Report to the NRA

The relevance to sheep husbandry practices in Australia of the UK Institute of Occupational Medicine (IOM) Report (*Epidemiological study of the relationship between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy, and neuropsychological abnormalities in sheep farmers and dippers)*.

Expert Panel on Organophosphate Sheep Dips

VOLUME II APPENDICES

15 February 2000

VOLUME II APPENDICES

APPENDIX A Membership of the NRA Expert Panel

JG (Jock) McLean, Chair
Yossi Berger (Australian Workers' Union)
Les Davies (Therapeutic Goods Administration)
Jack Dempsey (Therapeutic Goods Administration)
Peter Holdsworth (Agricultural and Veterinary Chemicals Association and Veterinary Manufacturers and Distributors Association)
Roshini Jayewardene (National Occupational Health and Safety Commission)
Robert Kenyon (Workcover Australia)
David Le Couteur (Clinician, Canberra Hospital)
Paul Martin (Veterinary Manufacturers and Distributors Association)
Brian Plane (Wool Council of Australia)
Mike Strong (Agricultural and Veterinary Chemicals Association)

Professor JG McLean: Bachelor of Veterinary Science (Sydney 1965), Doctor of Philosophy (Melbourne 1971), Diploma of Agriculture with honours (Hawkesbury 1959).
Swinburne University of Technology: Pro Vice-Chancellor, Division of Science, Engineering and Design 1994-1997. Professor Emeritus 1997.
Veterinary biochemist and toxicologist
National Health and Medical Research Council: Pesticides and Agricultural Chemicals Standing Committee 1978-1993; Committee on Toxicity 1985-1988
Stock Medicines Board of Victoria 1972-1987
Commonwealth Advisory Committee on Pesticides and Health since 1993
Joint FAO/WHO Expert Committee on Food Additives (Veterinary Drugs) – since 1987, Chair/WHO Chair since 1992.

Dr Yossi Berger works with the Occupational Health and Safety Unit of the Australian Workers' Union (AWU). He is currently editor of "Say Safety", the AWU National OHS Magazine.

Dr Les Davies has a PhD degree in neurochemistry, awarded by the Australian National University based on research conducted at the John Curtin School of Medical Research. Prior to joining the Commonwealth Department of Health as a Senior Toxicologist in late 1982, he had an active research career in biochemical pharmacology, at the Max-Planck Insitut für Biophysikalische Chemie in Germany, the Swedish Medical Products Agency, the University of Sydney, the Roche Research Institute of Marine Pharmacology in Sydney and the Australian National University.

Within the Department of Health he gained broad experience in toxicology within the areas regulating therapeutic drugs and then agricultural and veterinary chemicals. He is currently Manager of the Chemical Review and International Harmonisation Section, which is responsible for conducting toxicology and public health reviews of agvet chemicals under the Existing Chemicals Review Program (ECRP), as well as cooperating in international efforts to harmonise hazard and risk assessment methodologies for chemicals.

He has over 70 research publications in referred journals, in addition to several chapters in books and a number of conference presentations; he discovered (and provisionally patented) a number of pharmacologically active compounds over the course of his research career.

Mr John Dempsey completed his BSc (Hons) in 1974. During 20 years of research into mutagenesis and carcinogenesis he has worked as a Medical Researcher and Research Scientist at the Queen Elizabeth Hospital, Adelaide, the School of Medicine, Flinders University of South Australia, and the CSIRO Division of Human Nutrition, Adelaide. As a mature age student he completed the research for a PhD in the area of radiation and chemical carcinogenesis in 1994. He is currently a senior toxicologist within the Chemical Review and International Harmonisation within the Department of Health. He has broad toxicological experience gained within areas which regulate new and existing agricultural and veterinary chemicals. As a WHO temporary adviser he has been actively involved in international efforts to harmonise cancer risk assessment methodologies for chemicals.

Dr Peter Holdsworth is the Director of Scientific and Regulatory Affairs (Animal Health) for AVCARE which is the national association for crop production and animal health in Australia. Dr Holdsworth has a PhD in parasitology and over 20 years experience in medical and veterinary parasitology in Australia. For the last 15 years he has been involved in R&D of parasitological products for the animal health industry and more recently in the regulatory arena (both government and industry) and animal health products in Australia.

Dr Roshini Jayewardene has an MBBS from the University of Colombo, Sri Lanka. She is currently working in Occupational Medicine in the National Occupational Health and Safety Commission (NOHSC). Dr Jayewardene has been associated with the Agricultural and Veterinary Chemicals Section of NOHSC for the past 7 years and has been closely involved in the NRA’s Existing Chemicals Review Program since its inception.

Dr Robert Kenyon completed a PhD in Physical Chemistry from the University of NSW, a Technical Teacher Education Diploma, Sydney Teachers College, an MBBS from the University of Sydney and a Master Public Health, University of Sydney. He is also a Fellow of the Australian Faculty of Occupational Medicine. He was awarded the NH & MRC Public Health Travelling Fellowship in April-July 1988 and the Australian New Zealand Society Occupational Medicine prize for the Master of Public Health course in 1984. His career includes research, teaching and medical practice. His current position is Senior Occupational Physician with WorkCover NSW. He has been involved in many committees and expert working groups including:

NH & MRC Drugs & Poisons Schedule Committee	1989-present
Reference Group on Health Surveillance - nominee of the Australasian Faculty of Occupational Medicine (AFOM)	1995-present
Occupational Cancer Working Party – (AFOM)	1999-
ICOH Scientific Committee on Pesticides	1996-present

Dr David Le Couteur: MBBS (Hons I), FRACP, PhD, Grad Cert Ed.

Associate Professor at the Canberra Clinical School of the University of Sydney and Director of the Department of Pharmacology and Toxicology at the Canberra Hospital. Member of the Australian Drug Evaluation Committee and Advisory Committee on Pesticides and Health. Research interests include the toxicology and metabolism of pesticides in relationship to the aetiology of Parkinsons disease.

Dr Paul Martin has a B Sc (Hons) degree majoring in genetics and a PhD in Ecological Genetics. During more than 20 years with CSIRO, he undertook research on the genetic and ecological basis of resistance to anthelmintics and pesticides. Dr Martin is presently the Director of Resarch and Development for Virbac Australia and is an advisor to the VMDA.

Mr Brian Plain is executive director of Wool Council Australia. He has an extensive career in the agribusiness sector in consulting, marketing and management with tertiary qualifications in agricultural economics and financial management.

Dr Michael Strong has been employed in the agvet industry for more than 30 years. During that time he has been involved in the toxicology and metabolism of several organophosphate insecticides. A MSc was awarded in 1972 following studies on *in vitro* metabolism systems using diazinon as a model compound. In 1985 he was awarded a PhD for his studies on the physiological impact of acute and chronic fascioliasis on the livers of sheep and cattle. He was an inaugural member of an AVCARE task force established in 1987 to examine the toxicological and environmental impact of sheep ectoparasiticides residues in wool. Currently he is chairperson of this AVCARE Taskforce.

APPENDIX B ***Organochlorines in Australia,* paper presented to the UNEP/IFCS Regional Awareness Raising Workshop on Persistent Organic Pollutants.**

Presentation to the UNEP/IFCS Regional Awareness Raising Workshop on Persistent Organic Pollutants, Bangkok, Thailand, 25-28 November 1997

ORGANOCHLORINES IN AUSTRALIA

presented by
Stanford Harrison
Department of Primary Industries & Energy
Commonwealth of Australia

Introduction

The use of organochlorine (OC) chemicals built up during the 1950's, peaked around 1975 and was largely phased out by 1990. This paper and the accompanying chart present a general history of OCs in Australia - their introduction and removal from use in Australia's agricultural and pest control industries.

The Phase-out Process.

The use of OC pesticides in Australia reduced dramatically between the mid-1970's and the early 1980's. The phase-out process was not just driven by government bans and deregistrations, it was also driven by farmer perceptions that produce containing residues of these chemicals was less acceptable. The rapid reduction in use of these chemicals has led to a problem of collection and disposal of obsolete stocks, particularly stocks remaining on farms.

Alternatives were found for most uses, though these were most difficult to find for uses in Australia's tropical agricultural areas. Use of OCs as termiticides were the last registered uses in Australia, with particular difficulty being encountered in developing effective alternative approaches to preventing subterranean termite attack of buildings.

Chronological History of OC Use in Australia

The following is a chronology of the major events in the use of organochlorines in Australia over the past 60 years.

1939 DDT recognised as an insecticide.
1942 Benzenehexachloride (BHC) developed (includes lindane, which is the gamma isomer).
1944 DDT achieved world prominence when a typhus epidemic in Naples was overcome. 1.3 million people dusted to kill lice. After this, DDT became main agent for control of vectors for many deadly diseases.
1940's Development of chlordane, aldrin, dieldrin and heptachlor
1950's Registration in Australia of DDT, aldrin, lindane, BHC and dieldrin. Expansion of uses of OCs in Australia in agricultural and pest control industries.
1961 National Residue Survey established in Australia, monitoring residues in produce.
1961 Australian Standing Committee on Agriculture recommended that the use of OCs on food producing animals in external applications cease.
1961 and 1962 First OC restrictions in Australia. Registrations for OCs on food producing animals, and poultry ended except for use of DDT against buffalo fly in Queensland (and this use was deregistered in 1975).
1962 Publication of "Silent Spring".

