips;
- SP dips;
- pour-ons, spray-ons and spot-ons;
- endectocide injectables.

The information is extracted from Liddel (Liddel, 2000), discussion with Lesley Stubbings, Independent Sheep Consultant, Lesley Stubbings Sheep Consultancy and NFU representatives.

OP Dips

OP dips are the most effective form of control for all of the current sheep ectoparasites. They give 100% control and a 9 to 12 week protection against reinfestation after dipping.
The advantages of OP sheep dips include:

- broad spectrum action against mites, blowfly, ticks, lice and keds;
- treats and prevents infestation for 9 to 12 weeks;
- relatively short withdrawal period for sheep of 14 to 35 days post dipping;
- ectoparasite resistance to OP is not currently a problem;
- relatively cheap

The disadvantages of OP sheep dips include:

- operator health and safety concerns;
- environmental risks associated with disposal of spent dip;
- the dipping process is labour intensive;
- dipping can be stressful to sheep;
- operators should wear extensive PPE which may be uncomfortable;
- new dipping facilities may be expensive.

**SP Dips**

SP dips were developed in the early 1980s as a possible replacement for OP dips. SP dips do not give 100% control, unlike OP dips. Flumethrin does not control blowfly and is used mainly for the control of sheep scab mites, giving 6 to 8 week protection. Some cypermethrin products may be used against blowfly strike, sheep scab, lice and ticks, others against all five major ectoparasites, with 6 to 8 week protection. There is currently concern that ectoparasites could develop resistance to the effects of some SPs. SP-resistance has been found in various areas of Australia which has led to an increasing return to OPs for sheep ectoparasite treatment (personal communication National Registration Authority for Agriculture & Veterinary Chemicals, Australia).

The advantages of SP dips include:

- broad spectrum of control;
- active against scab mites, ticks lice and blowfly (except flumethrin);
- treats and prevents infestation for up to 8 weeks;
- short withdrawal period of nil to 12 days.

The disadvantages of SP dips include:

- environmental risks associated with disposal of spent dip;
- highly toxic to invertebrates;
- dipping can be stressful to sheep;
- highly labour intensive- may require 2 treatments 14 days apart;
- operators should wear PPE which may be uncomfortable;
- persistence not as good as for OPs;
- possibility of emerging resistant-parasites greater for SPs than for OPs.

**Pour-ons, Spray-ons and Spot-ons**
These were developed in the late 1980s as alternative application methods. There are currently 3 main active ingredients authorised for use in pour-ons: deltamethrin and cypermethrin (SPs) and cyromazine (insect growth regulator). Pour-ons are supplied in ready-to-use packs and are applied in a measured dose using an applicator gun either as a spray-on, spot-on or pour-on along the back of the sheep. The treatment spreads throughout the fleece of the animal within 48 hours.

Advantages of Pour-ons, Spray-ons, Spot-ons:

- ease of application, less labour intensive;
- SPs treat and cure for 4 to 6 weeks;
- better operator health and safety;
- need for PPE reduced;
- short withdrawal period of 3 to 7 days;
- cyromazine prevents blowfly strike for up to 10 weeks;
- do not require the use of expensive fixed-site dipping facilities.

Disadvantages of Pour-ons, Spray-ons, Spot-ons:

- not as effective against sheep scab and mites - risk of resistance emerging therefore higher;
- sheep may require repeat treatments and therefore time spent recollecting sheep;
- cyromazine only controls blowfly and is not effective against other ectoparasites;
- more expensive per treatment than dips.
- inappropriate use may led to resistance in some parasites using SPs.

**Endectocide Injectables:**

Injectable treatments, known as endectocides, were introduced in 1992 and contain one of three active ingredients: Ivermectin, Moxidectin and Doramectin. Ivermectin and Moxidectin products require two injections at 7 and 10 days respectively for control of scab mites; Doramectin products require one injection for control of sheep scab mites. Persistence varies between active ingredient: Ivermectin gives nil protection against scab mite reinfestation; Moxidectin gives 28 days protection; and Doramectin may give 18 to 21 days protection (but this is not authorised as a protective treatment).

Advantages of endectocide injectables:

- also effective against internal parasites;
- relatively safe for human operators;
- PPE not required;
- easy to administer.

Disadvantages of endectocide injectables:

- long withdrawal periods of 42 to 70 days;
- effective only against sheep scab mites;
- injection may cause local damage to sheep;
may require repeat treatment with time taken to recollect sheep;
• expensive in comparison to other chemical controls;
• sheep may be “missed out” for treatment as operators may think they have injected animals when they haven’t.
• under-dosing may be a problem, effective dosing is dependent on sheep weight.

10.3.2 Environmental perspective on substitution of OP dipping

Significant water pollution by sheep dip chemicals was identified as a problem in the late 1980s and in recent years the environmental dangers of sheep dipping have been increasingly highlighted to farmers (Virtue, 1997; Environment Agency, 1998 & 2000). The Groundwater Regulations, introduced in April 1999, cover both the storage of dip concentrate and disposal of spent dip; penalties for failure to comply include fines of up to £20,000 or a maximum of 3 months in prison. Under these Regulations, Environment Agency authorisation is required for the disposal of spent dip (all 65000 registered sheep farmers in England and Wales were sent an explanatory leaflet and application form in support of this). An investigation must also be carried out to ensure that there is no threat to groundwaters from sheep dipping. In addition, the Code of Good Agricultural Practice for the Protection of Water stipulates standards for the siting of dips and their construction.

The Groundwater Regulations do not distinguish between OP- or SP-based dips and even though there are disposal treatments for spent dips available to render them less hazardous, such treatments do not alter the handling requirements for spent dip under the Groundwater Regulations.

In 1998 a Sheep Dip Strategy was launched by the Environment Agency after wide consultation with the ‘sheep dipping industry’. This priced publication aims to work in partnership to tackle pollution problems arising from sheep dipping. Principally flock management and disease control methods which reduce chemical usage were considered, and guidance is provided on how to protect the environment. The Environment Agency has also produced free guidance (e.g. PPG12 sheep dipping) on facility siting and design, concentrate storage, preparation of wash solution, operation of the bath and disposal of spent dip and containers.

There is some agreement that the increased regulatory and advisory emphasis on the environmental impact of sheep dipping has resulted in the removal of many poorly sited, inappropriate plunge-dip structures on farms, and raised farmers’ general awareness of the pollution problem. There is some evidence that this has lead to practical environmental benefits, although the wholesale rebuilding or resiting of old dips structures to create state-of-the-art dips has not, and will not, occur in the sheep industry’s current depressed economic climate. In a June 2000 statement the Environment Agency highlighted the recent downward trend in sheep-dip pollution incidents in England and Wales - 34 in 1997, 27 in 1998, and 5 in 1999. The Agency noted that;

“the serious problems in 1997 and 1998 followed a big increase in the use of SP-based dips- reflecting farmers concerns with the possible health implications of OP dips.”
Of the 27 pollution incidents in 1998, 21 were SP related; in 1999 all 5 incidents were SP related. In the same June 2000 statement, the Environment Agency again stressed the greater dangers to the aquatic life from SPs:

“SP dips can have a devastating effect on our water environment - some being 100 times more toxic to aquatic life than OP dips............we want to build on this success (decrease in dip incidents) but realise progress could be hindered this year by an increase in SP compounds following withdrawal in December of OP products.............”

Such cautions about the dangers to aquatic life by SPs are widely and properly highlighted by experts within the industry, for example:

“a litre of dip wash (SP, high cis cypermethrin) will wipe out freshwater invertebrates for several kilometres downstream... so farmers using SP dips for the first time must take great care to avoid causing a pollution incident”- Dr John Vipond (Scottish Agricultural College) update on sheep dipping given at The Royal Highland Show June 1998.

In the same presentation, Dr Vipond stressed that only plunge dips and injectables can control scab, a major problem in Scottish flocks, but for hill farmers with tick infestations injectables offer no help. “Dipping is fundamental to our (Scottish) ability to stock these hills due to ticks....”

Thus many hill farmers, especially in areas where there is a risk of ticks, will have gone through the registration of a plunge-dip or mobile dip facility with the Environment Agency or moved to using a contractor. Their choice of chemical will be OP or SP, possibly largely driven by their reaction to media concerns about the health effects of OPs or their fear that a relatively small SP incident will be more environmentally apparent, leaving them liable to prosecution. For lowland farmers there may be greater choice for substitution.

Current and future efficacy of the treatments may influence substitution. Resistance may emerge in parasites to any chemical after protracted treatment. The emergence of SP resistance in Australia has recently caused a resurgence in the use of OPs, rather than SPs, to control some ectoparasites. Some parallel evidence of a similar phenomena may also have recently happened in the UK (see section 2.6). There have been sporadic reports of resistance to OPs such as propetamphos, but induced-SP resistance remains a more likely threat. The potential for resistance exists in situations where a 100% kill of parasite is not achieved. Diazinon is an effective anti-ectoparasite treatment, but the inappropriate use of SPs in dips, or more likely as pour-ons, may increase the potential for significant SP resistance in the UK. Concerns have also been raised about injudicious use of the avermectin injectables. Whilst being used for ectoparasite control, the same or similar chemicals are also used to treat debilitating endoparasite infestations in animals and humans. The concern has been raised that resistance in endoparasites may be produced by any widespread prophylactic use for ectoparasites (NOAH, personal discussion). The suggestion is that this may create similar problems with the historical prophylactic use of animal antibiotics and increased resistance in some bacteria that can threaten human health.

Concerns have been raised on an international basis about the injectables and their effect on ecosystems involving dung-bettles and other dung-loving insects. In the UK, certain
landowners have forbidden the use of injectable avermectins on their land by tenant sheep farmers. This is a complex issue which has not been entirely resolved, but there is growing evidence that the use of avermectin-like injectables may not pose a significant threat (NRA, 1998). The level of any effect is likely to depend on the nature of the climate, husbandry techniques, pasture and treatment regime.

In conclusion, there does not appear to be indisputable justification for the substitution of OP dipping on environmental grounds.

**10.3.3 Financial aspects for substitution of OP dipping**

Currently there are significant differences in the costs of treating sheep for ectoparasites. Table 10.3.3a gives an estimated cost to the farmer of the treatment per sheep having taken into account factors such as dip size, likely numbers dipped, number of treatments, weight of sheep etc. The data indicate that other treatments may currently be twice as expensive in use compared to OP dips, with the injectables costing around four times as much. Such price differences are likely to influence a farmer’s decision on substitution, although adoption of the strategies suggested above in section 10.1 may influence this cost structure.

Table 10.3.3a Treatment costs per sheep for farmer. (Liddel, 2000) using Veterinary Review January 2000 & Farm & Country Retailer January 2000. Largest pack size and no discount assumed.

<table>
<thead>
<tr>
<th>Product Group</th>
<th>Mean cost per sheep</th>
<th>Range of cost per sheep</th>
<th>relative cost compared to OP dip</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP dips</td>
<td>26.1p</td>
<td>13-40p</td>
<td>1</td>
</tr>
<tr>
<td>SP dips</td>
<td>48.0p</td>
<td>28-65p</td>
<td>1.84</td>
</tr>
<tr>
<td>pour-ons, spot &amp; spray-ons</td>
<td>59.7p</td>
<td>48-78p</td>
<td>2.29</td>
</tr>
<tr>
<td>injectables</td>
<td>112.0p</td>
<td>86-132p</td>
<td>4.29</td>
</tr>
</tbody>
</table>

**10.4 Chemical means of ectoparasite control requiring further study**

There is evidence that treatment of sheep for ectoparasites is increasingly being carried out by contractors using mobile facilities, or using ‘off-label’ methods to apply chemicals which are already used in approved processes, i.e. jetting and showering using OPs and SPs. In a review of sheep dip in Wales in 1999 by the Environment Agency (Dunstone, 2000), about 10% of 164 farms visited were using jetting or showering. This had increased from 6% in a similar survey carried out in 1998 (Hutchings, 1999). This earlier report noted that 6% of farms were using a ‘new system’ of pumped jetting or showering systems to soak the sheep without immersing them, this used smaller volumes of chemicals, but highlighted the high environmental risks and need for specific guidance. Interestingly both reports noted an overall decrease in static dipping and increased use of contractors and mobile facilities. The use of showering or jetting systems, although ‘off-label’ in the UK, is well established in many countries; investigation of their use in the UK is not new, for example HSL was involved in 1990 in a small trial of a showering system using propetamphos which looked at both animal and worker safety (Border Research, 1990).
We recommend that the appropriate regulatory bodies ensure that they have specifically considered the worker safety, efficacy of treatment and environmental risk from the use of showering or jetting systems. Furthermore, these issues need to have been addressed for contractors undertaking sheep treatment using differing types of mobile facilities.

10.5 Improving workplace risk controls by improving guidance to industry

Numerous studies have demonstrated that when carrying out plunge dipping, farmers tend not to comply with the recommended safe working practices, particularly with regard to PPE. This inevitably places them at greater risk of exposure. Farmers & farm-workers are not unique in their level of non-compliance and the area of health and safety behaviour has received increasing attention in the field of psychology. Some specific research has been undertaken in the perception of risk to organophosphate sheep dip (Pilkington, 2000; Carmody 2000). A number of psychological models for health behaviour have been developed which may help in suggesting means of changing behaviour towards improving compliance.

The environment and culture within which farmers and farm-workers work are probably strong influences on their attitude to risks. They work independently, often at demanding high levels of physical capability, for long hours and in inclement weather conditions. There remains a strong culture of ‘hanging down the farm from generation to generation’ and particularly live-stock farmers have been facing increasing financial pressures over recent years. The recent problems with BSE and foot-and-mouth in the UK have added to these economic pressures and problems with their self-image. Many of these problems are not solely seen in the UK. A study of Australian farmers (Cassell and Day, 1998) who face similar problems to UK farmers found some farmers to be in ‘basic survival mode’:

‘Farmers are an independent lot unaccepting of external controls which they see as infringing on their personal rights. They view farming as a way of life, not just a job and their independence is part of the farming culture and ethos’ (Cassell and Day, 1998).

There is also evidence (Hawton, 1998) from a recent study that a considerable proportion of farmers find difficulty in understanding official forms (56%), had problems with the level of record keeping now necessary (62%) and experienced problems with new legislation and regulations (49%). A questionnaire study (McGregor et al., 1998) of farmers attending two agricultural shows found that filling in ‘government forms’ and adjusting to ‘government regulations’ were two of the greatest causes of stress. These data may reflect the attitude of farmers, who are under increasing economic pressure, as described by Cassell and Day, but could also reflect some element of a real problem among sections of farmers in comprehension of some government’s written material. Given that the delivery of clear, straightforward, sector-specific guidance is a key action point in the HSC’s Revitalising Health and Safety Document, the latter possibility needs consideration. Also relevant is the current initiative of HSE in a programme called the 3Rs risk communication programme (..getting the right information, to the right people, in the right way). The research generated by the programme looks at optimising methods of getting comprehensible safety information into the workplace where it will be attended to by the relevant workers.

There is some evidence that farmers or farm-workers prefer verbal information and especially if it comes from those who they recognise as their peers. Pilkington (Pilkington, 2000) in a
study of risk perception in sheep dippers highlighted that an effective and popular way of
training and providing information to farm workers would be for courses led by other farmers,
or those closely associated with farmers, with appropriate training. Part of HSC’s strategic
plan 2000/2001 was to develop the role of intermediaries in ensuring the reduction of
workplace injuries and ill-health. There may be scope for extending the involvement of the
NFU, NOAH, agricultural colleges and agricultural merchants in imparting health and safety
advice or guidance. Obviously the potential problems of conflict of interest or commercial
profit need to be considered as well as ensuring the appropriate key safety messages are
promulgated. We note that at least one manufacturer of sheep-dip had in the past produced a
video of good working practices, but could give no firm indication of the success of this form
of communication.