1970 Australian Market Basket Survey commenced and included monitoring of residues in table ready foodstuffs.

By the early 1970s, all OC labels were required to carry cautions regarding application to crops or pastures (including grass clippings) to be eaten by feed-producing animals or poultry. In 1978 the wording was modified to mention the illegality of applying OCs to any soil which might in the future be used to grow produce which could be eaten by humans, food producing animals or poultry.

1972 Report from the Australian Academy of Science entitled "The Use of DDT in Australia". It recommended continued use of DDT where its use clearly outweighed the disadvantages, plus further emphasis on research for alternatives.

August 1972 Australian Agricultural Council recommended that all existing registrations for DDT should be reviewed as a matter of urgency, with a view to withdrawing all uses for which acceptable substitutes were available.

1974 Peak OC registrations and usage.

1970s During the early 1970s the Standing Committee on Agriculture formulated its policy of getting persistent OCs deregistered in all agricultural uses as soon as alternatives were available.

1975-1980 At the start of this period there were very large numbers of pest/commodity agricultural combinations for DDT, BHC and dieldrin; a lesser number for lindane and chlordane; and a few for aldrin.

In 1975, one or more OC-based products were registered for use against pests in a range of crops including most fruit and vegetables, cereals, rice, cotton, sugarcane, tobacco, almonds, macadamia, maize, sorghum, safflower, pasture and pasture seed crops. Other uses were against termites, and around livestock quarters, sheep pens, pig sties, poultry houses and food storage structures.

By the end of 1980, drastic reductions in the number of formerly approved pest/commodity combinations had occurred with corresponding reduction in use of OCs. Those that remained had in every case been carefully scrutinised by registration authorities to see whether continued use was necessary. Continuous pressure was maintained by relevant committees e.g. the Technical Committee on Agricultural Chemicals (TCAC), to reduce approved OC uses.

In 1981, the situation for use of OCs in agriculture was as follows: DDT: registration withdrawn in cotton, a few minor agricultural uses remained. BHC: only sugarcane remained, and it was deregistered in 1985-87. lindane: very few agricultural approvals remained, and they were deregistered in 1985. aldrin: only sugarcane remained of the agricultural uses, and it was deregistered in 1985. dieldrin: only sugarcane and bananas remained of the agricultural uses, and they were deregistered in 1985. endrin: all remaining agricultural applications were deregistered. chlordane and heptachlor: only a few pests on sugarcane were still allowed in agricultural applications, and baiting for termites in tree plantations in tropical areas.

By the end of 1985, virtually every one of the pest/crop/chemical combinations in agricultural applications had been deregistered.

1986 The Drugs and Poison Scheduling Committee reviewed the toxicology of heptachlor, aldrin, chlordane and dieldrin, following which the Public Health Committee recommended that only very limited use of these chemicals be allowed in agriculture, a code of practice be developed for pest control operators.

1987 Report from the Plant Health Committee of the Standing Committee on Agriculture entitled "Soil Insect Pests of Australia: Control Alternatives to Persistent Organochlorine Insecticides", which described alternatives to OCs for soil insect pests.

1987 Commencement of OC stocks recall programs by States/Territories.

May 1987 Food Safety and Inspection Service of thc US Department of Agriculture found DDT residues in Australian beef exports, and dieldrin and heptachlor soon after.

December 1987 Import prohibition on OCs into Australia, unless Ministerial approval had been obtained for each consignment imported.

February 1989 Report entitled "Health, Politics, Trade: Controlling Chemical Residues in Agricultural Products" completed by Australian Science and Technology Council, which looked, among other things, at the problem of OCs as persistent environmental contaminants of agricultural land now appearing as residues in produce.

September 1989 Conference "Organochlorine Residues: Strategies for Management and Research in Australia" held at Ballarat, Victoria.

November 1992 Release of Duggin Report "Cyclodiene Insecticide Use in Australia", which recommended the deregistration of aldrin and dieldrin when remaining stocks were exhausted, and use of chlordane and heptachlor to be continued for non-agricultural uses only pending the development of viable alternatives.

1993 Establishment of the National Registration Authority for Agricultural and Veterinary Chemicals (NRA), which took over the function of assessment and approval of agvet chemicals from pre-existing State bodies.

Jan 1994 NRA report *Use of organochlorines in termite control* published April 1994, recommending the phaseout of OCs used in termite control upon development of viable alternatives.

Jan 1994 Agriculture and Resource Management Council of Australia and New Zealand (ARMCANZ) decision to phase out remaining OC uses by 30 June 1995 (30 June 1997 in Northern Territory in recognition of special circumstances).

30 June 1995 Use of heptachlor and chlordane phased out in all States/Territories except the Northern Territory.

Feb 1997 Decision to extend use of heptachlor and chlordane as termiticides in the Northern Territory to exhaust current stocks and pending research into alternatives.

Nov 1997 Use of all OCs except mirex have been phased out in Australia. Remaining stocks of mirex to be used only for contained baits for termites in plantations of young trees in the Northern Territory, until stocks run out, which is expected in the near future.

Other organochlorine pesticides.

Toxaphene was registered briefly in the early 1960's for control of grasshoppers. Only small quantities used.
Mirex used only as a bait for termites in the Northern Territory.
Hexachlorobenzene (HCB) was used briefly in the 1960's. Only small quantities used.

Conclusion

Organochlorines were widely used in Australia's agricultural and pest control industries during the 1960's and early 1970's, though with initial restrictions on use occurring in 1961. This use fell dramatically during the late 1970's, and by 1981 most agricultural uses had been deregistered except for some tropical and minor uses. Use as termiticides was largely terminated by 1995, with in 1997 a single use of mirex as a localised termite bait remaining till stocks are exhausted. The rapid phase-out has created a problem with stocks of obsolete chemicals, and the search for alternatives has been particularly challenging in some tropical agricultural applications and in termiticide uses.

Acknowledgment

The chart and most of the information presented in this paper were prepared by Mr Richard Game,
Agricultural and Veterinary Chemicals Policy Section, Department of Primary Industries and Energy.

APPENDIX C **Case Report, McKenzie vs Harper and Ors**

Supreme Court of New South Wales

McKenzie v Harper & Ors T/as Allambie Pastoral Co Johnson v Harper & Ors T/as Allambie Pastoral Co Tiedemann v Harper & Ors T/as Allambie Pastoral Co Matter Nos R 400073/93; R 400074/93; R 400075/93 (8 October 1997)

Craig McKenzie v Harper & Ors t/as Allambie Pastoral Company

R400073/93
Robert tJohnson'v Harper & Ors t/as Allambie Pastoral Company
R400074/93
Allan Tiedemann v Harper & Ors t/as Allambie Pastoral Company
R400075/93
8 October 1997
Grove J
The Supreme Court of New South Wales Common Law Division

R400073/93 - CRAIG tMcKENZIE~ v HARPER & ORS t/as ALLAMBIE PASTORAL COMPANY
R400074/93 - ROBERT ~JOHNSON'v HARPER & ORS t/as ALLAMBIE PASTORAL COMPANY
R400075/93 - ALLAN TIEDEMANN v HARPER & ORS t/as ALLAMBIE PASTORAL COMPANY

JUDGMENT

HIS HONOUR: Three actions for negligence have been, by consent, heard together. The plaintiffs were members of a shearing team employed by the defendant partnership on their properties near Ariah Park known as Orana and Allambie. Each alleges that he is suffering from the effects of organophosphate poisoning sustained in the course of that employment

The leader of the shearing team was Bevan (Mick) "McKenzie who is the plaintiff Craig McKenzie's father. He also claimed similar injury and sued the partnership. His action was called on for hearing at the extension of the 1995 sittings of the Court at Wagga Wagga presided over by Master Malpass. The following circumstances can be ascertained from the Master's judgment delivered on 7 September 1995 which I treat, not as evidence in these cases, but as a record of the Court. Applications for adjournment made by the defendant were refused as were orders which would have enabled the reception into evidence of the views of Dr Russell, a scientist at the Division of Wool Technology of the CSIRO. In 1995 a prosecution initiated by Workcover was pending and Kevin Harper (the managing partner of the defendant) declined to answer questions at the hearing of Bevan McKenzie's action on the grounds that his answers might incriminate him. I mention these matters at the outset for two reasons. First, to explain references to "the four shearers" in the context of hearing actions by three plaintiffs and second, to note the significant difference in the evidential content of the current proceedings from the earlier hearing. In this instance Dr Russell and Kevin Harper gave extensive testimony. These are naturally not the only distinctions but the reference is sufficient to make the point of discrimination.

The taking of oral evidence extended over fifteen sitting days. A mass of exquisite detail was examined but there are common threads leading to the nub of the plaintiffs' cases on liability. The shearers were scheduled to commence at the shed on Orana on ~ March 1993. Substantial work was delayed by rainfall which had rendered the sheep wet and therefore unsuitable for shearing. Described by a variety of adjectives, the plaintiffs noticed an offensive smell of a chemical nature emanating from the sheep. They began to notice symptoms adverse to their general wellbeing. Unsurprisingly they did not all describe identical feelings of identical intensity progressing to debilitate them at an identical rate but I accept that each of them was relevantly affected by illness.

Noxious emanation from the flock acquired enhanced intensity by reason of the particularly closed atmosphere at the Orana shed. To an extent it was an outbuilding typical of the Riverina shed of history but it was originally a two stand facility which had been adapted for use by four shearers without any apparent increase in the apertures through which ventilation could pass.

It was the practice at Orana and for a time at Allambie to tar the sheep "on the boards". The tar was a chemical solution prepared by the defendant which was dispensed from its storage drum into a saucepan from which it was applied by a paint brush for treatment of fly blown sheep. "On the boards" expresses the use within the shed rather than outdoors. At some stage tar may have been applied by shaking from a bottle which was fitted with a perforated lid thus being operated as a spray shaker. Whether by paint brush or shaker bottle the cumulative result was that the shearers' clothing became saturated with tar as they manhandled the sheep. In that manner their bodies came to be in extended saturate contact with the chemical virtually day after day.

In due course the team moved to the Allambie shed. It was more modern and I note that the plaintiff Craig McKenzie assessed its ventilation as quite good. Nevertheless the offensive chemical-like smell continued to be detected and the shearers noticed their symptoms becoming acute.

Craig McKenzie suffered increasing headaches. He felt lethargic with general aches and pains. He had a sickness which he located in his stomach and he had diarrhoea and vomiting episodes. A rash erupted in his groin area.

Allan Tiedemann first noticed headaches and watering from his eyes while he was at Orana. His symptoms worsened as time passed. He noticed ill feeling in his stomach which he assessed as probably indigestion or heartburn and he took some antacid tablets. His symptoms were not relieved and he noticed that he was regurgitating bile. He noticed a nasty bitter taste in his mouth and itchiness on the arms, legs and head. A rash appeared on his skin.

Robert Johnson had joined the particular shearing gang in 1992. In the course of working at the defendant's properties he noticed a burning sensation on his skin surface about his hands, face and head. Headache developed and he self diagnosed the onset of influenza. He had stomach and diarrhoea symptoms. He denied vomiting but experienced a bile sensation in the throat which caused him to gasp and dry retch. He felt itches and what he described as more like little sores than a rash emerged.

It may be mentioned that "tarring on the boards" had continued at Allambie until something between a discussion and a confrontation about the presence of the pot of tar within the shed took place and Kevin Harper removed it. Thereafter sheep were tarred when required in the pens external to the shed.

The plaintiffs' claim that exposure to toxin caused the acute illness above described and also caused chronic illness which has destroyed their respective capacities to work as shearers and in a practical sense destroyed their capacity to work in most forms of remunerative occupation.

The foregoing barely provides a hint at why seemingly conventional litigation by employees against employer should involve such extensive hearing. Including its breakdown products the plaintiffs sought to inculpate an organophosphate known as diazinon as the cause of their illness both as to acute and chronic symptoms. Diazinon is extremely widely used in stock and agricultural activity throughout the world. It was revealed in evidence that there is current debate among medical and scientific researchers about the potential for harm, the nature and longevity of consequential symptoms and the causative mechanisms arising from exposure to organophosphates.

That currency was highlighted by peripheral references to claims being made in the United States by veterans of the Desert Shield and Desert Storm engagements in the Persian Gulf several years ago. Many now claim chronic disability symptoms. They were apparently exposed to organophosphates (not specifically diazinon) which were used to suppress insect pests and it was even said that some troops wore pet collars containing organophosphates to combat lice and fleas which abounded in the area. Organophosphates represent the family of substances from which chemical weapons commonly called nerve gases derive. The operative effect is by acetylcholinesterase inhibition. As in the case of collateral damage to humans from the use of chemical defoliants in another conflict, it appears that claims and counterclaims by "experts" will inhibit any rapidity in reaching an accepted analysis of the situation.

I refer to these matters of debate because a considerable proportion of the hearing was devoted to the expression of and the cross examination upon contradictory views about the possible after effects of organophosphate exposure. I emphasize that it is neither my task, nor within my abilities, authoritatively to resolve an issue upon which learned medical practitioners, scientists and chemists are in disagreement. The issue before the Court is whether, on the balance of probabilities breach of duty of care owed by an employer to his employees caused damage of a kind in circumstances where it was reasonably foreseeable that breach might cause such damage. It is not required that the employees prove that the employer foresaw or ought to have foreseen the mechanism by which particular damage occurred. In the context of the present cases the matter comes down to investigating whether it has been proved that the defendant negligently exposed the plaintiffs to dangerous chemicals as a result of which they suffered relevant harm. I am conscious that that amounts to a deceptively simple expression of the complexities in the evidence.

For reasons for which the parties are not responsible the hearing had a somewhat chequered course and it became practical to receive submissions in writing rather than orally. The documentation submitted was lengthy as it canvassed contradictions both in expert and non-expert testimony. It will not be necessary to refer to all the ingredients explored and argued in those submissions particularly in connection with the quest for scientific determination as the common law is relevantly concerned with probability.

I prefer the evidence of the plaintiffs to that of the defendant in relation to the events and circumstances at the shearing sheds over the relevant period. I recognize that some of the records concerning balings of fleece tended to provide a basis to contradict the extent of some of the plaintiffs' complaints and I conclude that their estimates of the number of maggots on affected sheep and the numbers of those sheep are likely to have been exaggerated but I am satisfied that the numbers of both maggots and affected sheep were substantial.

The credibility of the defendants was not assisted by events shortly after the shearers manifested acute symptoms. Kevin Harper gave Bevan McKenzie an empty container labelled Jetcon which he said was "what was on the sheep". Diazinon is not an active ingredient in Jetcon. Later on 21 July 1993 Daryl Harper (Kevin Harper's son) signed accident reports for Workcover in which he referred to claimed illnesses of poisoning (although this was omitted in the particular fonn relating to Allan Tiedemann) and in a section of it relating to "chemical involved" he repeated that the sheep had been jetted with Jetcon but added that some had been treated with Topclip (diazinon). A sample of the tar being used in the shed had been taken by the plaintiffs and subsequent analysis revealed that it contained diazinon.

I find that Daryl Harper was the authorized agent of the defendant partnership for the purpose of filling out the Workcover form. A record of conversation between Inspector Lancaster of the occupational health and safety bureaucracy and Kevin Harper on 23 August 1993 is of interest. Kevin Harper said that he usually mixed the tar and used diazinon and vetrazin. Later in the conversation he said that he did not jet sheep with a mixture of chemicals but still later he agreed that "some weaners" were jetted with a mixture of Jetcon and Topclip. His final remark was that the reason for mixing the chemicals was the vigour of the fly wave at that time of the year.

The then current label on a retail container of Topclip had bold print safety directions cautioning the user, inter alia, to avoid contact with skin; recommending the wearing of gloves and the washing of gloves and contaminated clothing after each day's use.

An employer intending to use the product would also have had access to a safety data sheet. The sheet current at January 1993 under a headline HEALTH HAZARD INFORMATION commenced:

"Health Effects. Note: Diazinon can be rapidly absorbed through the skin. Poisoning may occur due to cholinesterase inhibition"

Further in the document under PRECAUTIONS there is information about exposure potential that whilst swallowing and inhalation are unlikely under normal conditions of usage:

"Skin uptake is the main route of exposure. Harmful qualities of diazinon may be absorbed through the skin that is in direct contact with the product. Repeated minor exposure may have a cumulative poisoning effect".

Under ENGINEERING CONTROLS it is stated:

"No special requirement. Product is used outdoors".

I would not regard within a shearing shed (particularly the one at Orana) as being outdoors. Finally there are elaborate instructions expanding upon the advice endorsed upon the retail product label.

I am satisfied that Kevin Harper produced the Jetcon container (a non-diazinon chemical) in the circumstances that I have mentioned because he was well aware of the notified risks of exposure to diazinon, that he knew a substantial part at least of the flock mustered for shearing had been treated with Topclip which contained diazinon and he suspected that the illnesses of the plaintiffs were probably caused by exposure to it. The defendants ought to have foreseen that the use of tar containing that chemical ingredient in the circumstances described would create a risk of poisoning which is in fact what fell due upon the plaintiffs.

Absent matters of scientific debate to which I will tum, my findings in relation to the exposure of employees by the employer to a substance advertised as hannful without warning and without instituting the taking of the recommended precautions would upon demonstration of resultant harm, constitute a very straightforward case of entitlement to damages for negligence.

Causation of damage was denied by the defendants and in particular in the context that if there was some exposure to deleterious chemical it was insufficient to provoke permanent damage and alternatively, even if there had been some provocation of symptoms they could not progress into long term effects. In short, I understood the defendants' case to assert not only that there was no causative link between any exposure of the plaintiffs to chemical and their illnesses but to raise the question at what level exposure to diazinon can be inspirational of chronic symptoms.

The evidence is well nigh overwhelming that a sufferer of acute symptoms from organophosphate poisoning can develop chronicity of symptoms. I am persuaded that the preponderance of acceptable evidence leads to the further conclusion that acute exposure can cause the development of chronic symptoms without necessarily passing through a stage of acute symptoms. As Dr Jamal summarized, the focus of genuine debate is whether long term low level exposure to organophosphates can of itself precipitate chronic symptoms.