It has been suggested that the use of a case-study approach in future guidance on sheep-
ectoparasite treatment may help overcome any cultural barriers (‘us and them’) and help
lessen the reliance on written text. There is increasing complexity in decisions to be made by
farmers in securing sheep against ectoparasite infestations, where factors on human safety,
risk of environmental pollution, efficacy in treating sheep, flock management and comparative
cost analysis of the treatments all need to be considered. Care should be taken that the
guidance from regulatory authorities on any aspect of these factors does no increase in
complexity.

The Health Belief Model is one of a number of psychological models that can be used to
investigate behaviour concerning health and safety and identify ways of changing behaviour
(Nemcek, 1990; DeJoy, 1996). It has become increasingly validated. Largely the model points
to four main elements which influence one’s behaviour decisions related to health.

- Perceived susceptibility to the health problem;
- Perceived seriousness of the problem or condition;
- Perceived benefits associated with taking a particular action;
- Perceived barriers associated with taking the action; and
- Perceived self efficacy about one's ability to perform the behaviour.

(DeJoy, 1996)

Research has found that the two most powerful factors within the model are perceived barriers
and perceived susceptibility (Salazar, 1991). Innes (Innes, 1997) pointed out that education
and training programmes should focus on exploring perceived individual susceptibility and
perceived barriers to behaviour change. If perceived susceptibility is enhanced and perceived
barriers are lessened then there exists scope for behavioural change. Changing behaviour is
notoriously difficult but altering perceived susceptibility and barriers may be an easier task
which might, in turn, have an influence on behaviour. Possible changes to guidance and
labels currently available to farm workers probably provide the most appropriate opportunity
by which to influence their behaviour and compliance with good practice. The Health Belief
Model would suggest that information should make the workers feel personally at risk and susceptible.

Recommendations for improving the guidance to farm workers that have evolved from the Health Belief Model and other investigations include:

- Written word format should be minimised where possible
- Consideration should be given to including case studies in guidance.
- Dissemination of information should involve peers and intermediaries.
- Guidance should make the farm worker feel personally at risk and susceptible. This has been, to some extent, addressed in the new labels for containers.
- Guidance could be more hard-hitting. Farm workers need to know that OPs are a potentially dangerous substance and that the adverse effects could be severe for them.
- Perceived barriers to safe working practices warrant further exploration. The contradictory opinions about the practicability of using the recommended PPE for dipping may be such a perceived barrier. These perceived barriers should be addressed in future education, training, guidance and advice.
- Continued emphasis should be given to using plain English. The VMD are currently addressing this issue for product labels.

10.6 Discussion of qualitative assessment of workplace risk.

Strategies have been proposed by experts in sheep management that aim to reduce the use of chemicals to control sheep ectoparasites, whilst maintaining animal welfare standards and avoiding further financial drains on this hard-pressed agricultural sector. This sector includes not only farmers but also the UK meat, wool and leather industries. Elements of these strategies can be implemented from national to flock level, but much remains as a set of long-term goals. It is accepted that chemical treatments will play an important role in controlling infestations that would otherwise seriously affect flocks, farmers’ profits and the existence of a viable UK market in sheep meat, wool and leather. Non-chemical, prophylactic treatments, such as vaccines, currently exist only as research investigations but in the future these may lead to a reduction in the use of chemical treatments. At the moment, chemical methods of treating and controlling sheep ectoparasites are necessary. The choice of the chemical method used to control or treat the parasites is driven by its efficacy against the specific parasite, but cost and increasing consideration of both worker safety and protection of the environment are also involved. Thus the use of chemical ectoparasite treatments involves MAFF and its agencies, Environment Agency and the HSE in their respective regulatory, policy and guidance-giving functions. This is evidenced by both the level of collaborative government guidance published on sheep dipping and the internal government working groups, such as OGOP, which specifically relate to concerns about OP use in sheep treatment. For some areas of the UK, dipping using OP or SP will inevitably remain the pragmatic treatment of choice with the widest efficacy against the spectrum of parasites.

The safety of OP sheep dips towards humans has been raised as a matter of concern from around the late 1980s. Latterly the potential for SPs to cause severe and obvious environmental pollution problems has been widely publicised, especially via the Environment Agency and implementation of the Groundwater Regulations. As such this may set up a simplistic and
flawed debate about the ‘balance between human safety using OPs and environmental safety from using SPs’. Our analysis presented in sections 6 & 7 suggests that the current registration of the OP, diazinon, meets an approval process designed to ensure the health of users of pesticides, and the Groundwater Regulations (and their threat of prosecution for non-compliance) do not distinguish between OP and SP sheep dips. It may also be pertinent to highlight evidence of increased reporting of SARRS related to SP and other non-OP sheep ectoparasite treatments from around 1997 onwards. Several veterinary and animal health specialists have stressed the need to maintain a wide spectrum of effective chemicals against parasite treatments, especially in the light of resistance to specific chemicals emerging in parasites. In Australia this has led to clear evidence of sheep farmers resuming using OPs rather than SPs for treatment of some ectoparasites.

Recent studies by HSE’s FOD in 2000/2001 and the Environment Agency (Dunstone, 2000) have suggested a considerable recent improvement in the use of PPE, engineering control, influence of training and environmental protection compared with the early 1990s. However the use of appropriate PPE during sheep dipping was invariably patchy or poor when studied during the 1990s, and even today it has been commented that there remains room for improvement.
11. DISCUSSION: THE ROLE OF SUBSTITUTION & NEED FOR COST BENEFIT ANALYSIS

11.1 The role for substitution

We consider that our quantitative assessment of the OP (diazinon), which is currently approved by VMD for use in sheep dipping, would suggest it meets a pesticide approval/marketing criteria. This EU pesticide approval process has been established to prevent any adverse health effect of users and bystanders, i.e. ensure their health. Similarly plunge dipping with high-cis cypermethrin, which is the only combination of use and active ingredient that gives an approaching similar breadth of efficacy against UK sheep ectoparasites, also meets this pesticide approval criteria. Although SP dipping gives higher MOEs than OP dipping with diazinon in the quantitative risk assessment, the underlying philosophy of the EU risk assessment process for each chemical is in ensuring the prevention of any adverse health effects. This would suggest that for these two chemicals, and any chemicals, which have passed the approval process there is no immediate health-risk based reason for driving substitution. This may highlight the innate difference between the pesticide approval process and HSE’s approach to exposure to occupational chemicals and risk, which was highlighted in section 3.3.

The process for pesticide approval in the EU is to ensure that exposure will be below levels where there is any adverse health effect; it is solely health-based. (Regulators involved in carrying out this task well recognise the difficulty of implementing a Directive which essentially asks for proof of no likelihood of ill-health. In contrast, HSE’s approach in setting occupational exposure standards for chemicals are primarily health-based, but allow for technical and economic feasibility i.e. could accept some residual risk. Fairhurst (Fairhurst, 1995) discusses this in terms of uncertainty factors and risk.

Therefore substitution of those chemicals with their respective working practices which meet the pesticide approval or similar veterinary medicine worker safety process cannot be based around simple comparison of possible health-risks to the worker. It must involve other key drivers such as risk to the environment and efficacy of treatment.

We would emphasise that for some workpractices, such as pour-ons, risk assessments have not been done or are considered weak due to the lack of exposure data. There seems to be similar problems with risk assessments for the ‘off label’ techniques that are increasingly being used in the UK. For example, substitution of diazinon when used in a plunge dip by an SP-based jetting technique on simple grounds of the ‘lower human toxicity of SPs relative to OPs’ would move us from a position of ‘certainty’ about worker safety to a position where little could be presented in terms of evidence of safety.

11.2 Consideration of the need for cost benefit analysis.

The rationale for undertaking cost-benefit analysis would be, as we understand, if;

• there was a case for banning the remaining OP sheep dip, on the grounds of acute, short-term ill-health, in favour of other ectoparasite treatments or,
that there was a case for enforcing, as reasonably practicable, the adoption of working practices which go beyond those which are currently considered good practice.

In our view neither of these conditions are sustained and we consider cost-benefit analysis is not appropriate. The reasons for this view are below.

Within the worker-safety framework of the precautionary approach adopted in the UK for granting approval/marketing authorisation for pesticides dipping undertaken by farm workers with diazinon meets the criteria in relation to short-term ill-health. Because of the current lack of exposure data needed to carry out a risk assessment, we cannot comment on whether the criteria are met for contract workers. As such, in our view, on the basis of current scientific understanding, there is not an acute health-based case for banning diazinon dips in favour of alternative chemical means of ectoparasite control. However, we consider it essential that data is gathered to enable an assessment of the risks to contract workers to be made.

From field studies of sheep dipping there is obvious continued scope for improving control of exposure to OPs and other active ingredients. However, this is related to trying to improve compliance with the substantial amount of guidance already given by HSE and other bodies (government and non-government). The control measures described in the published guidance have been regularly reviewed and describe measures currently considered to be good practice. Similarly, there is scope for reducing the need for, and frequency of usage of, chemical methods for sheep ectoparasite control. However, this is in relation to measures which we understand may be considered to be current good-practice. Again there is no case for attempting to go beyond the identified current good practice.

No consideration has been given to the suggested longer-term ill-health effects associated with OPs as this was outside our remit.
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<table>
<thead>
<tr>
<th>Acetylcholinesterase or AChE</th>
<th>The enzyme found in nerve endings, the proper function of which is critical to the proper transmission of nerve signals. Same enzyme also found in the membranes of red blood cells.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACP</td>
<td>Advisory Committee on Pesticides</td>
</tr>
<tr>
<td>Active ingredient or a.i.</td>
<td>The ingredient in a veterinary medical product which has the medicinal properties or the ingredient in a pesticide product which kills the pest.</td>
</tr>
<tr>
<td>Acute Toxicity</td>
<td>In this report, acute toxicity is used to describe effects occurring over a short period of time (hours or a few days) immediately following exposure. This follows the definition used by Committee on Toxicity (COT, 1999).</td>
</tr>
<tr>
<td>Adverse effect</td>
<td>A level of functional impairment or damage to organs in the body that is considered to increase the likelihood of ill-health</td>
</tr>
<tr>
<td>ALARP</td>
<td>As Low as Reasonably Practicable</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Refers to the property of a chemical to cause inhibition of the enzyme acetylcholinesterase</td>
</tr>
<tr>
<td>AOEL</td>
<td>Acceptable operator exposure level. Term defined within the EU directives defining the approval of plant production products (pesticides). Defined as a systemic dose below which no adverse effect or ill-health will occur.</td>
</tr>
<tr>
<td>Biological Monitoring</td>
<td>Biological monitoring is the measurement of the amount of a hazardous substance or its metabolites in a person’s blood, urine or breath. This amount is used as an indicator of that person’s exposure.</td>
</tr>
<tr>
<td>Biological Effect Monitoring</td>
<td>Biological effect monitoring is the measurement and assessment of early biological effects caused by absorption of chemicals e.g. measuring plasma and erythrocyte cholinesterase activity in workers exposed to organophosphate pesticides.</td>
</tr>
<tr>
<td>Cholinesterase</td>
<td>Often used to describe an enzyme which is found in blood plasma and is distinct from acetylcholinesterase found in nervous tissue and red blood cells. Cholinesterase in plasma is inhibited by OPs but such inhibition does not have any known direct relevance to ill-health</td>
</tr>
<tr>
<td>Chronic Toxicity</td>
<td>In this report, chronic toxicity is used to describe effects of long duration. This follows the definition used in (COT, 1999).</td>
</tr>
<tr>
<td><strong>COSHH</strong></td>
<td>Control of Substances Hazardous to Health Regulations, 1994.</td>
</tr>
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<td>-----------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>COT</strong></td>
<td>Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Department of Health:</td>
</tr>
<tr>
<td><strong>critical effect</strong></td>
<td>The first adverse effect that occurs in a toxicity study as the dose increases or the most relevant and sensitive response measure for a particular chemical exposure</td>
</tr>
<tr>
<td><strong>CVMP</strong></td>
<td>Committee for Veterinary Medicinal Products</td>
</tr>
<tr>
<td><strong>DEFRA</strong></td>
<td>Department of the Environment, Food and Rural Affairs.</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>That amount of a toxicant taken in during the course of exposure be it by inhalation, ingestion or dermal routes. The term ‘systemic dose’ is often used order to completely distinguish from exposure.</td>
</tr>
<tr>
<td><strong>Ectoparasites</strong></td>
<td>Parasites which live on the surface of the host animal and are dependent on one or several characteristics of a host to complete the parasites’ own life-cycle.</td>
</tr>
<tr>
<td><strong>Ectoparasiticides</strong></td>
<td>Products used to control ectoparasite infestations.</td>
</tr>
<tr>
<td><strong>EMEA</strong></td>
<td>European Medicines Evaluation Authority</td>
</tr>
<tr>
<td><strong>Endoparasites</strong></td>
<td>Parasites which live within the body of the host animal at some period during their life cycle</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td>Amount of toxicant likely to available for uptake by a worker be it by inhalation, through the skin, or ingestion.</td>
</tr>
<tr>
<td></td>
<td>Potential dermal exposure refers to the amount of toxicant deposited (from air, splashes or contact with contaminated surfaces) on outer layers of clothing, be it protective or otherwise</td>
</tr>
<tr>
<td></td>
<td>Actual dermal exposure refers to the amount of toxicant deposited on the skin.</td>
</tr>
<tr>
<td><strong>Good Laboratory Practice</strong></td>
<td>The application of standardized, organizational processes and conditions under which laboratory studies are planned, performed, recorded and reported for the non-clinical testing of chemicals for the protection of man, animals and the environment.</td>
</tr>
<tr>
<td></td>
<td>It is set out in European Community law and implemented in the UK under The Good Laboratory Practice Regulations 1997.</td>
</tr>
<tr>
<td><strong>Hazard</strong></td>
<td>Hazard is a situation or a substance with the potential to do harm to people or damage to something that they value.</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>HSC</td>
<td>Health and Safety Commission</td>
</tr>
<tr>
<td>HSE</td>
<td>Health and Safety Executive</td>
</tr>
<tr>
<td>HSW Act</td>
<td>Health and Safety at Work Etc. Act, 1974</td>
</tr>
<tr>
<td>incidence</td>
<td>The ratio of the number of new cases over a period of time to the population exposed.</td>
</tr>
<tr>
<td>LC\textsubscript{50}</td>
<td>The concentration of a chemical causing death to half of a group of animals, fish, etc exposed to that concentration for a specified time period.</td>
</tr>
<tr>
<td>LD\textsubscript{50}</td>
<td>The dose (amount) of a chemical causing death to half of a group of exposed animals.</td>
</tr>
<tr>
<td>MAFF</td>
<td>Ministry of Agriculture Fisheries and Food- now see DEFRA</td>
</tr>
<tr>
<td>MEL</td>
<td>Maximum Exposure Limit - defined under COSHH. It is an atmospheric concentration.</td>
</tr>
<tr>
<td>MHSWR</td>
<td>Management of Health and Safety at Work Regulations, 1999</td>
</tr>
<tr>
<td>NFU</td>
<td>National Farmers Union</td>
</tr>
<tr>
<td>NRA</td>
<td>National Registration Authority for agricultural chemicals and veterinary medicines (Australia). Federal regulatory body in Australia</td>
</tr>
<tr>
<td>MOE</td>
<td>Margin of Exposure- the ratio of the defined NOAEL divided by the exposure estimate. Synonymous to ‘TER’- toxicity exposure ratio, used in the UK for non-agricultural approval process. Historically the term ‘Margin of Safety or MOS’ was also used.</td>
</tr>
<tr>
<td>MRL</td>
<td>Maximum Residue Limit. An MRL is the maximum concentration of residue resulting from the use of a veterinary medicine that is legally permitted or recognised as acceptable in or on food. It is used in determining whether a product meets the criterion of safety for consumers</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No Observable Adverse Effect Level- refers to a highest dose of chemical at which there is no adverse toxicological effect</td>
</tr>
<tr>
<td>NOAH</td>
<td>National Organisation for Animal Health- representative organisation for manufactures of animal health products</td>
</tr>
<tr>
<td>OEL</td>
<td>Occupational Exposure Limit - defined under COSHH</td>
</tr>
<tr>
<td>OES</td>
<td>Occupational Exposure Standard - defined under COSHH</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
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<td>--------------</td>
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</tr>
<tr>
<td>Uncertainty factor</td>
<td>This term is used within risk assessment methodologies to describe factor(s) that are applied in the extrapolation from animal toxicology studies to the human situation. It is synonymous with the term ‘assessment factor’ or ‘safety factor’</td>
</tr>
<tr>
<td>VMD</td>
<td>Veterinary Medicines Directorate</td>
</tr>
<tr>
<td>VPC</td>
<td>Veterinary Products Committee</td>
</tr>
<tr>
<td>pChE</td>
<td>Plasma cholinesterase also known as pseudocholinesterase or butyrylcholinesterase. Enzyme found in blood plasma which is inhibited by OPs, but has no obvious toxicological significance unlike AChE</td>
</tr>
<tr>
<td>PSD</td>
<td>Pesticide Safety Directorate - agency of DEFRA formerly MAFF.</td>
</tr>
<tr>
<td>Risk</td>
<td>Risk is the likelihood of a given degree of harm being suffered or damage being realised.</td>
</tr>
<tr>
<td>SARSS</td>
<td>Suspected Adverse Reactions Surveillance Scheme</td>
</tr>
<tr>
<td>Signs</td>
<td>Effects or changes in a subject that can be discerned by observation or clinical examination</td>
</tr>
<tr>
<td>SP</td>
<td>Synthetic Pyrethroid</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Effects or changes reported by, or perceived by the subject</td>
</tr>
<tr>
<td>Toxicant</td>
<td>Chemical capable of causing injury or adverse effect in a living organism</td>
</tr>
<tr>
<td>Toxicity</td>
<td>The ability of a substance to cause injury or an adverse effect in a living organism.</td>
</tr>
<tr>
<td>Toxicology</td>
<td>The study of the nature and capability of chemicals to cause injury or adverse effect. Often refers to the body of data collected from investigative studies on the effect of various doses of a chemical on animal species.</td>
</tr>
<tr>
<td>OP</td>
<td>Often used as a generic term for organophosphorus compounds which can inhibit acetylcholinesterase. In fact it should be noted that not all OP chemicals inhibit acetylcholinesterase.</td>
</tr>
<tr>
<td>OPs</td>
<td>Official Group on Organophosphates- a government interdepartmental forum</td>
</tr>
<tr>
<td>PSD</td>
<td>Pesticide Safety Directorate - agency of DEFRA formerly MAFF.</td>
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<tr>
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</tr>
</tbody>
</table>
APPENDIX A: THE PRECAUTIONARY PRINCIPLE