I should in deference to the time spent adducing the evidence and the continued debate in the counter submissions make some reference to the scientific literature. I observe that the focus of a lot of attention has been just what Dr Jamal described exemplified by Californian market crop workers who labour in the fields where the chemical is used for insect control. By the very nature of their occupation they are outdoors and perceptibly breathing spray or having some handling contact. The plaintiffs were not in this situation which I understand the investigators to refer to when they write of long term low level exposure. The shearers became saturated with the compound and continued to work in chemically immersed clothes. The precautionary advice on the Topclip safety sheet could not have been more directly defied in its warnings about direct skin contact and absorption by that route.

Once it is accepted, as I do, that the plaintiffs' descriptions of symptoms are generally reliable then it follows that they all suffered an acute phase of symptoms and much of the opinion as to queried development of chronic symptoms without passing through that phase becomes academic. I do not accept that any incompleteness in the records of Dr Mead undermines that finding, nor is it corrupted by seeking to analyse discrepancies between the detail of the respective plaintiffs' testimony and histories given to medical examiners. What is clear is that these shearers had worked consistently at their calling over substantial periods of time and they all detected something noticeably wrong with the conditions and the occurrences when they were operating upon the defendants' flock on this occasion. Their perception was confirmed by the actions of Kevin Harper which 1 have described. I would not have expected the plaintiffs to be as pernickety about recounting detail as scientists (or lawyers) but their actions impressed me as those of honest working men initially mystified by what had befallen them and, as events turned out, correct in their suspicions as to the source of their troubles being allied to the foul chemical smells which they had sensed.

I digress to deal with a particular matter. The defendants invited a conclusion that the matters complained of should be held to be unlikely to have been caused by organophosphate poisoning and it was sought to inculpate their admitted various, but in each instance substantial prior frequent ingestions of intoxicating liquor as causative of their symptoms. The results of liver function tests were adverted to. To this was added exploration of angiomata/spider naevi seen at examination particularly of Robert Johnson**.** Dr Milder (with some support from Dr Howes) seems to represent the high point of the defendants' case in this regard. I find it improbable that the plaintiffs' conditions are the result of alcohol abuse. If the defendants' contention is correct then four shearers almost simultaneously succumbed to their respective levels of alleged alcohol abuse by manifesting broadly similar patterns of symptoms. I do not accept that coincidence particularly when there is another more probable explanation, namely organophosphate poisoning. And on the evidence they were certainly contemporaneously exposed to the deleterious chemical. It is convenient also to mention that the experiences of Dr Howes and Dr Harvey concerning diazinon seemed principally involved in the consequences of ingestion by mouth (by accident or intended self harm) and their views about absorption through the skin lack a background of experience. I regard it as unlikely that the clear and definite statements in the Topclip data sheet derive from imagination.

One of the known attributes of diazinon is that it is chemically unstable and in decomposition it forms so-called breakdown products which are frequently more toxic than the initial chemical. As the hearing progressed and large volumes of scientific evidence were being adduced I formed an impression that breakdown product was a likely culprit in this instance but in the nature of things that cannot now be scientifically demonstrated nor do I need to make such a finding before the plaintiffs are entitled to succeed in their actions. In regard to the chemical properties of diazinon I accept Professor Crank's evidence as I do his other opinions generally.

I also express a preference for the evidence of Drs. Whyte and Dawson. As well as the appropriate formal qualifications they are clinicians practising in toxicology and they have had direct contact with the plaintiffs who were referred to them. Their evidence (more extensively that of Dr Whyte) not only dealt with their immediate consultations but with learning that was available from medical and scientific literature. A primary source for many of the witnesses seems to have been the publications of Professor Ecobichon and it is notable that his integrity is discernible in changes of view as the frontiers of knowledge broadened by research and discovery. Professor Ecobichon was an important member of world health bodies investigating the effects of exposure to cholinesterase inhibitors amongst other things. As a result of his research he came to recognize subtle changes which could in fact be wrought by toxic assault which had apparently been overlooked in former times.

Dr Whyte's evidence was directly in point and he testified that the shearers showed clear and unequivocal signs of acute organophosphate poisoning. The advantage of that contact was not shared by Dr Harvey or Dr Howes. Dr Jamal provided an impressive thesis in support of the consequence of permanent deficit in the plaintiffs as a result of the poisoning and I accept his evidence. It is important to reiterate that I am not embarked upon a commission of inquiry to assess preference for a selected scientific view but upon a determination of whether on the probabilities there has been breach of duty of care by employer towards employee and probable consequential damage. I conclude the plaintiffs have discharged the requisite onus of proof. On the issues of causation described above the defendants' case was heavily dependent upon the expressed views of Dr Russell.

A critical analysis of those views was undertaken by Dr Jamal. And vice versa. No point will be served by my attempting to epitomize those contradictions nor by my recitation of testimony which can, if necessary, be read in the transcript.

Ultimately my findings are that the defendants treated the sheep with a chemical mix containing diazinon which was made available for employees to use contrary to safety directions of which the defendants knew or ought to have been aware thereby exposing those employees to risks of injury which were unnecessary as they could have been avoided by compliance with safety directions. And, as stated, I am satisfied that that breach of duty was causative of injury.

Each of the plaintiffs should recover damages and I deal with those issues individually.

CRAIG McKENZIE

Craig McKenzie was born on 26 September 1964. He left school at aged sixteen and was employed in rural activity working as a shearer between 1981 and 1993. During that time he did some casual work with the Grain Handling Authority when he was not shearing.

I have mentioned the immediate symptoms which he experienced when working at the defendants' sheds. At the time of hearing he complained of a considerable constellation of symptoms including headache, stinging in the eyes, upset stomach, eruption of bile and dry retch, pain in the ribs, itch, loss of smell and taste, a bloated internal feeling, bowel and urinary dysfunction, skin rashes, transient ear pain and memory confusion.

In support of the plaintiff’s claim there was tendered a bundle of some twenty odd reports. Subject to qualification I accept the general thrust in those reports. In May 1995 Dr Mead a general practitioner who had seen all of the plaintiffs reported that it was certain that the shearers had suffered chronic organophosphate poisoning. She said that their physical and psychological symptoms showed no signs of improving and she was treating only in order to alleviate the symptoms. She thought they were totally unfit to work at their former type of work. I interpolate that she did not say that they were unfit for any form of work.

Mr Rawlings a psychologist opined that test results revealed a patten1 of deficits consistent with the known complications of organophosphate poisoning. He thought these could be categorized as fixed and included impaired memory and learning, reduced attention span and slowed rate of information processing. The plaintiff was seen by Dr Shand a psychiatrist on several occasions who mentioned the plaintiffs "never ending string of complaints" all of which he attributed to the poisoning because "he was as fit as possible beforehand". Urine testing arranged by Dr Shand in April 1996 was consistent with the history which the plaintiff gave to the doctor of consumption of palliative drugs to deal with some of his symptoms. Dr Shand thought that the physical component and secondary psychiatric disorders made it unlikely that the plaintiff would be employed in future. Dr Middleton a rehabilitation specialist took a gloomy view initially but conceded that if the plaintiff improved his fitness he would increase his prospects of being able to engage in, at least, light to moderate work.

I am satisfied that the plaintiff does suffer from a range of symptoms as described although I agree with the defendants' submission that he has engaged in some exaggeration thereof. The litany of complaints in evidence, to Dr Shand and to others seems to show an obsessive trait and some gauge of accuracy is available from the acknowledgment by Dr Whyte that for example the plaintiffis neuropathy was non dermatomal.

I note the essential failure of a computer course arranged by Miss Gooden of the Commonwealth Rehabilitation Service. She thought the plaintiff would be best suited in self employment or some part time occupation. She did not regard him as totally unemployable. The plaintiff has had and continues to have a significant interest in horses and he and his wife have taken some steps towards establishing a life away from Ariah Park in Victoria, which amongst other things would enable the interest in horses to flourish. I am satisfied that the plaintiff is unfit to work as a shearer and will not regain that ability but despite his symptoms he has residual capacity for making some earnings to sustain his livelihood if he chooses to exercise it.

Out of pocket expenses are agreed at $5,867 as is a figure of $1 1,804 to be included in damages to avoid the detriment identified by the High Court in Fox v Wood 1981 148 CLR 438.

On behalf of the plaintiff the claim for economic loss was presented thus. It was acknowledged that in the income years ending June 1992 and June 1993 a primary production loss was claimed. The plaintiff lived on a small holding and engaged in some (loss producing) rural pursuits. It was submitted that the Court should not simply extrapolate from financial history records an evaluation of lost earning capacity reflecting nett income figures after taxation. Subject to lost capacity being likely to be productive of loss, I agree with the proposition:

Graham v Baker 1961 106 CLR 340.

I am invited to observe that in the income years ending 1991, 1992, and 1993 the plaintiff had taxable incomes of $ 19,836, $ 11,432 and $26,056 respectively reducible to $ 16,949, $ 10,226 and $20,960 after tax. It was put that using these figures would under compensate the plaintiff as they had been affected by his primary production losses from small farm and horse operations and that his capacity should be measured against the ingredients of income related to shearing only. The plaintiff seeks to establish a nett loss to be projected from a capacity valued thereby at $329 per week. The above after tax figures average $309 per week.

The next step proposed by the plaintiff was to observe that $329 nett represented at the time approximately two-thirds of the average weekly earnings of all males in New South Wales. Therefore it was contended that future loss should be estimated against two-thirds of present average weekly earnings which is $370 per week nett on the statistics.