The Precautionary Principle was initially developed in the context of safeguarding the environment. In the Rio Declaration, which was adopted by governments at the United Nations Conference on Environment and Development in 1992, the principle was stated as follows:

‘Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation’.

The principle has since been used more widely, particularly in considering the potential for harm to people, and to animals or plants as well as the broader environment.

The manner in which the European Commission applies, or intends to apply, the precautionary principle is outlined in (European Commission, 2000). This communication notes the ongoing debate both within the European Union and internationally on how and when to use the precautionary principle and states that its aim is to provide input to this debate ‘but does not claim to be the final word’. Points made include the following:

• ‘where there are reasonable grounds for concern that potential hazards may affect the environment or human, animal or plant health, and when at the same time the available data preclude a detailed risk evaluation, the precautionary principle has been politically accepted as a risk management strategy in several fields’;

• ‘the precautionary principle, which is essentially used by decision-makers in the management of risk, should not be confused with the element of caution that scientists apply in their assessment of scientific data’;

• ‘a decision to take measures without waiting until all the necessary scientific knowledge is available is clearly a precaution-based approach’; and

• one of the European Commission’s aims in the communication is to ‘avoid unwarranted recourse to the precautionary principle, as a disguised form of protectionism’.
APPENDIX B: APPROVALS/MARKETING AUTHORISATION FOR VETERINARY MEDICINES

This appendix gives details of the following aspects of the marketing authorisation procedure for veterinary medicines:

- the role and membership of the VPC;
- the legislation, procedures and authorising bodies involved;
- the three criteria of safety, quality and efficacy upon which marketing authorisation is primarily based; and
- the aspects of the user risk assessment required from applicants for marketing authorisation which are specified in the European Commission guidance and legislation.

B1. The role and membership of the Veterinary Products Committee

The VPC is the Advisory Committee which provides expert opinion to Ministers with respect to the safety, quality and efficacy of veterinary medicines. It is on the basis of this advice, where appropriate, that decisions on approving and licensing products are taken. The VPC is a statutory body constituted under Section 4 of the Medicines Act 1968.

The members of the VPC are independent and are appointed on the basis of their expertise in disciplines relevant to human and animal health or the environment together with two lay members. (The members are listed in the VPC’s Annual Reports - see for example (Medicines Act 1968 Advisory Bodies, 1999).) Part of the remit of OGOP has been to consider whether the collective expertise of the members of the VPC and its supporting panels (as well as other advisory committees related to OPs) was in line with that needed to bring specialist views relating to OP products to bear on all questions where Ministers might need them. The outcome (OGOP, 1998) was recommendations to extend the range of expertise on aspects of public health, namely:

- the appointment to the VPC of an occupational health expert;
- the appointment to the VPC’s Medical and Scientific Panel (on which the VPC depends heavily regarding human health issues relating to OP products) of an epidemiologist, a toxicologist, and an expert on occupational health or occupational hygiene to supplement the expertise of officials; and
the appointment to the VPC’s Human Suspected Adverse Reactions Appraisal Panel of an expert in occupational health or occupational hygiene, and giving consideration to also adding a medical epidemiologist and a clinical neurologist.

B.2 Legislation, procedures, and authorising bodies

The procedures for authorising the marketing of veterinary medicines in the UK are summarised in two available publications (VMD, 1997; OGOP, 1998). Product licensing was introduced under the UK Medicines Act 1968. From 1 January 1995 licensing was replaced by approval/marketing authorisation controlled under European Community law which is implemented by the UK Marketing Authorisations for Veterinary Medicinal Products Regulations 1994. The relevant European Community directives and regulations are set out in (European Commission, 1998a).

Essentially, an application for marketing authorisation for a veterinary medicine product is made to the regulator by the manufacturer. The manufacturer prepares an Application Dossier consisting of administrative information and a demonstration that the three criteria of quality, safety and efficacy (described below) are met. Marketing authorisation of the veterinary medicine product is then subject to an assessment of the product’s safety, quality and efficacy by the regulator. There are three procedures by which for marketing authorisation may be granted:

- the Centralised Procedure where evaluation of the application is by the EMEA giving marketing authorisation valid in all member states;
- the National Procedure where evaluation of the application is by a National Authority giving marketing authorisation in a single member state; and
- the Decentralised Procedure allowing ‘mutual recognition’ whereby following authorisation is by a single member state, National Authorities in other member states can recognise that approval and give approval in those member states.

The EC Committee for Veterinary Medicinal Products (CVMP) advises EMEA on authorisations under the centralised procedures.

The UK National Authority for marketing authorisation is the Veterinary Medicines Directorate (VMD), an Agency of the Ministry of Agriculture Fisheries and Food (MAFF). The VMD carries out a scientific evaluation of the application from the manufacturer, taking advice from independent experts in the Biologicals Committee and Scientific Secretariat where appropriate. Where the application is considered satisfactory and provided it is not for a new active ingredient, or application to a new animal species, or a novel method of application, then marketing authorisation is granted by the VMD. Otherwise, the evaluations are considered at the monthly meetings of the VPC. Appeals by applicants are heard by the VPC or, where the appeal is against the VPC advice, by the Medicines Committee which advises Ministers on all matters relating to human and veterinary products.
Those products which were sold before the introduction of the Medicines Act 1968 were initially exempt from licensing or marketing authorisation procedures. Evaluation was subsequently carried out under a review by the VPC of all veterinary medicinal products available in the UK. For example, this applied to organophosphate sheep dips. The marketing authorisation for a product may be suspended or revoked if new information indicates that an approval is no longer appropriate.

**B.3 Three criteria: quality, safety and efficacy**

The criteria which must be met for marketing authorisation to be granted are set out in European Commission legislation and guidance. Under EEC Regulation No. 2309/93 it is stated that ‘in the interest of public health it is necessary that decisions on ... authorisation ... should be based on the objective scientific criteria of the quality, the safety and the efficacy of the medicinal product concerned to the exclusion of economic or other considerations’. It is further explained (European Commission, 1998b) that the ‘primary purpose of any rules governing medicinal products is to safeguard the public health. However, this objective must be achieved by means which do not hinder the development of the pharmaceutical industry or trade in medicinal products within the community’.

The criteria for quality, safety and efficacy are outlined in box B1.

Where the product is for use on food producing species, marketing authorisation is also subject to a full or provisional Maximum Residue Limit (MRL) having been established by the CVMP for the active ingredient.

**B.4 The user risk assessment**

Directive 81/852/EEC states that the safety documentation within the Application Dossier shall show ‘the potential risks which may result from the exposure of human beings to the medicinal product, for example during its administration to the animal’ and must give ‘a thorough discussion of any risks for persons preparing the medicinal product or administering it to animals, followed by proposals for appropriate measures to reduce such risks’.

Further details on the information required in the Application Dossier is detailed in a Notice to Applicants (European Commission, 1998c) referred to later as the Notice. This is not a legal document but rather guidance presenting the harmonised views of the Member States on how the legal requirements may be met. The term ‘user safety’ is used to cover exposure to people through administering the medicine, handling treated animals, bystanders etc.
Three Criteria: Safety, Quality and Efficacy

1. Safety

All veterinary medicines must be capable of being used safely and without causing harm:

- to the animal being treated;
- to the people making, handling or administering medicines or handling treated animals;
- to the consumer of food products derived from treated animals; and
- to the environment.

2. Quality

All veterinary medicines must be manufactured in suitable licensed premises with:

- ingredients of appropriate purity, in the correct proportions and correctly processed;
- appropriate quality control procedures;
- containers that are robust with secure closures; and
- labelling that is accurate and informative.

3. Efficacy

All veterinary medicines must be effective:

- against the specified disease in the named species of animal;
- at the dose rate, frequency and duration of treatment recommended; and
- by the route of administration specified.

Box B1. Summary of the criteria of quality, safety and efficacy based on that in (VMD, 1997).

The applicant is asked to present Safety Documentation which includes a demonstration of the potential risks to user safety. This should give coverage of:

- toxicity,
- exposure, and
- risk management proposals such as protective clothing.
Box B2 reproduces the complete list of user safety information specified. It can be seen that the risk assessment includes evaluating the risk in order to reach conclusions including risk management proposals. It can also be seen that while the Notice indicates important elements of the risk assessment, such as identifying the end user, it does not specify how the risk assessment should be carried out, rather this is left to the judgement of the applicant and the expert. (In addition to the term ‘risk assessment’ the Notice also refers to ‘demonstrating risk’, and ‘assessment of the hazard’. The distinction between these terms does not appear to be defined.)

In addition to the Safety Documentation, the Application Dossier should include a Safety Expert Report, prepared by an expert, which includes ‘comment on the outcome of the applicant’s user risk assessment including the adequacy of any proposed warnings’. The expert also lists relevant studies or published papers together with a summary and their comments on its quality and interpretation of results, gives comments on the importance of flawed or missing studies and the relevance of the substance tested to the final product, and specifies any additional studies which they may consider necessary.

The Notice also specifies that studies submitted to demonstrate safety of chemicals to man should be conducted and reported in accordance with Good Laboratory Practice (GLP).

In the same way that the Notice does not seek to specify how the user risk assessment should be carried out by the applicant, the approach to be used by either the EMEA or National Authorities, in evaluating it is not prescribed.
User Safety

An assessment of the hazard presented by the product for users should be presented, incorporating the following aspects:

1. An appraisal of the inherent toxicity or other harmful effects such as flammability of the active substance or other components, including, as appropriate, studies on:
   - skin irritation
   - eye irritation
   - skin sensitisation
   - percutaneous toxicity, including in vitro absorption studies
   - inhalation toxicity
   - known adverse reactions to similar products

2. An appraisal of the exposure of the user, or others who may come into contact with the product, e.g. animal handlers, children, etc. in relation to the pharmaceutical form of the product and method of administration:
   - route and degree of exposure, e.g. inhalation of vapours and dusts (including information on particle size analysis and dust generation during typical usage); skin contact (including splashing and handling animals after application); ingestion (including accidental/deliberate misuse); and accidental self-injection
   - frequency of use and volume used on each occasion
   - identification of the end user, e.g. vet, farmer, small animal owner
   - worst case calculations may be helpful in assessing the potential risk

3. Conclusions including risk management proposals regarding, as appropriate:
   - contraindications and safety warning phrases
   - handling technique
   - other methods of controlling user exposure, e.g. engineering methods such as dust, vapour or gas extraction and packaging, such as appropriate pack sizes and special closures
   - protective clothing
   - action to be taken in the event of accidental exposure, e.g. self-injection, ingestion, etc.
   - advice to doctors
   - Occupational Exposure Limits (OELs) - if these have been set
   - sufficient information to enable the user to do a risk assessment, if applicable

Box B2: The User Safety Details Required in the Safety Documentation within the Application Dossier for Marketing Authorisation (European Commission 1998c).
APPENDIX C: APPROVAL FOR MARKETING OF PESTICIDES AS PLANT PROTECTION PRODUCTS (PPP) IN THE EUROPEAN COMMUNITY.

Much of this annex is taken from the report ‘Recommended Method For The Establishment of Acceptable Operator Exposure Levels (AOELS)’ August 2000 prepared under the FAIR programme of the EU 4th Framework programmes for research (ICPS, 2000). Authorship included staff from ICPS (Italy), TNO (Netherlands), IEH (UK), GSF (Germany) and FIOH (Finland). We are grateful to Prof. Len Levy for supply of the final report and discussions on the subject.

Introduction

Pharmaceuticals, biocides, pesticides and general chemicals occupationally encountered are all regulated within the EU. This regulation is in terms of either an approval process for their use, or for the case of general occupational chemicals in terms of risk management in controlling exposure. The approval scheme for plant protection products is described below.