The plaintiff’s submission of course is premised upon a total loss of earning capacity which is contrary to my finding. It is also to be remembered that I am required to exercise judgment and not purely arithmetical skills. Nevertheless the performance of calculations is a desirable exercise to provide guidance and to test conclusions.

The plaintiffs submitted calculation was to approach the matter in this fashion:

$329 x 216 weeks = $71,064

$370 x 855.7 (the multiplier for 33 years to take the plaintiff to age 65 at the authorized rate of discount on the 5 percent tables) less 15 percent for vicissitudes = $ 169,117

The defendants raised the issue of the plaintiffs likely retirement. It was contended that retirement from shearing would have been more likely at 55 years than 65 years. Having regard to the plaintiffs lifestyle I think it probable that he would have ceased his energetic work as a shearer if the tort had not intervened at about the age of 60 when I expect he would have devoted himself to his horse and rural activities which to date have been productive of advantageous tax loss but which were focuses of the plaintiffs stated ambitions. On that hypothesis I do not think there is demonstrated a probable tort-induced economic loss in the plaintiffs years between 60 and 65.

The elapsed time since the tort is now approximately 230 weeks. I accept that the plaintiff did not have a residual capacity of assessable value between the date of tort and for about two years thereafter but later than that I consider that he ought to have exercised a residual capacity which would have developed by then and which I would evaluate from that point and for the future as a representative figure of about one third of his uninjured earning capacity.

Subject to variations to take account of my findings the approach suggested on behalf of the plaintiff for the establishment of a weekly guide figure seems to me to be reasonable for the purpose.

I would award the plaintiff $61,810 for loss to date and $ 167,217 for future loss derived from the following guide calculations:

$329 x 104 (total loss in first 2 years) = $34,216
$219 x 126 (loss of two-thirds capacity from that point to date) = $27,594

$247 (two-thirds of $370 per week) x 796.7 (5 percent discount factor for 28 years) less 15 percent for vicissitudes = $ 167,217

A further item was claimed for future medical treatment. It is described in submissions as a "small buffer" of $20 per week. On indications to date the expenditure by the plaintiff is likely to be nearer to $100 per year than $20 per week. On the authorized tables the claim of $20 per week over the plaintiffs statistical life expectancy of 44 years capitalizes at $ 18,890. In my view $ 1,889 is appropriate.

The final ingredient of damage is non economic loss. The applicable figure for a most extreme case is $159,562. The defendants submit that the statutory threshold established by s 151H ofthe Workers Compensation Act 1987 will not be met. As is implicit in my assessment of damages for economic loss I reject that submission. It was submitted that the amount should not exceed a proportion of 30 percent of a most extreme case. The plaintiff contended that a proper proportion is 75 percent. Allowing for the plaintiffs comparatively young age and the total effect of all of his symptoms I conclude that an appropriate proportion is 60 percent.

The ingredients of the plaintiff s damages then will be:

Out of pocket expenses	$5,867
Fox v Wood	$11,804

Economic loss to date	$61,810
Future economic loss	$ 167,217

Future medical expenses $1,889

Non economic loss	$95,737
Total:	$344,324

It is agreed that the plaintiff has received worker's compensation benefits to the extent of $67,097 and the submissions on his behalf acknowledge deductibility of that figure. The plaintiff should therefore recover judgment for $277,227.

ALLAN TIEDEMANN

Allan Tiedemann was born on 5 April 1946. He left school at aged fourteen and worked as a rabbit trapper and woodcutter and commenced shearing in 1966 which calling he followed until the events presently under consideration. He supplemented his shearing with some continuing woodcutting activity. The evidence showed that he had been a man of considerable physical strength.

The plaintiffs immediate complaints of symptoms in 1993 have already been mentioned. At the hearing he complained of headache two or three times per week, sensations of burning and watering in the eyes, syncope, itch, bowel dysfunction, biliousness, taste disturbance, lack of energy and memory loss. I accept that the plaintiff has these symptoms from time to time and that the situation is likely to continue in the future. I also find that there was an element of exaggeration in his descriptions which is confirmed by admissions in cross examination that he had been more active than his initial evidence portrayed. I am persuaded that some selectivity was also likely to have intruded itself into the histories given to examining medical practitioners. However, subject to qualifications, I generally accept the thrust of medical evidence tendered on his behalf. This consisted of a bundle of some seventeen reports. Mr Rawlings the psychologist reported test results which demonstrated attentional deficit which he presumed to be the result of organophosphate poisoning as well as low average range intelligence and low executive functioning. He thought the plaintiff should be considered unemployable on th value which he could exercise if he chose. Dr Shand thought that the continuing complaints of the plaintiff (listed in his report of 9 April 1996) both physical and cognitive were attributable to organophosphate poisoning. Dr Middleton was gloomy in her prognostications. Although I have concluded that the plaintiff has residual capacity of value, having regard to his extreme reliance on physical prowess and the attrition upon it by his symptoms I assess that residual capacity as only 20 percent of his uninjured earning capacity. I consider he would have reached the point of that residual capacity being exercisable two years after the tort.

Establishing a basis for the award of economic loss is complicated by the history that the plaintiff was prone to periods of unemployment before the events with which this case is concerned. In the income years ended 1992 and 1993 he received unemployment benefits to the extent of $7,098 and $5,669. During part of 1992 the plaintiff was recuperating from a hernia operation.

It is submitted by the plaintiff that 1992 should be ignored and that by a method not dissimilar from that adopted in relation to the claim by Craig McKenzie guide figures should be established. By that method a factorial loss of $307 per week for the past is presented which proportions as three-fifths of all male average weekly earnings at the relevant time. Applying that proportion to current statistics produces a figure of $350 per week nett.

In this case I am persuaded that there is rather more force in a submission on behalf of the defendant. It is observed that if the plaintiffs methodology was adopted (without discarding 1992) the plaintiff's earnings from shearing would, on a weekly nett basis be in the years l 990, 1991 and 1992 $310, $ 162 and $ 165 producing an average of $212. If one took the year which ended with the tort in April 1993 the plaintiffs average can be calculated at about $225 per week nett. The point of the submission was to invalidate the basis upon the plaintiff proposed a factor of $307 per week. Some account should be taken of the disruption caused by the hernia operation. I consider a fair figure as a guide would be $225 per week derived between July 1992 and April 1993. In appearance Allan Tiedemann presented overall as what I think many people would describe as a gentle giant. I have less confidence in the defendants' proposition that he may not have continued as a shearer for longer than Craig McKenzie in the sense that he may not have retired at 60 because his once powerful body suggested persistence at heavy work, but on the other hand he had manifested gaps in employment all of which was not consequent upon the need to recuperate from one particular operation. Doing the best I can I would set his notional retiring age at age 62.

Out of pocket expenses are agreed at $887. The Fox v Wood requirement is also agreed at $8,109.

I would award the plaintiff $46,080 for economic loss to date arrived at from the following calculations which I have performed for guidance.

For the first two years after the tort:

$225 x 104 = $23,400

Thereupon to date allowing for residual capacity of 20 percent $ 180 x 126 = $22,680.

The average weekly earnings of all males in New South Wales since the time at which the guide figure of $225 was established have increased by approximately 14 percent and l have therefore enhanced that figure accordingly and then reduced the result by 20 percent representing residual capacity in order to establish a factor for continuing loss at $205 per week.

$205 x 444.2 (the authorized 5 percent discount factor taking the plaintiff to age 62) less 15 percent for vicissitudes = $77,402.

I would award the plaintiff that sum.

Claim is also made for a small buffer for medical expenses. The agreed out of pockets give some oblique indication of the frequency with which the plaintiff seeks and is likely to seek the assistance of health professionals. It is proposed that I should award $20 per week for 27 years (his statistical life expectancy) which capitalizes at $15,660. Expenditure to that extent is unlikely and what expenditure the plaintiff may incur is closer to a tenth of that sum. I would award $1,566.

Finally I consider the ingredient of non economic loss. The plaintiff s condition is similar to but not identical with that of Craig "McKenzie' but he is somewhat older and the span of time during which he must tolerate his afflictions and handicaps is predictably less. The prescribed figure for a most extreme case remains set at $159,562. The defendants submitted that I should hold that the plaintiff has not suffered sufficient damage to fulfil the threshold requirement but as would be apparent from the foregoing I reject that submission. It was submitted that I should not set his proportion at greater than 20 percent of a most extreme case. The plaintiff submitted 65 percent was the appropriate proportion. I assess 50 percent. There will therefore be an ingredient of damage for this item of $79,781.

The ingredients of damage are:

Out of pocket expenses	$887
Fox v Wood	$8,109

Economic loss to date $46,080

Future economic loss	$77,402
Future medicals	$1,566
Non economic loss	$79,781
Total:	$213,825

Subvention received by way of worker's compensation amounts to $51,751 and l am invited to make the necessary adjustments. The plaintiff should therefore recover judgment for $162,074.

ROBERT JOHNSON

Robert Johnson was born on 26 July 1945. He left school at aged 15 and after working as a stationhand for about three years took up and continued shearing until 1971. He was himself a shearing contractor for a time. He had purchased and worked a farm and also worked as a real estate salesman and a truckdriver on occasions. He returned to shearing in about 1989 and testified that he would have continued until retirement at about 65 or 66 years of age.