Increasingly this EU system is superceding existing national systems for pesticide approvals or national systems are being integrated into the EU system. The EU approval process lays down an harmonised general approach that considers the efficacy and risks to plants, human and animal health and the environment.

The Process

The Council Directive 91/414/EEC of July 1991 provided the framework for the regulation of pesticide composition, marketing and use, to protect human health and the environment. The Directive aims to provide for a harmonised system in the EU for the authorisation and marketing of agricultural pesticides. The driving force for harmonisation is to ensure a high level of protection for human health and the environment, while preventing unnecessary barriers to trade in agricultural pesticides and plant products.

Three target groups of the population are identified for protection; pesticide operators, re-entry workers and bystanders. “Bystanders” covers a heterogeneous population which may include incidentally exposed people or residents who live in proximity of treated crops. Groups who may be particularly susceptible to pesticide toxicity, such as infants, children unhealthy subjects and the elderly, may be considered as part of the “bystander” category.

The EU community maintains a list of active substances (a.s.) which must meet certain requirements especially with regard to human health and the environment for their inclusion. This list, which is termed Annex I (Directive 91/414/EEC), defines those a.s. which can be part of any pesticide products regulated by individual member states. Applicants seeking inclusion of an a.s. on Annex I must supply a dossier of information to allow evaluation of potential risks to human health and the environment. The information required is detailed in Annex II of Directive 91/414/EEC. A further set of information detailed in Annex III is required for at least one preparation of the a.s. in order to evaluate the efficacy and risks of the a.s. in practical use. Annexes II & III have been amended since 1991 in defining better the data requirements and tests methods. Inclusion on Annex I for an a.s. depends on the central decision-making of the Standing Committee on Plant Health, but appraisal of the dossier for a specific a.s. and rapporteur to the Standing Committee is carried out by a member state.
Directive 91/414/EEC and the subsequent 94/79/EC concern themselves with the data necessary to establish an AOEL (Acceptable Operator Exposure Level) defined as the maximum amount of a.s. to which the operator may be exposed without any adverse effect. An AOEL applies to operators re-entry workers and bystanders. Directive 91/414/EEC states that no authorisation for an a.s. or PPP should be granted if the estimated operator exposure, according to the proposed conditions for use, exceeds the AOEL.

Member states are responsible for authorising pesticide products which contain one or more of the a.s. included in Annex I of 91/414/EEC. Applicants seeking authorisation for such as plant protection product (PPP) must submit a dossier of information to support the application under Annex III as noted above. Directive 94/79/EC specifies that data on exposure must be provided to permit an assessment of the extent of exposure to the a.s. and other toxicologically relevant compounds in the product likely to occur under proposed conditions of use. An estimation of operator exposure, using where available, a suitable calculation model must always be made and reported. Actual exposure data must be provided where the risk assessment indicated that a health-based limit value is exceeded or where no appropriate calculation model exists to estimate exposure.

Member states must adhere to a number of Community principles, criteria and data requirements concerning efficacy, risks to plant human and animal health and the environment. These general rules are laid down in article 4 of 91/414/EEC and Directive 97/57/EC which established Annex VI to 91/414/EEC. Member states are required to evaluate operator exposure to the a.s. under the proposed conditions of use including by preference realistic data on exposure or a suitable and validated calculation model. The regulatory framework specifies that the evaluation should take into account the toxicological studies in Annex II of 91/414/EEC and the results of the evaluation including the AOEL.

A PPP may be authorised for an initial ten years if the a.s. is/are listed in 91/414/EEC and when the product is used properly and under normal conditions it is sufficiently effective, has no unacceptable effects on plants, human or animal health or on the environment, including groundwater. A member state receiving a request for authorisation of a PPP already authorised in another member state must allow the marketing of that product in their country, except where it can be demonstrated that agricultural, plant health or environmental conditions are not comparable to those in the member state who granted the authorisation.

Figure C1 details the scheme for authorisation of plant protection products within the EU.

The AOEL plays a pivotal role in the authorisation of PPPs at the stages of inclusion of an a.s. in Annex I by the European Commission and member states and authorisation of specific PPPs containing a.s. on Annex I by individual member states using Uniform Principles laid out in 97/57/EC as Annex VI of 91/414/EEC. While these general rules are laid down, harmonised guidance on specific criteria and procedures to establish AOELs for pesticides in the EU has not yet been officially agreed. A number of initiatives over the years have attempted to ensure an harmonised approach to the establishment of AOELs. In May 1997 UK’s Pesticides Safety Directorate hosted a meeting of representatives from member states’ regulatory bodies and the agrochemical industry which produced draft guidance; a further initiative on producing guidance on establishing AOELs was discussed at Orta (Italy) in March 2000.
Whilst there is substantial agreement of the fundamental process of AOEL setting, there are not unanimous views on some important issues. One contentious issue that remains is that some experts argue for more than one AOEL (up to three) based on the pattern, duration and frequency of operator exposure. The actual setting of the various AOELs is still based solely on the intrinsic toxicity of the a.s. Such an approach is driven by trying to avoid unnecessary conservatism in the overall evaluation. On the other hand other experts are concerned that such an approach may underestimate risk if, for example, extensions of use in some geographical areas from the original agronomic recommendation or use of the PPP by contractors may result in different levels and duration of exposure. Essentially the first approach suggests that the AOEL is established from the toxicology dataset but with consideration of the likely exposure pattern. The second approach suggests that the AOEL is established only on the toxicological data dossier, irrespective of exposure. This latter approach implies one AOEL as a toxicological benchmark to be used in the overall risk assessment process rather than a risk assessment benchmark in itself, which would necessarily include considerations on exposure. Such differences may be reflected in the way the appropriate regulatory authorities within individual member states apply their assessments. Figure C2 attempts to describe the fundamental risk assessment and management process on which there is substantial agreement and the divergence in opinion on AOEL setting.

Key regulatory issues arising from the AOEL approach

The regulatory approach to controlling exposure to pesticides in agriculture differs from that used for chemicals in other occupational settings

- Unlike most other chemicals, pesticides (biocides & pharmaceuticals) are specifically designed to kill or cause harm.
- Limits of occupational chemicals assume an 8-hour average working day and that inhalation is a key route of exposure. Agriculture working patterns are generally not reflected by the 8 hour working day and the dermal route is the major route of exposure.
- It is noted that ensuring the proper use of agricultural pesticides (following labelling instructions, method & timing of application and the use of protective clothing) is often more difficult than ensuring the safe use of chemicals in other occupational settings. Because AOELs are set as part of risk assessment process rather than for risk management purposes, these problems must be recognised and appropriate safety margins built into the AOELs.
- The Uniform Principles for decision-making in Annex VI of Directive 91/414/EEC state that an AOEL must apply not only to pesticide operators, but also re-entry workers and bystanders. It should ensure that an AOEL established in accordance with any associated guidance provides sufficient protection from adverse effects resulting from non-occupational exposure.
- Inclusion of an a.s. on Annex 1 means that it has been demonstrated that the established AOEL will not be exceeded under at least one proposed condition of use for one or more preparation containing the a.s. It is expected that uses for a.s. and PPPs will be extended. An harmonised approach to the establishment of AOELs should provide a framework to ensure adequate protection as proposed conditions of use change.
- It is important to note that AOELs were established for pre-registration risk assessment purposes and not as a means of checking compliance or control for occupational or control
purposes. This is in contrast to Occupational Exposure Limits (OEL) which are set on the assumption that any worker may be exposed in any situation to the substance of concern without the benefit of protective equipment and that the OEL will therefore be part of a control strategy, using monitoring if necessary.

- AOELs take no account of technical or economic feasibility. Standard setting (e.g. OELs) for occupational chemicals in member states often take such factors into account, as well as being health-based.

Figure C1 summarises the regulatory framework for agricultural pesticide approvals in the EU, taken from Report “Recommended method for the establishment of acceptable operator exposure levels AOELs” FAIR PL98-3663. Aug 2000.
**Hazard identification**

The data requirements of Annex II of Directive 91/414/EEC include:

- Toxicokinetic studies which aid the understanding between exposure, internal dose and adverse effects. OECD guidelines and Directive 87/302/EEC describe the necessary studies. The data requirements are usually limited to an oral rat study, although interspecies differences may need to be explored to help in the animal-human extrapolation.
Information on percutaneous penetration, absorption distribution, metabolism and excretion is also important.

- Acute, short-term and long term toxicity studies must include two acute studies using two different exposure routes. Eye and skin irritation and sensitisation are also usually required. Short-term toxicity testing must be based on oral 90 day studies in both rat and dog, but may also include 28 day studies. Repeated-dose studies via dermal and inhalation may be necessary. A long-term oral toxicity study in rats and carcinogenicity study in mouse must always be conducted. It should be noted that while intermittent operator exposure is typical, no such specific data are required in the dataset.

- Mutagenicity and genotoxicity testing are used to predict possible genetic damage in humans, both genetic damage in offspring and carcinogenic effects. The studies used are standardised in-vitro tests and in-vivo tests which are based on the outcome from the in-vitro assays.

- Reproductive effects are assessed by using a multigeneration study in rats over two generations and a developmental toxicity study in rat and rabbit. Reproductive toxicity includes effects on male and female fertility.

- Assessment of neurotoxic effects relies on several acute, short-term, long-term and reproductive toxicity studies in animals. A delayed neuropathy study in accordance with OECD guidelines must be performed for a.s. of similar or related structures to those capable of inducing delayed neurotoxicity, such as organophosphates. It is noted that there is ongoing consideration of enhancements to existing protocols. Concerns relate to the sensitivity of existing tests to detect subtle delayed effects and note has been made that many endpoints incorporated in the current test panels are not specific markers of neurotoxicity.

- Use of human data. According to Directive 94/79/EEC medical data for the recognition of the symptoms of poisoning and data on first aid and therapeutic measured must be submitted. Data may include medical surveillance of manufacturing plant personnel, direct observation of poisoning cases, epidemiological studies, volunteer studies, diagnosis of poisoning, specific signs of poisoning and clinical tests. It is common for the available human database to be considered of insufficient quality and quantity for risk assessment by regulatory bodies. This may be due in part to the regulatory bodies lack of experience in interpreting human data and a lack of understanding about the extent of human data that can be ethically obtained. The report (ICPS, 2000) noted the value that; (a) even limited human data can be in reducing uncertainties involved in interpreting animal studies (b) that basic toxicokinetic and metabolism studies can be generated from field studies or volunteers studies of less than 10 subjects and (c) that relevant toxicological observations in humans can be made that comply with all relevant ethical principles guiding biomedical research.

Extrapolation of the available toxicological data to the human situation is generally necessary because the data is very largely animal-based. Issues that need to be considered include difference in sensitivity between experimental animals and humans (interspecies), differences between individuals (intraspecies) and uncertainty caused by limitations of the toxicological database. In practice, an experimental threshold e.g. a NOAEL from animal studies is divided by specific assessment factors to set AOELs.
Conventional default assessment factors of 10 are used for both the interspecies and intraspecies extrapolations. These account for the often quoted 100-fold reduction or “risk factor” of the appropriate NOAEL to define the AOEL. However, additional assessment factors may be introduced related to (a) the importance of the health consequence related to the critical adverse effect associated with the NOAEL (default 1, in practice vary from 1-10), (b) levels of confidence in the database may cause a change from the default value of 1, (c) significant differences in metabolism dependent on the route of exposure (route-to-route extrapolation), this may lead to a call for further studies or the use of an additional assessment factor to address this uncertainty.

The overall assessment factor is established from multiplication of the separate factors, which are not necessarily independent. There are concerns that this may lead to an overly conservative factor being applied. There has also been some debate that the use of allometric scaling within the inter-species extrapolation and an understanding of the true nature of intraspecies variation, especially for workers, may lead to a reduction of the 10-fold default factors.

Exposure Assessment

For pesticide registration activities, exposure assessment mostly relies on predictions of exposure levels for typical scenarios of exposure based on the use of generic exposure databases. Such general exposure databases are found in the POEM, EUROPOEM, PHED models used to assess worker and bystander exposure. The EUROPOEM expert group have proposed a tiered approach in exposure assessment in the regulatory process:

- first tier- reflects the most conservative approach by using worst case assumptions on everything, including dermal/inhalation absorption and the use of no protective personal equipment (PPE). Comparison of this worst case estimated exposure estimate with the appropriate AOEL estimates the “risk ratio” - this should be below 1 for each route of exposure to pass.
- second tier- if the first tier fails then the effects of PPE on reducing exposure should be considered as well as relevant knowledge on dermal and inhalation absorption. The estimated exposure may again be compared with appropriate AOELs with respect to the risk ratio.
- third tier- The database of exposure data may be small or even non-existent. The estimated exposure in the second tier may also still be above the AOEL. In this case to convince the regulatory bodies a well-designed study is needed to show exposure is below the AOEL under actual use. This should preferably use biological monitoring that is interpretable in terms of human toxicokinetics. The calculated risk-ratio remains the ultimate test for the PPP. A fourth tier for re-entry workers is also available.

Whilst the majority of exposure assessments relies on predictive models, the August 2000 FAIR PL98-3663 report noted that some factors and assumptions within these models are relatively ill-defined and some exposure scenarios have small data sets to base further predictions. For example, the effects of appropriate PPE are assumed to have a default value of 10 for exposure reduction in the EUROPOEM model, but this is not well substantiated. In fact limited studies using biological monitoring data, which can estimate internal absorbed dose,
suggests a much lower protective factor of around two. Exposure assessment for “pour-on” pesticide applications under POEM(UK) is difficult due to the small size of the appropriate database.

Thus predictive models of exposure are widely used in the regulatory process. Field studies may be considered under Annex II, and according to Annex III actual exposure data for the relevant exposure routes must be reported where estimation of operator exposure indicates that the AOEL may be exceeded. Actual exposure data from field studies must also be reported when no appropriate exposure calculation model or no appropriate data are available to do the estimation. Such studies may include biological monitoring. The August 2000 FAIR PL98-3663 report on AOEL setting (ICPS, 2000) suggested that more prominence should be given to the use of biological monitoring as a properly designed biomonitoring study may provide accurate evaluation of the absorbed dose for the specific exposure scenario and also aid further validation of the generic models. Data on the absorbed dose defined from biological monitoring data can be used for comparison with AOEL, which is defined as an internal dose.

Future needs

A number of enhancements in the setting of AOELS and their use in the regulatory process were suggested in the report “Recommended method for the establishment of acceptable operator exposure levels (AOELs)” Aug 2000 FAIR PL98-3663. submitted to DG VI of the EU.

1. Investigate an “intermittent exposure” toxicological model which would more closely resemble the agricultural situation.
2. More attention should be paid to the possibility of route-specific differences in toxicokinetics as most animal data is produced via the oral route.
3. More prominence should be given to the use of the use of human biological monitoring, which may refine exposure predictions, substantially reduce uncertainties in animal-to-man and intraspecies extrapolations and help refine the choice of assessment factors.
4. More mechanistic toxicological studies would help assess the relevance of inter-species extrapolation of critical end-points.
5. Toxicological end-points of the endocrine, immune and neurological systems deserve further study in terms of improved test requirements in Annex II.
6. Currently combinatorial toxicity studies for PPPs containing more than one a.s. are limited to acute toxicity testing. Further investigation of the possible interaction effects of multiple a.s. are needed.
7. Human data if collected properly are relevant for AOEL setting, but seldom available. Epidemiological studies of post-registration monitoring would be useful to demonstrate the presence or absence of effect. This may be extremely useful in the re-registration phase (after ten years), where the validity of the original AOEL can be confirmed.
8. Further investigation of the basis of the assessment (uncertainty) factors and their combination should be carried out to avoid undue conservatism. Factors determining human variability and the possible use of allometric scaling should be further investigated.
APPENDIX D: BRIEF REVIEW OF RELEVANT PAPERS USED IN EXPOSURE ASSESSMENT

1. Review Of Exposure Papers


Occupational Hygiene
This report describes a collaborative study (comprising a pilot study and a main study) undertaken by HSE and the Institute of Occupational Measurement (IOM). The pilot study was undertaken to evaluate and refine a visual assessment proforma which had been developed to record working practices and the extent and duration of workers’ skin and clothing contact with sheep dip. The main study evaluated exposure during sheep dipping operations using diazinon. Fourteen different dipping operations were studied involving 38 individuals. The authors reported that splashing was caused by a variety of factors mainly related to working practices such as the speed of dipping, the method for sheep entering the bath, the interaction between dipping team members and general operator fatigue during long sessions. The use of appropriate protective clothing was generally poor with personal hygiene and standards of housekeeping variable. Hazard perception was reported as being generally inadequate. The authors reported that some workers were visible soaked, particularly paddlers and chuckers, while some helpers were hardly splashed. HSE’s fluorescence method was used to estimate dermal exposure to dip. The technique was in its field trials stage so may have underestimated exposure, particularly that from concentrate. The highest recorded whole body and hands exposure was 720µg on a paddler. Inhalation exposure of six workers was measured during the pilot study and found to be less than the analytical detection limit of the method (<0.01mgm⁻³). The OES for diazinon is 0.1mgm⁻³.

The study suggested that the most important cause of exposure was from handling concentrated dip with direct splashes from working strength dip less important.

The study describes common practices and seems close to a ‘real-world’ study - there are variations in methods of dipping- ‘the primary determinant on variation in methods used for dipping is training, attitude, strength and experience of the individuals carrying out the task’

The authors stated that ‘the evidence that is presented in this report does not point to a high body uptake of organophosphate chemicals by any of those who took part in the study nor to any significant biological effect on the body’ - even though ‘there is clear documented evidence from the occupational hygiene surveys, however, that whilst farmers were aware that they were working with hazardous chemicals when carrying out dipping, their appreciation of the hazard had little effect on practice. Several were soaked in sheep dip by the end of the dipping session’.

Biological monitoring
Urine samples were collected pre-, post-work and following day. Diazinon metabolites were detected in pre-dipping samples from 15 out of 36 people suggesting previous exposure.
Sixteen individuals showed no increase in urinary metabolite levels pre to post-dipping - the remainder ranged from 1 to 56 nmol/mmol. Thirty out of 36 exhibited an increase in metabolite concentration from pre-work to the following morning - ranging from 1 to 146 nmol/mmol the mean was 22.6 and the median 16 nmol/mmol. Urine metabolite levels showed no association between increases in metabolites and particular occupations or dipping bath type. The authors considered individual work practice to be the overwhelming explanatory factor for increased exposure. Medical questions in the questionnaire, conducted at the time of the study, were confined to significant medical problems and skin condition - although the report states ‘none of the participants in the study reported feeling unwell following the dipping session, apart from the subject who developed a skin reaction’.

Blood samples were collected prior to dipping and immediately post dipping. The largest decrease in plasma cholinesterase activity was 14% accompanied by a decrease in red cell cholinesterase of 2%. Even the largest decrease is still within the variation expected within a normal, unexposed population. The largest decrease in red cell cholinesterase was 10% (1 individual) no workers showed a clinically significant (30%) depression.


Occupational Hygiene

This work was undertaken by IOM for NOAH. The study had two phases; the first phase measured exposure using patches on sampling suits a) worn on the outside of protective clothing and b) underneath protective clothing. Subjective assessment of exposure was also undertaken. The second phase used subjective assessment of exposure and biological monitoring of pesticide metabolites in urine and biological effect monitoring of cholinesterase activity in blood of the same individuals. The dips used contained diazinon or propetamphos.

The results from patch and whole suit were presented as microgramme active ingredient per patch or per suit part. If the concentration of active ingredient in the “in use” product is known the results can be expressed as volume of formulation rather than per weight of active ingredient. In this way, the exposure to other active ingredients used in other formulations can be estimated. In order to compare exposures from one sheep dipping operation to another the results are normalised by expressing as contamination per unit time. i.e. the dermal exposure is expressed as ml of formulation per minute. This approach is used by HSE’s Biocides and Pesticides Assessment Unit (BPAU) who supplied the values they derived from IOM’s ‘whole suit worn outside normal/protective clothing’ data. We converted the ‘whole suit worn beneath protective clothing data’ in the same way. This is discussed in more detail in section 6.2.2 where these data are used for prediction of systemic dose.

The results from patches and whole suits worn on top of protective clothing could be considered to be representative of actual dermal exposure where PPE was not worn. The values ranged from 0 to 31.45ml of “in-use” fluid per minute. There were 30 values, the median value was 0.6ml/minute and the 95th percentile value was 2.91 ml formulation per minute.

The results from patches and whole suits worn beneath the protective clothing could be considered to be representative of actual dermal exposure where PPE is worn. The values
ranged from 0 to 0.12ml in-use fluid/minute. There were 30 values, the median value was 0.005ml/minute and the 95th percentile was 0.043ml “in-use” formulation per minute.

The maximum amount of active ingredient on an entire sampling suit worn beneath protective clothing, an indication of the degree of penetration, was 6mg. Although 90% of values for suits were less than 1mg.

Results were from 12 different farms. Seven farms were using a diazinon containing formulation and five using a propetamphos containing formulation. From the information given we calculated the actual concentration of active ingredient in the bath. Diazinon concentrations ranged from 0.05% to 0.2% i.e. a factor of four difference, propetamphos concentrations ranged from 0.002% to 0.1%. Four different dipping methods were used; four short swim baths (approximately 4m), four long swim (approximately 20m), four circular baths with an island and four circular baths without an island.

The duration of dipping varied from 45 minutes to 150 minutes. The mean time was approximately 100 minutes. The dipping rate ranged from 100 to 370 sheep/hour, the mean rate was approximately 200 sheep/hour

**Biological monitoring**

Biological monitoring included both urinary metabolites of diazinon and cholinesterase estimations but on different days to the exposure assessment so the comparison between external and internal exposure is not direct. During the biological monitoring part of this study, compliance with the recommended protective equipment was not as good as in the first exposure assessment part. The exposures and dipping were carried out for longer and splashing scores were also higher so exposure might be higher in the biological monitoring part of the study. This study also produced some urine values for chlorfenvinfos - measured as the dichlorobenzoic acid. The levels found were similar to the ethyl phosphates from diazinon but there is no data on relative metabolism.

The highest urine metabolite concentrations seen were 227 and 138 nmol/mmol (total ethyls). Most showed increases after dipping of <20nmol/mmol (only two >20) with mean increase of 23.6 nmol/mmol creatinine. The two highest values were considered as outliers (but no obvious cause). The levels of metabolites found were similar to the earlier IOM study. This study was unlike the Blachford & Davison (1991) study but like the earlier IOM study in that metabolite levels in pre-shift next day samples were higher than post shift samples. The study speculates about routes of exposure and mentions ingestion as a possibility. In all studies there is not a simple relationship between the characteristics of dipping - number of sheep dipped, bath type, care in concentrate handling, handling sheep, splashing, occupation, brand of dip or personal hygiene. The similarity of results may be due to contamination of unprotected areas e.g. face, hands. The study speculated about inhalation as a route of exposure, although a previous IOM study found little in a small number of air samples. This study found no association between following morning urinary metabolites and concentrate handling.

The cholinesterase results showed no significant (>15% for erythrocyte or >15% for plasma-HSL) depression in cholinesterase.
This study also notes the ‘complexity’ of the dip - including faeces etc and speculated about endotoxins, bacteria etc.

The reported levels of metabolites of chlorfenvinfos were none detected in pre-dip samples and 5 of 14 showed metabolites post dip corresponding to 20 to 47 nmol chlorfenvinfos/mmol.

**IOM 1999 study, 3 phases- (Sewell, 1999; Pilkington, 1999 a & b)**

This study was carried out in summer 1996 and was the first since the sale and supply of dips was restricted to people holding a certificate of competence. It involved one day surveys of 20 dipping sessions involving only diazinon-based dips. Its objective was to develop a model for uptake of organophosphates based on simple task, procedural and behavioural aspects of sheep dipping and to validate the model by comparisons with urinary organophosphate metabolites. The surveys involved observation and recording of activities including the frequency of handling the concentrated dip; the extent and time of contact with dip wash, protective clothing; hand washing; smoking and eating habits and any significant incidents. Urine samples were collected before work, immediately after after work and the following day. Urine was analysed for metabolites of diazinon using a well validated method and internal quality assurance scheme.

**Biological monitoring**

The results of the urine alkyl phosphate analysis from 50 individuals showed that the mean value for total ethyl phosphate metabolites was $18.6 (± 32.9 \text{s.d}) \text{nmol/mmol creatinine}$ in samples collected the following day. The median value was 9 and the maximum value 128 nmol/mmol.

The most important source of exposure was considered to be skin contact with concentrate, mostly on the hands, when handling the concentrate container. The urine metabolite levels increased with increasing handling of OP concentrate. Increased splashing also increased urinary metabolites. The authors considered that eliminating or reducing skin contact with concentrated dip to be essential to improve control of exposure. They thought this could best be achieved by improving the design of concentrate containers, the effectiveness of gloves and the working practices of individuals.

**Rees H (1996) ‘Exposure to sheep dip and the incidence of acute symptoms in a group of Welsh sheep farmers’**

This study looked at 23 sheep farmers and one dipping contractor thought to be typical of hill sheep farming. It used a questionnaire (although it is not clear whether this was self administered) to examine working methods and estimated absorption of OP before, immediately after and six weeks after dipping by measuring plasma cholinesterase, erythrocyte cholinesterase and dialkylphosphate urinary metabolites.

Subjects reported inadequate handling precautions and significant skin contamination with dip. Two men reported underdiluting dip concentrate for use. Both had significant depression erythrocyte cholinesterase after dipping which indicated some absorption, but this did not
reach levels usually associated with toxicity and was interestingly not associated with plasma cholinesterase depressions. It is not clear whether the symptom of these two men were caused by OP exposure. Measurements of dialkyl phosphate urinary metabolites in a single specimen of urine voided shortly after the end of dipping could not be correlated with the assessed individual exposure.

The authors concluded that sheep dipping is strenuous and dirty work and sheep farmers find it difficult to wear personal protective equipment and avoid skin contamination with dip. ‘In this limited study, farmers did not seem to have significant organophosphate toxicity, despite using inadequate handling precautions’

**Blatchford & Davison HSE internal report - 1991**

**Occupational Hygiene**

This study by HSE looked at 43 sheep-dippers on 25 sites. Blood samples were taken for cholinesterase estimations and measurement of blood solvent levels. Urine samples were collected for analysis of dialkylphosphate metabolites. Personal air monitoring using tenax tubes was also carried out as well as some surface contamination monitoring using cholinesterase based patches.

The analysis of blood samples results showed 30 of 37 plasma cholinesterase results were lower than the baseline values but only one depression was at a significant level of 17% and without any reported symptoms of ill-health. In contrast the erythrocyte acetylcholinesterase results showed that 30/37 were higher in the post-dip samples.

A table of symptoms was included at the end of the report. For the dip period under study (and previous dips) symptoms reported by subjects were 20%(47%) headaches, 20%(11%) thirst, 10%(53%) tiredness, 10%(5%) paraesthesiae, 40%(0%) sore throat, 0%(11%) nausea, 0%(5%) vision, 10%(5%) chest symptoms.

In this study 40% of dips used propetamphos and at the time there was no biological monitoring method for this. An attempt was made to look for free propetamphos instead and some was found in two of 19 samples. Of the 24 dippers using diazinon, 8 subjects had no detectable levels of metabolites, one of these had a plasma cholinesterase level depressed by 15% possibly due to previous exposure. Eight people had previous day exposure or were contract dippers. Four cases were reported as having higher diethylthiophosphate, two of whom were father (dipping) and son (collected sheep), and a third was a contractor in contact with dipped sheep. Diethylphosphate (DEP) was found in only 3 subjects, two used Diazadip (not used by others) and two had recently cleaned out old dip from the bath raising the possibility of DEP arising from old oxidised dip. Urine diethylthiophosphate (DETP) ranged from none detected to 87 nmol/mmol creatinine, diethyl phosphate from none detected to 34 nmol/mmol creatinine. There was no relation between symptoms and urine metabolites or cholinesterase activity. The authors reported that the levels of metabolites were ‘10 times lower than those reported in American studies, when no symptoms occurred’. Some general symptoms were reported and the authors speculated about solvents or phenols bacteriostats as the cause. The tenax tubes used for atmospheric sapling detected phenol in the range 0.05 - 4ppm, most results were at the lower end of the range. Other (unquantified) organic substances were also detected.
Stewart P and Fears T (1999) Exposure received from application of animal insecticides, American Industrial Hygiene Association Journal, 60, no 2, 208-212

This study used a fluorescence technique to estimate exposure during use of pour-ons for treatment of ectoparasites on hogs.

The exposure determinants evaluated in this study were the application method, the level of protection from clothing, work practices (poor or not), the volume of a.i., the total volume of a.i/dye/water mixture, application duration.

Apart from pour-ons the techniques assessed in this study are not seen in the UK. They included low and high pressure jetting via a lance supplied from a bulk storage tank and backpack application. There were 10 observations for pour-ons (out of a total of 20 measurements), 8 were less than the limit of detection. The two farmers who became contaminated from use of pour-ons had very high exposures (a.i concentrations of 4716μg and 15036μg). Unfortunately it is not possible to glean from this report what the active ingredient in the pour-on was or its concentration and therefore these values cannot be used for generic risk assessment.

The authors commented that; ‘the method of pesticide application was also important in the exposure levels. Eighty percent of farmers using the pour-on method had no measurable exposure even though the insecticides was in the concentrate form. That no detectable exposure occurred was likely because there should be little aerosolisation of the mixture with this method and therefore little drift or back splash. The two farmers who received measurable exposures had very high exposures, but neither wore what was rated as protective clothing. Thus it appears the insecticide exposure received from pouring the insecticide onto the animal can be low or unmeasurable if the proper protective clothing is worn’.

Most of the exposures during high pressure spraying appeared to come from back splashing or rubbing against wet animals or fences rather than drift.

Analysis of determinant information collected suggested that the pour-on method was associated with larger volumes of a.i, lower total volume and longer application duration's than other methods.