His immediate complaint of symptoms in 1993 have been recorded. At the hearing he claimed to suffer headaches, aching and watering of the eyes, shortness of breath, stomach pains, biliousness, bowel dysfunction, leg pains, syncope, deterioration in memory and concentration, low energy level, itch, transient taste disturbance, insomnia and adverse reaction to heat.

A bundle of seventeen reports was tendered on his behalf and subject to qualification I generally accept the content of those reports. l consider however that the plaintiff overstated his symptoms to an extent and the opinions reflect that exaggeration.

Examination and testing of the plaintiff revealed signs suggestive of liquor overindulgence, angiomata, clubbing of fingers and liver function abnormality which in the light of his own testimony as to alcohol intake gave a basis for fair prognostication that the plaintiff was unlikely to achieve uninterrupted employment life as a shearer to aged 65 or 66.1 would select age 60 as a more probable terminus of working life. He had also begun to suffer back symptoms before the occurrences which are the subject of this litigation and there must be some doubt as to whether in any event he would have long remained fit enough to work as a shearer. However, unlike Craig McKenzie and especially Allan Tiedemann he had a broader range of experience and ability to fall back on, the question being whether his capacity so to do has not also been adversely affected or destroyed.

The psychometric testing by Mr Rawlings was interpreted to show maintenance of basic intellectual function at average level but impairment of ability to learn and recall new material either verbal or non verbal. Concentration deficit was also detected as was a defect in memory function. Dr Shand thought that the plaintiff's complaints accumulated to make him unemployable. He noted that the plaintiff was receiving a disability pension. Dr Middleton opined that physically the plaintiff could handle no more than very light sedentary work which would need to be performed without deadline or other stress precipitant. It is hard to conceive of employment within those parameters.

Realistically I do not think the plaintiff has any valuable residual ability as he was, even if principally as a result of long term alcohol abuse, extremely vulnerable when he was afflicted by the organophosphate poisoning.

The plaintiffs evidence disclosed his itinerant work habits and I accept the defendants' submission that the projected figures advanced on behalf of the plaintiff are tainted with improbability. In the financial year ended 1992 the plaintiffs nett average weekly earnings were approximately $125

which compare relatively unfavourably with social security benefits. For the financial year ending in June 1993 - recognizing the practical termination in April - an average of $235 can be established. The suggested figure advanced on behalf of the plaintiff of $335 per week has no acceptable derivation.

I would use $235 per week as the more reliable guide and using the growth of 14 percent already noted as the climb in average weekly earnings of all males in New South Wales, use $268 per week as a guide figure for the future.

The out of pocket expenses are agreed at $1,447. The Fox v Wood ingredient is agreed at $14,763.

Applying the above findings I award $54,050 for economic loss to date being $235 for 230 weeks.

For future economic loss I award $74,097 guided from calculation as follows:

$268 x 345.6 (the authorized 5 percent discount figure taking the plaintiff to age 60) less 20 percent for adverse vicissitudes = $74,097

I have selected a 20 percent discount for vicissitudes because in addition to rejecting the probability of the plaintiff remaining in employment beyond aged 60 I believe regard should be paid by reason of the factors adumbrated above to a real potential that the plaintiffs remunerative activity would be interrupted even before then.

A small buffer claim for medical treatment at $20 per week is also made. The plaintiff's life expectancy is statistically 26 years. For reasons coordinate with those which I gave in relation to the other plaintiffs the capitalized sum of 515,375 is rejected and I would award the plaintiff $1,538 for this ingredient.

Finally I turn to non economic loss. I explicitly do not suggest that the situation of the plaintiff and Allan Tiedemann are identical but in all the circumstances I consider the proportion against a most extreme case appropriate to this plaintiff is also 50 percent. Again the defendants submitted that the threshold had not been fulfilled and submitted that the proportion should not exceed 20 percent. The plaintiff submitted that the appropriate proportion was 65 percent.

The ingredients of damage therefore are as follows:

Out of pocket expenses $ 1,447

Fox v Wood	$14,763
Past economic loss	$54,050
Future economic loss	$74,097
Future medicals	$1,538
Non economic loss	$79,781
Total	$225,666

As in the other cases I am invited to adjust the subvention received by way of worker's compensation payments in an agreed sum, which in this instance is $51,823. There will therefore be judgment for the plaintiff for $ 173,843.

I direct entry of judgment against the defendants for each plaintiff as follows:

Craig McKenzie, - $277,227
Allan Tiedemann - $ 162,074
Robert Johnson - $ 173,843

Subject to application, I order the defendants to pay each of the plaintiff's costs of the actions. The hearing raised matters of particular complexity, that complexity being magnified by the evidential content which the defendants sought to include and did present and, irrespective of my view as to the strict relevance of all of it, preparation of response on behalf of the plaintiffs was compelled. It was appropriate to brief two counsel and the costs are to include fees for two counsel accordingly.

APPENDIX D Overview of biological monitoring of worker exposure to organophosphate insecticides

a) Cholinesterase testing

Organophosphate insecticides act by complexing with, and inhibiting the action of, acetylcholinesterase in the nervous system. This results in accumulation of the neurotransmitter acetylcholine in nerve synapses and the disruption of signals within the nervous system. Besides acetylcholinesterase in the nervous system there are also esterases in other body systems, the main ones being acetylcholinesterase in red blood cells and butyrylcholinesterase in the plasma. Access to the latter esterases, in venous blood, is easier than to nervous system acetylcholinesterase so they are generally used as a measure of exposure to OP (or carbamate) pesticides and as a surrogate measure for the effect of the OP pesticides on cholinesterase in the nervous system.

When an OP complexes with acetylcholinesterase some regeneration of the enzyme occurs but “aging” of the OP-enzyme complex can also occur resulting in irreversible deactivation of the enzyme and the production of OP metabolites which are cleared via the urine. Plasma cholinesterase activity usually drops before, and recovers more quickly than, red blood cell cholinesterase activity.

Difficulties in interpretation result from wide intra-individual and inter-individual differences in cholinesterase activities, genetic variation, gender difference, use of medications, health status, pregnancy and the timing of blood sample collection in relation to exposure. Ideally a “baseline” cholinesterase activity (2 samples collected between 3 and 14 days apart and averaged) should be determined in a non-exposure period for all workers who handle OP insecticides. The percentage depression of cholinesterase activity in a sample collected soon after working with OPs is then calculated by reference to the worker’s baseline values. If a baseline value is not available for an individual worker cholinesterase activities are compared to “normal population” reference ranges and significant exposure may pass undetected. Estimation of baseline cholinesterase activities is recommended for all workers who work regularly with anticholinesterase pesticides.

Ideally, both plasma and red blood cell cholinesterase levels should be measured and the results interpreted by a doctor who has knowledge of the pesticides used, workplace hygiene, any symptoms experienced and the health status of the individual.

The main use of routine cholinesterase screening has been to detect workers who are significantly exposed to organophosphate pesticides and whose enzyme activities are so low as to put them at risk of acute toxic symptoms on further moderate exposure. This is generally taken to be a depression of 40% in plasma cholinesterase activity or 30% in red blood cell cholinesterase activity compared to the persons baseline measurement or to the lower limit of the normal population reference range. It should be noted that the National Health and Safety Commission (NOHSC) use a 20% cutoff in determining the need for confirmatory sampling. Frequently cholinesterase depression is assumed to accurately reflect the absorbed dose of OP pesticide but this should be regarded with caution.

For example, the analytical methods used by the WorkCover NSW laboratory are modifications of the Ellman method for red blood cell cholinesterase (*Ellman, G L; Courtney, K D; Andres, V and Featherstone, R M; 1961, Biochem. Pharmacol. 7, 88 – 95*) and of

Knedel and Bottger for plasma cholinesterase (Knedel, M; Bottger, R; 1967, Klin. Wochenschr, 325 – 327)

b) Monitoring urine metabolites

Organophosphate insecticides absorbed into the body are metabolised by various processes and excreted in the urine. Unchanged insecticide may also be excreted in the urine. For example diazinon forms the metabolites DEP (diethylphosphate) and DETP (diethylthiophosphate) which are passed in the urine shortly after exposure.

The analytical test is a very sensitive one and can detect metabolites present in the urine in the low parts per billion level. Urine metabolites are often detectable when no shift in cholinesterase activities can be measured.

The analytical method used by the WorkCover NSW laboratory is a modification of the Health and Safety Executive, UK analytical method (*Nutley, B P; Cocker, J; Pesticide Sci. 1993, 38, 315 – 322).*

c) Advantages and disadvantages of the OP biomonitoring methods

The following points illustrate the main advantages anddeficiencies of the methods but should not be taken to be an exhaustive list.

(i) Cholinesterase measurements on venous blood samples.

Advantages:

- This test is a functional test since it reflects the "reserve" cholinesterase capacity of a worker exposed to anticholinesterase pesticides. The results might suggest the need to remove the worker from further potential exposures to prevent symptoms developing.
- The test has been the standard method used for monitoring significant OP exposure for many years. It is also analytically easy, relatively inexpensive and results can be available very rapidly.
- The "exposure standards" for the allowable percentage depression appear to be reliable guides to prevent excessive exposure leading to overt symptoms of OP poisoning.
- The blood sample, while best collected the day after exposure, can give a fairly reliable indication of significant exposure if collected within a week or so.

Disadvantages:

- Trained personnel are required to collect blood and it is relatively invasive compared to collection of urine samples.
- Ideally a baseline should be available for regularly exposed workers.
- The apparent cholinesterase activity depression, compared to the baseline or to the population range, is not a sensitive estimate of the *low level exposures* that have received increased attention in recent times.
- It is not a measure of exposure to specific anticholinesterase pesticides since the common biological effect of the class of is measured.
- Different methods are used by different laboratories therefore the same laboratory should always be used.

(ii) Urine metabolite monitoring

Advantages:

- The collection of urine samples does not require trained personnel and can be done by the worker. However it is important to provide correct sample labelling, including times of exposure and collection.
- The analytical method is generally very sensitive and detects low level exposures.
- Presence of OP metabolites in the urine is absolute evidence of exposure and may be useful for example in legal proceedings

Disadvantages:

- The analytical procedure is relatively sophisticated, and therefore expensive, and is not routinely available in a wide range of laboratories or in the field.
- The method is not entirely specific for a particular pesticide if a number of OPs have been used since identical alkyl phosphate metabolites may come from a number of pesticides.
- Clearance of the pesticide and metabolites from the body is relatively rapid therefore “spot” urine samples may be difficult to relate to peak exposures. Collection of 24 hour urine samples is not suitable for routine monitoring.
- There are no reference standards (biological exposure indices) for specific pesticides available.

APPENDIX E Summary and overview of the June, 1999 UK Institute of Occupational Medicine (IOM) report on organophosphate sheep dips.

Summary and overview of the June, 1999 UK Institute of Occupational Medicine (IOM) report on organophosphate sheep dips

Prepared by

Chemicals Review and International Harmonisation Section,
TGA, Department of Health and Aged Care
September, 1999

Institute of Occupational Medicine, Edinburgh. Technical Memorandum Series. May 1999. Epidemiological study of the relationships between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy, and neuropsychological abnormalities in sheep farmers and dippers.

Summary

Research aims and design

The broad aim of the study was to investigate the hypothesis that prolonged exposure to organophosphorus (OP) sheep dip may cause chronic ill-health. Specifically, the aim was to show whether cumulative exposure to OP sheep dips was related to clinically-detectable nerve damage (neuropathy). It is important to note that the study had three main parts or phases, but the entire study was conducted blind (ie. the data from each phase was not available to those conducting the other phases).

Phase 1 - development of a model of systemic exposure to OPs during sheep dipping

Phase 1 involved 20 one-day surveys of dipping sessions at farms, mostly located in the border region of England and Scotland:

- recording the activities performed by individuals involved in the dipping operations (eg. the frequency and extent of handling concentrate dip; the extent and time of contact with dip wash; protective clothing worn; smoking and eating habits);
- measuring levels of urinary metabolites before and after dipping to assess uptake;
- using the above data to develop a mathematical model relating the uptake of OPs to task characteristics.

Phase 2 - a cross-sectional field study of sheep dippers and of individuals not occupationally exposed to OPs, to examine the relationship between cumulative history of exposure to OPs and indices of effect

The Phase-1 exposure model was applied in the Phase-2 field study. This was based on two areas of the UK (the Scottish Borders/Ayrshire/Lothians and Herefordshire/Worcestershire) with a relatively high density of sheep farming. It involved 612 sheep dippers who had experienced at least three days of sheep dipping. In addition, 160 individuals from the same geographical areas who had not been exposed to OP sheep dips were included (53 pig and chicken farmers/farm workers and 107 ceramic workers). Exposure- and symptoms-questionnaires and quantitative sensory tests were completed for each participant. The data were analysed to determine whether abnormalities were associated with exposure to OP dip.

Phase 3 - detailed neurological and neuropsychological studies of a sub-group of Phase-2 subjects at a clinic to validate the results obtained in the field.

The clinical study included a similar symptoms questionnaire and tests as phase 2 and a range of other tests designed to assess neurological and neuropsychological abnormalities. Its purpose was essentially to validate the Phase-2 findings and to provide more detailed data on a sub-set of individuals. Phase 3 involved 79 sheep dippers. It included only individuals who had been exposed to sheep dip.

It is noted that in Phase 2, the neuropathy scores from the field survey were used to select subjects for Phase 3. This was done without consideration of exposure status as the exposure data was not processed until Phase-3 clinical investigations were completed.

It was only after the Phase-3 clinical examinations had been carried out and the exposures calculated by the model from Phase 1, that the exposure- response relationship was examined in the Phase-2 data analysis.

Key findings

Key findings Phase1

- The study found that the most important source of exposure to OPs was contact with concentrate dip, which occurred almost always on the hands and usually as a result of handling the concentrate container during the preparation and replenishment of the dipping bath. Levels of urinary metabolites were found to increase with the frequency of handling of the concentrate containers. Larger flock sizes tended to result in more replenishment of the bath and hence more handling of the concentrate. Generally one person at each farm had responsibility for handling dip-concentrate, usually the paddler, the individual responsible for submerging the sheep in the dip wash.

- Increased splashing with the dilute dip-wash was found to be positively associated with an increase in urinary metabolites for a subset of individuals who had not been exposed to dip-concentrate. Splashing with dip-wash was related to the primary task of the worker and the type of bath.

- A linear regression model was developed which describes the relationship between uptake of OPs as assessed by post-dipping urinary metabolite levels and exposure to both the dip-concentrate the dip-wash, with a weighting for their relative importance. The model explains 62% of the variation in this Phase 1 study, which analysed a single day's dipping across a representative selection of farms. It is acknowledged that the model does not explain all of the variation between individuals. Some variation will arise due to variation in absorption, metabolism and excretion of OPs between individuals as well as laboratory measurement error.

- The authors state that the study confirmed the results of the earlier work (Niven et al, 1993 and Niven et al, 1996) particularly in relation to dip-concentrate being the most important source of exposure.

Key findings Phase 2

- Results showed higher rates of symptoms between OP exposed sheep dippers compared with non-exposed workers. Symptom score was related to indices of cumulative exposure to OPs. There was also a strong regional difference, with a higher prevalence of reported symptoms in England compared to Scotland, among subjects of the same age and occupational group, and sensory symptoms were more commonly reported than motor symptoms.

- The critical exposure factor seemed to be contact with concentrate in that markedly higher rates of reported symptoms (adjusted for other factors) were reported among those who had at some time been principal concentrate handlers. After adjusting for this there still remained a much higher prevalence of symptoms among English subjects compared to Scottish subjects.

- There was no evidence that cumulative exposure to OPs was associated with impairment of measured sensory thresholds for hot, cold and vibration.

- Age was found to be positively related to all three sensory test thresholds. In addition, males had higher thresholds, on average, than females. Adjusting for age and sex there were inconsistent differences among the occupational groups between the two countries for sensory thresholds.

Key findings Phase 3

- Detailed neurological investigations found that only about half the 23 subjects classified in the clinic (on the basis of symptoms questionnaire and QSTs) as having "probable/definite neuropathy" and about 30% of the 34 individuals classified as having "possible neuropathy" had clear evidence of neuropathy as diagnosed by a neurologist from nerve conduction changes or signs. Small fibre populations were affected more than large fibre populations. The neuropathy described was predominantly of a sensory type both symptomatically and neurophysiologically and was characteristic of distal, chronic axonopathy with no acute features. Autonomic nervous system symptoms were commonly reported by the “no neuropathy” and “possible neuropathy” groups, but less commonly by the “probable neuropathy group”.
- In general the neuropsychological tests do not show strong evidence of a direct relationship between impaired neuropsychological performance and cumulative exposure to OP sheep dips; no evidence for such a relationship was found across a wide range of indicators. It must be accepted that the sampling design of the clinical study was not optimal for this purpose.
- Subjects classified in the clinic as being "probable/definite" cases of neuropathy were more likely to self-report poorer general mental health and greater anxiety and depression than subjects classified as in the “no” or “possible neuropathy” groups.

Background to the IOM report

UK government actions

The research was carried out between November 1995 and April 1999 by the Institute of Occupational Medicine (IOM) in Edinburgh which was awarded a £500,000 contract for research into the possible long-term human health effects of OP sheep dips, in collaboration with the Institute of Neurological Sciences in Glasgow. The research was commissioned in response to a recommendation from the Medical and Scientific Panel of the Veterinary Products Committee on the need for epidemiological research into the effects of OP sheep dips. The research was jointly funded by the Health and Safety Executive, the Department of Health and the Ministry of Agriculture, Fisheries and Forests (MAFF). The conduct and results of the research are reported in three companion volumes. The aim of the study as a whole was to investigate whether cumulative exposure to sheep dip OPs is related to clinically detectable measures of neuropathy. Phase 1 of the study developed an exposure model linking uptake of sheep-dip OPs with objectively assessed parameters such as primary task performed by the sheep-dipper. This model was applied in Phase II which studied the relationships between cumulative exposure to OPs and clinically relevant indices of peripheral neuropathy using a cross-sectional field study of sheep farmers and dippers. Phase III studied the clinical features of a sub-group of subjects from Phase II.