The authors concluded that exposure determinants that may be predictors of exposure are method of application, level of protective clothing and quality of work practices. The pour-on method generally resulted in negligible exposure levels.
APPENDIX E: EXAMPLES OF CALCULATIONS USED FOR EXPOSURE PREDICTION

**TABLE 1**

<table>
<thead>
<tr>
<th>Predicted daily dose from a 4 hour dipping session using diazinon dip with no protective clothing and median body exposure to correct strength in-use dip</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body</strong></td>
</tr>
<tr>
<td>Volume of surface contamination with in-use dip (mls/min)</td>
</tr>
<tr>
<td>(Median value taken from IOM 1994 outside suit)</td>
</tr>
<tr>
<td>Clothing</td>
</tr>
<tr>
<td>Penetration/Transfer (%)</td>
</tr>
<tr>
<td>Actual dermal exposure per hour (ml/hr)</td>
</tr>
<tr>
<td>Total for 4hr day [max from IOM 1994] (ml/day)</td>
</tr>
<tr>
<td>ai concentration (%)</td>
</tr>
<tr>
<td>Volume of ai on body (ml/day)</td>
</tr>
<tr>
<td>Assumed absorption through skin (%)</td>
</tr>
<tr>
<td>Volume of ai in body per day (ml/day)</td>
</tr>
<tr>
<td><strong>Weight of ai in body per day (mg/day)</strong></td>
</tr>
<tr>
<td>(Assumes density = 1 (ie. 1ml = 1g))</td>
</tr>
<tr>
<td><strong>Hands (dipping)</strong></td>
</tr>
<tr>
<td>Total probable contamination to hands of in-use dip (mls)</td>
</tr>
<tr>
<td>(Value taken from Roff et al 1993)</td>
</tr>
<tr>
<td>ai concentration (%)</td>
</tr>
<tr>
<td>ai on hands (ml/day)</td>
</tr>
<tr>
<td>Assumed absorption through skin (%)</td>
</tr>
<tr>
<td>Volume of ai in body per day via hands (ml/day)</td>
</tr>
<tr>
<td><strong>Weight of ai in body per day via hands while dipping (mg/day)</strong></td>
</tr>
<tr>
<td>(Assumes density = 1 (ie. 1ml = 1g))</td>
</tr>
<tr>
<td><strong>Total ai in body from dipping operations(mg/day)</strong></td>
</tr>
<tr>
<td><strong>Hands (mixing and loading)</strong></td>
</tr>
<tr>
<td>Total probable contamination to hands of dip concentrate per handling (mls)</td>
</tr>
<tr>
<td>(Value taken from POEM)</td>
</tr>
<tr>
<td>Typical number of handlings in a four hour day</td>
</tr>
<tr>
<td>Typical ai concentration (%)</td>
</tr>
<tr>
<td>Expected protection from gloves (%)</td>
</tr>
<tr>
<td>(Value taken from POEM)</td>
</tr>
<tr>
<td>Typical ai on hands (ml/day)</td>
</tr>
<tr>
<td>Assumed absorption through skin (%)</td>
</tr>
<tr>
<td>Volume of ai in body per day via hands (ml/day)</td>
</tr>
<tr>
<td><strong>Weight of ai in body per day via hands when mixing and loading (mg/day)</strong></td>
</tr>
<tr>
<td>(Assumes density = 1 (ie. 1ml = 1g))</td>
</tr>
<tr>
<td><strong>Total ai in body from mixing, loading, and dipping operations (mg/day)</strong></td>
</tr>
</tbody>
</table>
Table 2

| Highest predicted daily dose from a 4 hour dipping session using SP dip with protective clothing and 95%ile body exposure to correct strength in-use dip |
|---|---|
| **Body** |  |
| Volume of surface contamination with in-use dip (mls/min) | 0.043 |
| (95%ile value taken from IOM 1994 outside suit) |  |
| **Clothing** | permeable |
| Penetration/Transfer (%) | 5 |
| Actual dermal exposure per hour (ml/hr) | 0.129 |
| Total for 4hr day [max from IOM 1994] (ml/day) | 0.516 |
| ai concentration (%) | 0.02 |
| Volume ai on body (ml/day) | 0.000103 |
| Assumed absorption through skin (%) | 3 |
| Volume of ai in body per day via hands (ml/day) | 0.000003 |
| **Weight of ai in body per day (mg/day)** | 0.003096 |
| (Assumes density = 1 (ie. 1ml = 1g)) |  |
| **Hands (dipping)** |  |
| Total probable contamination to hands of in-use dip (mls) | 18 |
| (Value taken from Roff et al 1993) |  |
| ai concentration (%) | 0.02 |
| ai on hands (ml/day) | 0.0036 |
| Assumed absorption through skin (%) | 3 |
| Volume of ai in body per day via hands (ml/day) | 0.000108 |
| **Weight of ai in body per day via hands while dipping (mg/day)** | 0.108 |
| (Assumes density = 1 (ie. 1ml = 1g)) |  |
| **Total ai in body from dipping operations(mg/day)** | 0.111096 |
| **Hands (mixing and loading)** |  |
| Total probable contamination to hands of dip concentrate per handling (mls) | 0.2 |
| (Value taken from POEM) |  |
| Typical number of handlings in a four hour day | 3 |
| Typical ai concentration (%) | 10 |
| Expected protection from gloves (%) | 90 |
| (Value taken from POEM) |  |
| Typical ai on hands (ml/day) | 0.006 |
| Assumed absorption through skin (%) | 3 |
| Volume of ai in body per day via hands (ml/day) | 0.00018 |
| **Weight of ai in body per day via hands while mixing and loading (mg/day)** | 0.18 |
| (Assumes density = 1 (ie. 1ml = 1g)) |  |
| **Total ai in body from mixing, loading, and dipping operations (mg/day)** | 0.291096 |
### Table 3

Predicted daily dose from a 4 hour dipping session using propetamphos dip with no protective clothing and 95%ile body exposure, no gloves during concentrate handling

<table>
<thead>
<tr>
<th>Body</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of surface contamination with in-use dip</td>
<td>2.91</td>
</tr>
<tr>
<td>(95%ile value taken from IOM 1994 outside suit)</td>
<td></td>
</tr>
<tr>
<td>Clothing</td>
<td>permeable</td>
</tr>
<tr>
<td>Penetration/Transfer (%)</td>
<td>5</td>
</tr>
<tr>
<td>Actual dermal exposure per hour (ml/hr)</td>
<td>8.73</td>
</tr>
<tr>
<td>Total for 4hr day [max from IOM 1994] (ml/day)</td>
<td>34.92</td>
</tr>
<tr>
<td>ai concentration (%)</td>
<td>0.032</td>
</tr>
<tr>
<td>Volume of ai in body per day (ml/day)</td>
<td>0.011174</td>
</tr>
<tr>
<td>Assumed absorption through skin (%)</td>
<td>4</td>
</tr>
<tr>
<td>Volume of ai in body per day (ml/day)</td>
<td>0.000446</td>
</tr>
<tr>
<td>Weight of ai in body per day (mg/day)</td>
<td>0.446976</td>
</tr>
<tr>
<td>(Assumes density = 1 (ie. 1ml = 1g))</td>
<td></td>
</tr>
<tr>
<td>Hands (dipping)</td>
<td></td>
</tr>
<tr>
<td>Total probable contamination to hands of in-use dip</td>
<td>18</td>
</tr>
<tr>
<td>(Value taken from Roff et al 1993)</td>
<td></td>
</tr>
<tr>
<td>ai concentration (%)</td>
<td>0.032</td>
</tr>
<tr>
<td>ai on hands (ml/day)</td>
<td>0.00576</td>
</tr>
<tr>
<td>Assumed absorption through skin (%)</td>
<td>4</td>
</tr>
<tr>
<td>Volume of ai in body per day via hands (ml/day)</td>
<td>0.00023</td>
</tr>
<tr>
<td>Weight of ai in body per day via hands (mg/day)</td>
<td>0.2304</td>
</tr>
<tr>
<td>(Assumes density = 1 (ie. 1ml = 1g))</td>
<td></td>
</tr>
<tr>
<td>Total ai in body from dipping operations(mg/day)</td>
<td>0.677376</td>
</tr>
<tr>
<td>Hands (mixing and loading)</td>
<td></td>
</tr>
<tr>
<td>Total probable contamination to hands of dip concentrate per handling (mls)</td>
<td>0.2</td>
</tr>
<tr>
<td>(Value taken from POEM)</td>
<td></td>
</tr>
<tr>
<td>Typical number of handlings in a four hour day</td>
<td>3</td>
</tr>
<tr>
<td>Typical ai concentration (%)</td>
<td>40</td>
</tr>
<tr>
<td>Expected protection from gloves (%)</td>
<td>0</td>
</tr>
<tr>
<td>(Value taken from POEM)</td>
<td></td>
</tr>
<tr>
<td>Typical ai on hands (ml/day)</td>
<td>0.24</td>
</tr>
<tr>
<td>Assumed absorption through skin (%)</td>
<td>4</td>
</tr>
<tr>
<td>Volume of ai in body per day via hands (ml/day)</td>
<td>0.0096</td>
</tr>
<tr>
<td>Weight of ai in body per day via hands (mg/day)</td>
<td>9.6</td>
</tr>
<tr>
<td>(Assumes density = 1 (ie. 1ml = 1g))</td>
<td></td>
</tr>
<tr>
<td>Total ai in body from mixing, loading, and dipping operations (mg/day)</td>
<td>10.277376</td>
</tr>
</tbody>
</table>
**APPENDIX F: TABLE OF PRODUCTS (at 2000) APPROVED TO TREAT SHEEP ECTOPARASITES**

<table>
<thead>
<tr>
<th>Product Description</th>
<th>Active Ingredient</th>
<th>Concentration</th>
<th>Application Method</th>
<th>Container Size</th>
<th>Dilution/Dispensing Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayticol scab &amp; tic dip</td>
<td>flumethrin</td>
<td>6%</td>
<td>2.5 &amp; 5l</td>
<td>1l</td>
<td>1 litre for each 900 litre water</td>
</tr>
<tr>
<td>Crovec (pour on)</td>
<td>cypermethrin</td>
<td>1.25%</td>
<td>2.5 &amp; 5l</td>
<td>5 - 40ml depending on bodyweight</td>
<td></td>
</tr>
<tr>
<td>Youngs endecto applicator gun</td>
<td>cypermethrin</td>
<td>1.25%</td>
<td>2.5 &amp; 5l</td>
<td>5 - 40ml depending on bodyweight</td>
<td></td>
</tr>
<tr>
<td>Provinsec</td>
<td>amitraz</td>
<td>125g/litre</td>
<td>250ml, 1l &amp; 5l</td>
<td>1 litre in 250l water</td>
<td></td>
</tr>
<tr>
<td>Ecofleece sheep dip</td>
<td>cypermethrin</td>
<td>10%</td>
<td>1, 2, 5l</td>
<td>1 in 500</td>
<td></td>
</tr>
<tr>
<td>Oramec drench</td>
<td>ivermectin</td>
<td>0.08%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmonds gold fleece dip</td>
<td>diazinon</td>
<td>60%</td>
<td>1, 4l</td>
<td>600ml dip to 900l water</td>
<td></td>
</tr>
<tr>
<td>Panomec injection for cattle &amp; sheep</td>
<td>ivermectin</td>
<td>1%</td>
<td>50ml, 200ml, 500ml containers</td>
<td>0.1ml/5kg bodyweight max. size syringe 2.5ml</td>
<td></td>
</tr>
<tr>
<td>Paracide plus</td>
<td>diazinon</td>
<td>16%</td>
<td>2, 5, 10l</td>
<td>1 part dip to 400 part water</td>
<td></td>
</tr>
<tr>
<td>Provenec</td>
<td>cypermethrin</td>
<td>1.25%</td>
<td>5l flexi packs</td>
<td>5 - 40ml</td>
<td></td>
</tr>
<tr>
<td>Robust dip</td>
<td>high cis cypermethrin</td>
<td>10%</td>
<td>1 dip in 400-1000l water</td>
<td>11 dip to 1000l water</td>
<td></td>
</tr>
<tr>
<td>Taktic spray* or dip</td>
<td>amitraz</td>
<td>125g/litre</td>
<td>250ml, 1l &amp; 5l co-extruded bottle with screw cap</td>
<td>1 litre in 250l water</td>
<td></td>
</tr>
<tr>
<td>vector</td>
<td>cypermethrin</td>
<td>1.25%</td>
<td>2.5 &amp; 5l</td>
<td>5 - 40ml depending on body wt.</td>
<td></td>
</tr>
<tr>
<td>Vetrasin pour on</td>
<td>cyromazine</td>
<td>6%</td>
<td>2.5 &amp; 5l</td>
<td>5 - 40ml depending on body wt.</td>
<td></td>
</tr>
</tbody>
</table>

*no details of how should be used as a spray. Hazard warnings; may cause sensitisation by skin contact. Harmful if swallowed. Irritating to eyes & skin.

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APPENDIX G: PERSONAL PROTECTIVE EQUIPMENT

Sheep dipping HSE AS29 (rev2):

The current specifications for the recommended personal protective equipment (PPE) are as follows:

- Face Shield- for use with the concentrate and recommended for use during dipping to protect the head, face and hair from splashing.
- Boiler Suit or similar.
- Bib Apron or waterproof coat - made of nitrile or PVC.
- Wellington Boots.
- Non-lined synthetic rubber gloves (heavy duty gauntlet style PVC or nitrile at least 0.5mm thick and at least 300mm long).
- Waterproof leggings or trousers made of nitrile or PVC.

The AS29 leaflet also gives the following advice regarding the use and maintenance of the recommended personal protective clothing:

- It should be a good fit and should be serviceable,
- Wash concentrate off personal protective clothes immediately as it can penetrate protective gloves and clothing.
- Wash skin if you get a lot of dipwash on it and put on clean clothes and protective clothing.
- Remove and replace damaged protective clothing.
- Avoid touching the surface of protective clothing which may be contaminated with dip chemicals.
- Wear trousers/ leggings over the boots and wear the sleeves of waterproof suits over the gloves and overall sleeves inside the gloves.
- Always wear recommended PPE. Woollen pullovers, tee-shirts and tracksuits do not keep dip off the skin.
• Avoid working with sheep still wet from dipping. If you do have to, wear the recommended PPE.

• In the weeks following dipping, dip residues remain on the sheep. If they must be handled, you should wear coveralls and wellington boots. It is also good practice to wear good quality synthetic rubber disposable gloves. If the sheep are wet you should also wear waterproof trousers and coat.

• PPE manufactured after 30 June 1995 must be CE marked. You must check that it is suitable for dipping. PPE manufactured before June 1995 can be used as long as it gives sufficient protection.

Comments that have been made to the project team on this guidance and the specific issue of PPE include:

The HSE guidance is very comprehensive in its specification of PPE and gives a very detailed description of what should be worn and when. Some of the description has been noted as quite vague. For example, “PPE manufactured before this can still be used as long as it gives sufficient protection.” The worker reading the leaflet is unlikely to know what ‘sufficient protection’ entails. Some concerns have been raised about how effective such written guidance may be in changing health and safety attitudes to dipping across all those involved in the activity. It was suggested that everyone working with or coming into contact with OP sheep dips should undergo at least a basic compulsory training session that includes information about the hazards of working with OP sheep dips, the importance of minimisation of exposure through use of protective clothing, correct use and maintenance of protective clothing and the potential consequences of non-compliance with recommended working practice.

The practicability of wearing the recommended protective clothing during heavy, physical labour, often in warm temperatures seemed to show strong polar attitudes. There were strong arguments from within HSE and veterinary representatives associated with animal healthcare firms, that the recommended clothing was practical, whereas equally strong comment from sections of the farming community presented the counter argument.

The following section examines studies and surveys which have investigated compliance with PPE

**Health and Safety Executive. Field Operations Division. Sheep Dip Survey 1990.**

*Summary:* Visited 25 dipping sites, recruited on a voluntary basis. Examined exposure and absorption of organophosphate dip by operators.

*Relevant Aim(s):*
• To address the need for correct and consistent guidance on protective clothing suitable for sheep dipping. To investigate manufacturers advice on protective clothing and examine equipment issued free by manufacturers.
Findings:

- Manufacturers’ only recommendations for handling of concentrate were to advocate the wearing of protective gloves and faceshield.
- Recommended protective clothing for use with dilute dipped and when handling freshly dipped sheep varied but generally included use of wellington boots and a waterproof bib apron.
- The clothing actually worn by dippers varied from jeans, T-shirt and wellington boots to full protection, including airstream respiratory protective equipment.
- The study found that where boots, coats and leggings are worn that they are generally those used for normal work-wear and not specially designed or purchased for dipping operations.
- Most farmers were found to use gloves of the incorrect type and place them next to the dip concentrate when they have poured the dip, offering the possibility of contamination.

Recommendations:

- Two layers of clothing resists penetration. A single layer does not.
- The study advocates the use of wellington boots and personal clothing (shirt and trousers) covered by: waterproof leggings (polyurethane or nylon) with a fisherman’s smock worn over the shirt; or a boiler suit and apron.
- A face shield should be worn when handling dip concentrate
- Advised eye protection (chemical safety spectacles) during dipping.
- Gloves recommended by manufacturers should be made of nitrile material rather than butyl rubber or neoprene.
- Gloves must be rinsed after use and replaced when damaged.
- There is no need to wear gloves during the actual dipping operation unless a wooden handled dipping stick is used.
- The use of respiratory protection is not necessary during dipping.


Summary:
The study involved detailed surveys from 696 farms and 1800 people. The survey was initiated following indications from HSE inspectors that proper precautions were not being taken.

Relevant Aims:

- Establishing the types of personal protective equipment available and worn.

Findings:

- Practices revealed in the survey demonstrated “a complete disregard for the basic rules for protecting health”.
- Individuals used feet or hands to immerse sheep on 48 of the farms.
- On 353 farms, no faceshield was worn while mixing the dip concentrate.
- Over 60% of establishments did not even possess a faceshield.
- Around 75% of individuals had gloves available but only 50% wore them for dipping.
- Wooden handled dipping poles were used on 460 of the farms.
- On 124 farms, dip was removed from the dip bath using a bucket.
- The latest advice from manufacturers on the personal protective equipment required during dipping goes several steps beyond what the majority of sheep dippers provide and wear.

**Recommendations:**
- If advice in relevant guidance documents is followed then the risk of ill-health from sheep dipping should be reduced markedly.


**Summary:**
Conducted a study of sheep dipping from 1992 to 1993 to assess the adequacy of guidelines for protective clothing and working methods to protect sheep dipping operators against skin exposure to OP sheep dips. The study was comprised of two phases and involved 13 farms.

**Relevant Aims:**
- To establish degree of OP penetration through protective clothing when recommended work practices are followed.
- To determine effectiveness of protective clothing in controlling skin contact and contamination of clothes.
- To determine the body uptake of OP during sheep dipping when recommended working practices are followed.

**Findings:**
- Penetration of insecticide through recommended protective clothing is minimal.
- Individuals sheep dipping frequently resorted to non-recommended working practices and regularly became soaked with working strength dip.
- Poor protection was often caused by incorrect use of protective clothing.
- Incorrect use of protective clothing may be due to a lack of understanding by farmers of how protection is achieved and maintained.
- Wearability of protective clothing is important. PVC garments, as recommended in the 1992 National Office of Animal Health (NOAH) guidelines may be uncomfortable to wear in hot weather and disposable garments are not robust enough for dipping.
- Protective clothing may impose a real physiological burden on the wearer, possibility of heat stress.
- However, the use of the protective clothing as recommended by NOAH in 1992 did result in minimal contamination and can be regarded as adequate if used correctly.

**Recommendations:**
- Substitution of OP with a different insecticide or use of a different application method such as a pour-on or showering should be undertaken carefully so that ‘substitution’ did not pose different human or environmental toxicology problems.
Methods for segregating/ enclosing the dipping process (e.g., mobile dipping facilities) should be further explored.

Improved education and training in the correct use and maintenance of protective clothing is an essential part of any control strategy.

The physiological burden of wearing protective clothing during dipping operations should be investigated. This is imperative in the light of increasing pressure to wear protective clothing during dipping.


Summary:
Fourteen different sheep dipping operations were studied which involved 38 individuals. The study was designed to undertake an occupational hygiene evaluation of sheep dipping practices.

Relevant Aims:
- To conduct a full descriptive occupational hygiene assessment, including video and photographic records, of five major sheep dipping methods to rank the potential for and extent of operator exposure and to establish working practices contributing to this exposure.

Findings:
- Use of protective clothing varied widely between farms and between individuals at farms.
- Gloves were seldom worn.
- Wellington boots were worn by 95% of individuals.
- Waterproof overtrousers were worn by 74% of individuals.
- Only 1 of the 38 individuals wore a face visor when handling the concentrate.
- Condition of protective clothing was mixed.
- Misuse of protective clothing was frequently observed.
- Incorrect removal of gloves and unfastening or removal of jackets were the two most frequent examples of misuse observed.
- At only 2 of the 14 sites sampled was any protective clothing cleaned after use.
- Protective clothing at 12 of the 14 sites is likely to be contaminated when stored.
- Poor understanding of the principles involved in protection were frequently observed.

Recommendations:
- Protective clothing would probably be efficient if worn correctly, maintained in good condition and decontaminated after use.
- Effective training awareness programmes should be instigated to minimise lack of use of protective clothing and misuse of protective clothing.
- Research on the effectiveness of different materials for protective clothing should be considered with the aim of identifying fabrics which could be worn with minimal operator discomfort.

Summary:
Farm personnel from 20 farms were studied during their usual dipping practice. This included an examination of the protective clothing worn; hand washing; smoking and eating habits and any other significant incidents. A total of 60 farm workers were studied. Farms were recruited via telephone calls, personal visits and through the help of farming associations.

Relevant Aims:
- To develop a model for uptake of OPs based on a simple task, procedural and behavioural aspects of sheep dipping and to validate the model by comparisons with urinary OP metabolites during various dipping procedures.
- To identify, where appropriate, methods for the improved control of exposure to OP dips during sheep dipping operations.

Findings:
- The most important source of exposure to OPs was hand contact with the dip concentrate.
- The protective clothing worn by all individuals in the study was assessed as offering less than adequate protection. This was especially the case for gloves when handling concentrate.
- Protective clothing not meeting the HSE recommendations were commonly observed.
- Even where protective clothing is of an adequate quality it may become contaminated by inappropriate use or failure to wash it after dipping.
- Protective clothing is subject to immense wear and tear during dipping operations.
- Gloves were worn by about 50% of individuals handling dip concentrate. None of these gloves were considered to offer good protection each time concentrate was handled.
- Protective clothing was most likely to be worn on the lower half of the body.
- The use of control measures for exposure was patchy, fragmented and variable.
- Based on the sample in this study, it is likely that the protection offered by protective clothing has been underestimated

Recommendations:
- Protective gloves are vital in controlling exposure to OP dips and their efficacy requires further investigations. The protection afforded by different glove types in relation to the different sheep dip products needs particular attention. Wear and tear issues, including break through times in the workplace and the effects of washing also warrant further investigation.
- The importance of hand exposure when handling concentrate suggests container design should be improved.

Summary:
A 1992 survey of 30 farmers in Ireland.

Findings:
- Only 10% of farmers wore gloves while dipping.
- 32% wore a waterproof coat, leggings and wellingtons.
- 26% wore only leggings and wellingtons.
- 32% wore only wellingtons.
- None of the farmers wore the recommended protective clothing when handling the concentrate.
- Recommended clothing may be uncomfortable to wear during dipping but it does prevent contamination.
- Of the 30 farmers surveyed, 18% did not read manufacturers labels on sheep dipping products.


Reviewed various documents and study findings and pointed out that:
- Individuals observed during sheep dipping frequently resort to non-recommended working practices and regularly become soaked with working strength dip.
- Penetration of insecticide through recommended protective clothing is minimal.
- Efficacy of protective clothing is reduced through incorrect use and worker resistance to wearing the full kit.
- Studies have reported that recommended protective clothing is seldom worn.
- Leather belts, watch straps and shoes are a potential source of longer term exposure, as leather absorbs the dip. This has been overlooked.

Recommendations:
- Contamination of sheep dip operators can be prevented by the correct use of protective clothing. Users of sheep dip must be educated to treat OP dips with the greatest respect.
- Adequate point of sale advice is necessary to ensure understanding of safe use and disposal.
- Labelling alone cannot achieve the desired outcome where exposure is concerned.


Summary:
A self-report questionnaire study based on 29 sheep dip workers. The questionnaire included items addressing current level of knowledge about OPs and safe working practices, perception of risk in relation to use of OPs and general attitudes towards risk taking.

Relevant Aims:
• Exploration of the relationship between sheep dippers knowledge and risk perception of OP pesticides, and their observed and self-reported behaviour during dipping.
• To assess whether differences in perception of risk influences compliance with guidance on safe practice.

Findings:
• 32% of respondents do not always wear gloves when handling concentrate.
• 57% of respondents do not always wear gloves immediately after dipping.
• 43% of respondents do not always wear the recommended protective clothing.
• 11% of respondents smoke or eat during the dipping process.
• 11% of respondents do not always wash their hands after the dipping session.
• 33% of respondents do not always clean their protective clothes after use.
• Risk knowledge seemed to be a more important determinant of protective clothing use than did personality. Lack of knowledge about the need to wear appropriate gloves was more evident than for other types of protective clothing.
• Individuals with the highest risk knowledge levels were less likely to eat or smoke during dipping, were more likely to avoid splashes with dilute dip and were more likely to wear gloves.

Recommendations:
• Effective training could be expected to improve risk knowledge which is an important variable in relation to safe handling of concentrate, routes of exposure and effective use of personal protective equipment.
• Such training would be most effective if provided by members of the farmers’ own peer group who have themselves received training on specific topics.

Data Regarding the Use of Protective Clothing from the Veterinary Medicines Directorate’s Annual Appraisal Panel for Human Suspected Adverse Reactions to Veterinary Medicines.

Summary:

The Veterinary Medicines Directorate (VMD) Appraisal Panel for Human Suspected Adverse Reactions (SARs) to Veterinary Medicines produces an annual report of all cases of suspected adverse reactions in humans to veterinary medicines considered during the previous twelve month period. The reports from 1991/1992 to 1995 contain information regarding the use of protective clothing. In the 1995 report, known use of protective clothing in relation to SARs is reported from reports dating back to 1948. The reports detail the use of protective clothing in relation to the outcome category of SAR reported.

SAR outcome categories are as follows:

• Category 1: Clinical signs and symptoms typical of exposure to cited veterinary medicine (formulation) combined with corroborating evidence (e.g. in the case of OP dips, cholinesterase depression).
• Category 2: The balance of evidence based on current knowledge, circumstances, clinical symptoms and signs, or biochemical evidence (where
appropriate) is consistent with ill health due to exposure to the cited veterinary medicine (formulation).

- **Category 3:** There is strong evidence including medical reports that the symptoms are not related to the use of the cited veterinary medicine (formulation).

- **Category 4a:** The reported ill health is not consistent with the known potential ill health effects of the cited veterinary medicine (formulation) given the exposure circumstances, but the implied association cannot be entirely discounted in the light of current knowledge.

- **Category 4b:** The evidence may be consistent with exposure to the cited veterinary medicine being the cause of the reported ill health but alternative explanations/confounding factors were involved. E.g., Pre-existing conditions.

- **Category 5:** Insufficient data were available to make a conclusion on the case. These may include those which are historical reports (often passed to the VMD by a third party), where further information is unavailable/unobtainable, or current reports where follow up data is unavailable/not provided.

**Acute:** Signs and/or symptoms which begin soon after exposure and cease shortly after exposure ends.

**Chronic:** Signs and/or symptoms which persist after single, repeated or long term exposure.

### (1) Report to the Veterinary Products Committee of Appraisal Panel Meetings 1991-1992:

**Use of Protective Clothing:**

Where information regarding protective clothing was available:

- Full protective clothing was worn in 9% of the reported incidents. Full protective clothing comprises waterproof trousers or leggings, waterproof bib-apron or waterproof coat/jacket and rubber gloves.

- Partial or unsuitable clothing was worn in a large proportion of the incidents:
  - no gloves or unsuitable gloves were worn in 25% of reported incidents.
  - no waterproof bib-apron or waterproof coat/jacket was worn in 14% of reported incidents.
  - no waterproof leggings were worn in 8% of reported incidents.

- Protective clothing was not worn at all in 2% of the incidents.

- 32 reported incidents were deemed to be “likely” (to be caused by OP sheep dips) under the categorisation system in place in 1991/1992. Of these:

  - only 3 of the cases wore full protective clothing,
- 20 wore partial protective clothing,
- 3 wore unspecified protective clothing,
- 2 wore nor protective clothing at all,
- there was no information available for 4 cases.

• There were also several incidents where contaminated protective/ personal clothing was not cleaned/ changed from one day or dipping session to the next.

Appraisal Panel 1991/1992 Recommendations:
• Label warnings need to specify when and what sort of personal protective equipment should be worn.
• When the HSE report on dip design is published, wide publicity should be given to the standard of control and protective clothing that should be provided and used. The Panel hopes these standards will be enforced by the appropriate authorities.
• The following protective clothing must be worn when working with OP sheep dips or handling freshly dipped sheep: non-lined synthetic rubber gloves (heavy duty gauntlet style PVC or nitrile at least 0.3mm thick), wellington boots, waterproof trousers or leggings and waterproof coat or bib-apron (made of nitrile or PVC). When handling sheep in the weeks following dipping overalls, wellington boots and gloves should be worn. If the sheep are wet, waterproof trousers and coat should also be worn. Hands and exposed skin should be washed after handling sheep.

(2) Report to the Veterinary Products Committee of Appraisal Panel Meetings 1993:

• Of the 92 reported incidents relating to OP sheep dips:
  - 2% wore full protective clothing,
  - 38% wore partial or unsuitable clothing,
  - 4% wore unspecified clothing,
  - 9% wore no protective clothing,
  - No information was available for 45% of cases.

• Of the 25 Category 2 cases:
  - 2 wore full protective clothing,
  - 12 wore partial/ unspecified protective clothing,
  - 10 wore no protective clothing,

No recommendations regarding use of personal protective equipment were given in the 1993 Report.

(3) Report to the Veterinary Products Committee of Appraisal Panel Meetings 1994:

The Panel considered 82 suspected cases of acute adverse reactions to OP sheep dips of which:
  - 18% wore full protective clothing,
  - 10% wore unspecified protective clothing,
  - 10% wore no protective clothing,
  - 48% wore partial or inadequate protective clothing,
- No information was available for 12% cases
- Use of protective clothing was not applicable to

- Of the 24 Category 2 acute SARs to OP dips:
  - 5 wore full protective clothing,
  - 1 wore unspecified protective clothing,
  - 4 wore no protective clothing,
  - 13 wore partial/ inadequate protective clothing.
  - protective clothing did not apply in 1 case.

Appraisal Panel 1994 Recommendations:
- The Panel noted that more than 50% of reports stated that adequate protective clothing had
  not been worn or that no protective clothing was used. This underlies the need for
  improved working practices during sheep dipping and underpins the need for the Certificate
  of Competence training scheme.

(4) Report to the Veterinary Products Committee of Appraisal Panel Meetings 1995:

The Panel considered 62 suspected cases of acute adverse reactions to OP sheep dips of
which:
  - 13% wore full protective clothing,
  - 13% wore no protective clothing,
  - 45% wore partial/ inadequate protective clothing,
  - 7% wore unspecified protective clothing,
  - 15% provided no information regarding use of protective clothing
  - Use of protective clothing was not applicable in 7% of cases.

- Of the 2 Category 2 acute SARs to OP dips:
  - 2 wore partial or inadequate clothing.
The 1995 Report provided historical information using data from reports received dating back to 1941 to examine the extent of protective clothing reported to be worn by year of onset of suspected adverse reaction (acute and chronic cases). The following figures do not include cases where protective clothing was not specified or was not applicable:

<table>
<thead>
<tr>
<th>Year of SAR onset</th>
<th>Total Relevant SARs</th>
<th>Full Protective Clothing Worn (% of total SARs)</th>
<th>Inadequate Protective Clothing Worn (% of total SARs)</th>
<th>No Protective Clothing Worn (% of total SARs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1948 to 1980</td>
<td>3</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>1981</td>
<td>2</td>
<td>50</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>1982</td>
<td>4</td>
<td>25</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>1983</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1984</td>
<td>7</td>
<td>29</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td>1985</td>
<td>12</td>
<td>25</td>
<td>67</td>
<td>8</td>
</tr>
<tr>
<td>1986</td>
<td>6</td>
<td>0</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>1987</td>
<td>11</td>
<td>18</td>
<td>73</td>
<td>9</td>
</tr>
<tr>
<td>1988</td>
<td>19</td>
<td>21</td>
<td>63</td>
<td>16</td>
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<tr>
<td>1989</td>
<td>17</td>
<td>24</td>
<td>71</td>
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<td>20</td>
<td>35</td>
<td>45</td>
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<td>32</td>
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<td>66</td>
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<tr>
<td>1994</td>
<td>7</td>
<td>0</td>
<td>71</td>
<td>29</td>
</tr>
<tr>
<td>1995</td>
<td>4</td>
<td>0</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>All Years Total</td>
<td>268</td>
<td>37%</td>
<td>65%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Note: Some SARs are not included in the above table as the date of onset was not specified by the reporter.

In 45% of SARs, reporters did not provide any information on protective clothing. The Panel Report points out that the requirements for protective clothing have been refined over the years.

Appraisal Panel 1995 Recommendations:
- Stressed the need for improved working practices during sheep dipping and underpins the need for the Certificate of Competence scheme.

(5) Report to the Veterinary Products Committee of Appraisal Panel Meetings 1996:

The 1996 Panel Report contains little information regarding the use of protective clothing other than to state that of all SARs received related to OP sheep dips:
- Only 7% wore full protective clothing
- Inadequate protective clothing was worn in more than 64% of reports.
Appraisal Panel 1996 Recommendations:

- Since there has been no improvement in the proportion of reports where adequate protective clothing had been worn, the need for improved working practices is re-affirmed. This underpins the need for the Certificate of Competence scheme.


The Panel Reports from these three years do not contain data regarding the use of protective clothing.
APPENDIX H: GUIDANCE AVAILABLE TO FARM WORKERS ON HEALTH AND SAFETY ASPECTS OF SHEEP DIPPING

This appendix examines a range of guidance available to farm workers concerned with health and safety issues in sheep dipping. The guidance examined is produced by two main sources: the Government in the form of information booklets and leaflets and the sheep dip product manufacturers in the form of product labels and information sheets that accompany product purchases.

Government Issue Guidance:

Sheep Dipping AS29 (rev 2) 1998. Health and Safety Executive

This leaflet deals specifically with sheep dipping practices and is issued free of charge to all farms. It contains comprehensive information concerning sheep dipping, including health and safety aspects. It is designed to be used in conjunction with product labels and advises the reader to refer to product labels at various points throughout the leaflet.

In addition to providing information on practical sheep dipping matters, the leaflet informs farm workers of their requirements under the COSHH Regulations 1994 and gives advice on safe disposal with consideration to the environment.

The leaflet takes a step-by-step, COSHH type approach with the first consideration being whether or not the reader actually needs to treat for ectoparasites. Information is provided on alternative methods of treatment such as pour-ons and injectables.

Sheep Dipping AS29 (rev 2) encourages the reader to think about who might be harmed and how this may occur. It also details control measures that might need to be taken including engineering controls and the use of personal protective equipment. The engineering controls and personal protective clothing sections of the leaflet are very comprehensive and include detailed descriptions and diagrams. Advice is also given on keeping records of the action taken and on the safe disposal of spent dip.

Finally, information is given regarding health surveillance should employees become ill, what to do if there is an accident or illness including symptoms of OP and non OP adverse effects. Contact numbers are given for reporting ill health effects associated with sheep dipping.


This free publication covers all aspects of health and safety in agriculture and is not specifically aimed at people conducting sheep dipping.

There is, however, a small section concerning the use of veterinary medicines including sheep dips. This section is very brief but encourages the reader to think about substituting less
hazardous products, using safer application methods such as injectables and pour-ons and safe disposal of the dip. The section also contains occupational health advice regarding washing clothing and skin and refraining from eating, drinking and smoking during dipping and refers readers to label instructions for the use of PPE.

**Veterinary Medicines. Safe Use by Farmers and Other Animal Handlers AS31 1998. Health and Safety Executive.**

The advice given in this information leaflet which is freely distributed is very similar to that given in the HSE's AS29 (rev2) leaflet but is not specifically related to sheep dipping. Indeed, it covers the use of all veterinary medicines that may be used by farm workers or animal handlers. Like AS29, the approach taken is covering the steps necessary to comply with the COSHH 1994 Regulations.

It does not, by its very nature contain information pertaining specifically to precautions that should be taken specifically when dipping sheep but covers the safe use of all veterinary medicines that might be used by farm workers.

There is a comprehensive references list a the back where farm workers can get further specific advice. There are also contact numbers for reporting adverse ill health resulting from the use of veterinary medicines.

**Agriculture: Your Health and Safety Carry Card. IAC(L) 102 1998. The Health and Safety Executive.**

This free carry card, clearly designed to be kept in a wallet or pocket for ease of access is issued to workers in the agriculture sector to provide information on the health risks associated with work in agriculture.

The card contains general information regarding potential health and safety hazards such as noise, vibration, working with animals and working in extreme weather conditions. It also contains brief section on hazardous substances, specifically citing sheep dips as being such. The information provided is very brief but is designed to get agricultural workers to begin to consider health and safety aspects which they may not have done previously.

**Sheep Scab. A Farmers Guide 1999. ministry of Agriculture, Fisheries and Food (MAFF), Scottish Executive Rural Affairs Department, National Assembly for Wales.**

This is a free publication focusing specifically on sheep scab. Since sheep scab is most effectively treated by dipping with OPs or SPs, the booklet is mainly concerned with the appropriate and effective use of these products.

This booklet gives comprehensive information about sheep scab, how to detect it, it's effect on sheep health, how to avoid it by flock management and flock protection techniques and, inevitably, how to treat it.
The booklet gives a brief description of OPs and SPs and points out that they should always be used according to the manufacturer's instructions as they contain highly toxic chemicals. It does not give specific advice regarding the use of PPE or other control measures but does refer readers to COSHH 1999 and the HSE's AS29 (rev2) leaflet on sheep dipping. The booklet also stresses the importance of training for the safe use and disposal of sheep dips and gives information for the reporting of suspected adverse reactions.

**Use Sheep Dips Carefully! 1993. MAFF/VMD.**

This single-sided poster was distributed nationally to all sheep farmers. It outlines the precautions that should be taken when dipping.

The information presented by the poster is very limited and it seems to serve the purpose of being a tool to prompt memory of other guidance than a guidance tool in its own right. For example, it informs the reader to wear the protective clothing specified on the label and in the leaflets issued by manufacturers and suppliers. It also refers farm workers to their local HSE office for information regarding COSHH.

**Sheep Dipping (laminated poster)1999. AHDA, BVA, HSE, NFU, NOAH, NPTC, NSA, RPSGB, VMD**

This laminated poster is provided with every sale of OP sheep dip, along with two pairs of protective gloves. It is meant to be displayed somewhere near to where dipping is carried out to aid the memory of those people participating in dipping as to their health and safety requirements.

It is designed to be used in conjunction with the product label information and the first point made on the advice sheet is that the product label should be read and recommendations made on it complied with. It also refers readers to their sheep dip supplier should they need further information.

This poster stresses good practice but other information must be available and be read for it to be effective. It does pay a great deal of attention to PPE use and contains a diagram of a person correctly dressed for dipping along with supporting text stipulating the correct specification of the PPE.

It also refers dippers to the HSE's AS29 (rev 2).

**Manufacturers Guidance:**

This section covers information sheets, product labels, leaflets and booklets freely distributed by sheep dip manufacturers with sales of their products.
Sheep dip manufacturers were identified through interrogating the Compendium of Data Sheets for Veterinary Products 2000-2001 (NOAH, 2000). Not all companies responded to the request for information but those who did and who provided information are included in this section.

The VMD also provided colour copies of some labels for sheep dip containers.

It is important to note that the labels on OP dips changed after December 2000 as the moratorium on OP sheep dips products was lifted with certain stipulations, one of them being the design of the product container which from the date must be fitted with a tap to release the product into a measuring jug. This was designed to minimise operator exposure.

Manufacturers stress that they do not have any control over the health and safety information that they print on their labels. This is imposed upon them legislatively and concerns have been expressed by the manufacturers over the vast amount of health and safety information that they must now put on product labels. Some feel that such vast amounts of written advice are counterproductive and that users are discouraged from reading it because of the small font required to fit all the information onto the product label.


A comprehensive guide for the safe and effective use of sheep dipping. Contains numerous photographs to accompany and support the text and so appears very reader-friendly. The use of correct PPE is stressed and the then current PPE is demonstrated photographically with text supporting the specifications of the clothing.

The leaflet contains useful practical tips such as the ideal weather conditions to dip in, ideal times of the day to dip, practical issues on getting sheep gathered and into the dip bath and housekeeping for the dipping area. It also contains brief information on the safe disposal of spent dip.

Young's Robust: Leaflet accompanying product purchase.

This is a high-cis cypermethrin sheep dip product (non-OP). The glossy leaflet accompanying the product when purchased contains comprehensive information regarding ectoparasites and directions for use of the product. It also contains a section regarding operator and environmental warnings. The operator warnings are very thorough with separate sections on what PPE should be worn and what precautions should be taken when handling the dip concentrate, when working with diluted dips and freshly dipped sheep and when handling sheep in the weeks following dipping.

There is also a substantial section on environmental warnings, with users being advised to contact the Environment Agency or it's Scottish or Irish equivalent, should they have any doubts or queries.

Readers are also referred to the HSE’s Sheep Dipping AS29 (rev2) guidance.

Coopers have produced this free booklet which is distributed with their OP sheep dip products. It contains a wealth of information regarding ectoparasites: how to identify them, control options and Coopers' product efficacy information. It contains information on product use, including good dipping practice advice.

This booklet contains a section on safety and legislation, citing the Health and safety at Work Act, 1974 and COSHH Regulations 1988, both of which cover the use of sheep dips.

The information given regarding contra-indications, protective clothing, safety precautions and medical advice to users' is highly comprehensive. The print font, however, is extremely small as there is so much information to cover.

**Sheep Dip Product Labels**

Product labels were supplied either by the manufacturers themselves or by the VMD for the following dip products:

* Deosan Fly Dip (OP dip)
* Osmonds Northern Fly Dip (OP dip)
* Nutrivet O.P. Summer Fly Dip (OP dip)
* Paracide Plus Fly and Scab Sheep Dip (OP dip)
* Coopers All Seasons Fly and Scab Dip (OP dip)
* Young's Robust (High-cis cypermethrin dip)

Product labels were also provided by some manufacturers for injectable and pour-on products.

Of these products, the following were on the market during the 2000/2001 season (Compendium of Data Sheets for Veterinary Products 2000-2001. NOAH, 2000):

* Coopers All Seasons Fly and Scab Dip (OP dip)
* Paracide Plus Fly and Scab Sheep Dip (OP dip)
* Young’s Robust (High-cis cypermethrin dip)

The VMS supplied the new labels which came into force in December 2000 for Coopers’ All Seasons Fly and Scab Dip and for Paracide Plus Fly and Sheep Dip. The new information on these labels was associated with the new safety tap and seal extractor tool kit provided with this product.

Information from the VMD states that product labels are currently undergoing a plain English campaign.
Analysis of the labels from various manufacturers shows that they do, indeed, contain very similar advice with slight variations depending on the active ingredients contained within.

The health and safety information content of the labels is highly comprehensive with detailed instructions regarding the fitting, use and removal of the new safety tap, directions for use of the product, preparation of the dip bath, protective clothing (including diagrams) and safety precautions, medical information, etc.

In addition to the new section regarding use of the safety tap and seal extractor tool kit, it is noted that there is also a section, on the then new labels called “directions for use”. This boxed text appears to be far more hard-hitting regarding the pertinence of the health and safety hazards than information provided on the old labels. The directions for use, for example, point out that health and safety information on the label is “for your own safety” and that the product is “dangerous to people, animals and all wildlife large and small, if proper precautions are not taken”. Such information is likely to be effective as it is designed to make the reader feel more personally vulnerable to the potential adverse effects than, for example, is the older advice which states “(active ingredient). is a ORGANOPHOSPHORUS compound. DO NOT USE if under medical advice not to work with such compounds.” This older information immediately excludes anyone who is not under medical advice not to work with such compounds. Inadvertently, it may discourage people who are not under medical advice from reading the further safety information provided as they may not deem themselves to be personally vulnerable.

The new laminated sheet (“Sheep Dipping”) which is now provided with each purchase of OP sheep dip encourages the reader to read the product labels. This, too, however, might be more effective if it made the reader feel that they were more personally vulnerable to the potential adverse effects of OP sheep dip products. If displayed as intended, then all people participating in the dip should see this laminated sheet. This may not be the case with the product label. As such, this sheet, when revised, might benefit from containing information regarding the personal hazards to all involved people, the potential severity of exposure and how this hazard can be reduced by correct use of PPE during dipping. Currently the sheet gives information on wearing protective clothing but does not state why it needs to be worn, other than the fact that sheep dip is absorbed through the skin. Nowhere on this sheet is there any information about the potential danger of OP sheep dip. The words “danger”, “dangerous”, “hazard” or “hazardous” are not used at all.

The importance of making the reader of the label feel personally vulnerable to the potential danger is outlined in the main report. Briefly, the Health Belief Model, which has been substantiated by numerous studies, claims that people will adhere more to health and safety advice if it makes them feel personally vulnerable, if the effects are perceived to be potentially severe, if the return outweighs the cost of compliance and if perceived barriers to changing behaviour are minimal.

**Improvements to Guidance and Labels.**

There are several recommendations for improving the guidance to farm workers that have evolved from past research and from anecdotal evidence:
• Written word format should be minimised where possible
• Consideration should be given to including case-studies in guidance.
• Dissemination of information should involve peers and intermediaries.
• Guidance should make the farm worker feel personally at risk and susceptible. This has been, to some extent, addressed in the new labels.
• Guidance could be more hard-hitting. Farm workers need to know that OPs are a potentially dangerous substance and that the adverse effects could be severe for them.
• Perceived barriers to safe working practices warrant further exploration. These perceived barriers should be addressed in future education, training, guidance and advice.
• Advice should be given in plain English. The VMD are currently addressing this issue for product labels.