The IOM report will be considered by the Committee on Toxicology (COT) Working Group on OPs which was set up in 1998 under the chairmanship of Professor Frank Woods, to review the evidence on the possible ill-health effects of OPs. The implications of its report later this year for veterinary medicines, pesticides and human medicines will be considered by the UK Government's other independent scientific advisory committees in this area (the Veterinary Products Committee, the Advisory Committee on Pesticides and the Committee on Safety of Medicines respectively).

The responsible minister also asked the Veterinary Products Committee and the Advisory Committee on Pesticides to consider urgently whether the IOM study affects their advice on the safety of OPs and whether further measures are necessary in advance of the completion of COT's review. The responsible minister has also initiated discussions with the representatives of the manufacturers to discuss what action they will be proposing in response to the report, in particular to the findings on concentrates.

The UK Government expects to receive the report from COT, and the advice from its other independent expert advisory committees before the end of 1999.

History of UK sheep dipping practice

Sheep scab has always been a problem for farmers. It is a contagious disease caused by a mite which feeds off the skin of the sheep. It is an all year round disease, although mites are more active during the winter. The mites cause intense irritation to the sheep, leading to self-inflicted damage in addition to that caused by mite activity. In an untreated outbreak there will be deaths from starvation and secondary bacterial infection. Ticks are responsible for potentially fatal illnesses among sheep such as louping ill (viral disease; progressive incoordination leading to paralysis, coma and death), tick-born fever and lamb pyaemia (septicaemia leading to abscess formation in joints, liver and lungs).

Spring dips are used to control ticks, and dips are often twice as concentrated as those used at other times of the year to control other external parasites. In Scotland there is a second tick emergence in the autumn which can be severe locally. Blowflies infest the fleece and can create open wounds making the sheep vulnerable to more extensive infection. Summer dipping is used for blowfly control. Lice and keds cause irritation and fleece damage and generally result in sheep of poor physical condition. Autumn dipping is used to control these parasites. Plunge dipping as a technique for controlling external parasites was introduced in the early 1800s.

These early dips included arsenic and sulphur. Over the next century substances used against scab included copper sulphate, boron compounds, tar acid derivatives and sulphur. In Britain compulsory dipping began in 1906, and the substances used were lime, sulphur, arsenicals or phenolics. It was noted that outbreaks of sheep scab were more common between November and March, and MAFF made autumn dipping compulsory. The range of substances listed above continued to be commonly used and there was little progress towards eradication of sheep scab until the approval in 1948 of hexachlorocyclohexane (HCH) formulated with high concentrations of phenolics to prevent bacterial degradation. Later, another organochlorine DDT was approved, and DDT and HCH continued to be the most common insecticides used for sheep external parasites. Dieldrin was added to HCH preparations in the mid 1950s after being found to be successful for control of blowfly maggots, lice and keds. It continued to be commonly used until the mid 1960s, when organochlorines were gradually withdrawn. OP dips including chlorfenvinphos and diazinon were available in the 1960s, and by 1970 there were 67 approved formulations, 49 of which contained the organochlorine HCH. Dips containing HCH were still available until the end of 1984.

After 20 years with no outbreaks, sheep scab emerged as a problem again in England and Wales in 1972, possibly on sheep imported from the Republic of Ireland. Sheep scab also reappeared in Scotland, having been absent since 1941. Since 1972 successful eradication has not been achieved. Due to the re-emergence of scab, compulsory national dipping was re-introduced in 1976. It was compulsory to dip once a year in mid-summer from 1976 to 1983 inclusive, except in 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. Between 1984 and 1988 inclusive, two compulsory national dips were required (midsummer and autumn) each year. Between 1976 and 1988 inclusive, dipping was subject to supervision. In 1989 the farmer was required to give the local authority prior notification. For the following 2 years no prior notification of dipping was required. Deregulation occurred in mid 1992, when responsibility for control of sheep scab transferred from MAFF to the livestock holder.

HCH remained the only pesticide approved for scab until 1980, when diazinon was also approved. In 1983 propetamphos was also approved. Organophosphates provide broad spectrum protection against blowflies, lice, keds and ticks, and have also been used for these purposes during a similar timescale. Limited data from Scottish surveys of pesticide usage on sheep between 1978 and 1993 is shown in Table 1, and gives some indication of volumes of dips used just in Scotland (Bowen et al, 1982; Bowen et al, 1983; Shave et al, 1993). While sheep dipping was compulsory in the UK between 1976 and 1992 as a sheep-scab control measure, the spectrum of OP agents used in the UK for sheep dipping is limited and differs from that used for other applications. The only agents approved for current UK use are propetamphos and diazinon (Ray, 1998). However licenses have expired for a number of agents only relatively recently (Browning, 1995; see Table 2).

Although OPs are less persistent than organochlorines such as dieldrin, they need to be applied more frequently, and are potentially more toxic to terrestrial wildlife. They are usually supplied as concentrates in a solvent base and are formulated to enhance adsorption and persistence on the skin and fleece of the sheep. Concentrate dip may contain up to 60% active ingredient, and until the early 1990s contained up to 20% phenols. In order to treat scab effectively, immersion of the sheep is required for one minute. Although plunge dipping is still the most widely used technique, other methods and preparations are increasingly being used. Plunge dipping from a pit used to be the most common method used, with the plunger submerging sheep with his hands. More recently this has been replaced by plunge dipping using a dipping stick or paddle. Other techniques now used to apply insecticides include those that utilise a knapsack applicator and spray gun (known as the pour-on method) and sheep showers.

Additionally it should not be assumed that the agents to which a sheep dip worker may have been exposed in the 1990's is limited to these organophosphate insecticides. The synthetic pyrethroid flumethrin was approved as a dip for scab in 1984. Other pyrethroids are effective against other ectoparasites, for example, cypermethrin is available as a pour-on for ticks and lice, and as a spray-on for blowfly maggots. Treatment for headfly are now commonly carried out with pour-on. Deltamethrin is effective as a spot-on for controlling blowfly larvae, ticks and lice. An insect growth regulator (IGR) cryomazine has also been available as a pour-on since 1989.

Table 1: Estimates of dip usage (millions of litres) from surveys conducted by the Scottish Agricultural Science Agency

Chemical	**Year**		
	1978	**1983**	**1993**
Chlorpyrifos	6.7	3.38	
Chlorfenvinphos	17.08	17.81	
Diazinon	1.17	8.46	9.63
Chlorfenvinphos/phenols			4.46
Propetamphos /phenols			16.19

Table 2: OP agents no longer licensed for sheep dipping in the UK

Agent	**Year of licence expiry**
Bromophos	1988
Chlorpyrifos	1989
Iodophenos	1990
Coumaphos	1991
Chlorfenvinphos	1994

The use of OP sheep dips in Australia

An NCRIS search of OP sheep dip products of interest to the UK study revealed the following information on their Australian registration status (as at 9/8/99).

Table 3: OP agents registered at any time for sheep dip use in Australia

Registered for use as dips	Registered - no current sheep uses	Registration expired
Chlorfenvinphos	Chlorpyrifos	Carbophenothion
Diazinon	Coumaphos (4 products)	Bromophos
Propetamphos (5 products)		Iodofenphos

Detailed summary of IOM Report

Phase 1: Development and validation of an organophosphate uptake model for sheep dippers. Report no. TM/99/02a; Sewell C, Pilkington A, Buchanan D, Tannahill SN, Kidd M, Cherrie B and Robertson A.

Objectives

This phase of the study set out to define the factors important to the uptake of OP dips during sheep dipping operations. The objectives were: to develop a model for uptake of OPs based on simple task, procedural and behavioural aspects of sheep dipping, and to validate the model by comparisons with urinary OP metabolites during various dipping procedures. Also, to identify, where appropriate, methods for the improved control of exposure to OP dips during sheep dipping operations.

Methods

QA methods were applied to data collection, sample analysis and data analysis/storage. The study involved one day surveys of twenty dipping sessions at farms mostly located in the Scottish Borders. A total of sixty farm workers were studied, up to four at each study site. Both farmers and contract dippers were included and a range of bath types; long/short swim, circular, circular with island, and mobile were investigated. In order to limit the number of variables, only farms using diazinon dips were studied.

Each survey involved observation and recording (scoring grids, videos, photographs) of the activities performed by individuals including: the frequency and extent of handling the concentrate dip; the extent and time of contact with dip-wash (working strength dip); protective clothing worn; hand washing; smoking and eating habits, and any other significant incidents. Occupational hygienists made these observations and also conducted a questionnaire about activities for the 72 h prior to dipping.

Workers were described as Paddlers (plunges sheep under the dip), Chuckers (feeds sheep into bath) and Helpers (herds sheep to bath). Workers were also asked to provide urine samples before and after work and 24 h later, and some sub-samples from dippers and controls were spiked in the field for QA purposes. All surveys were conducted during the time of summer-dipping against blow fly; the authors reported that dipping practices were comparable at other times of the year.

Uptake measurements

Measurements were made of the urinary metabolites diethyl phosphate (DEP) and diethylphosphorothioate (DEPT); the metabolite concentrations were first corrected for levels of urinary creatinine and expressed as nmol per mmol of creatinine.

Exposure indices

Exposure indices (table 4) included: **exposure to concentrate** modified by the use and quality of gloves; **exposure to dip-wash** assessed by scoring a snapshot picture of the splashing pattern on individuals at four times during the dipping session, and calculating an index based on area splashed by the time spent dipping and modified by the quality of protective clothing; **exposure via ingestion** based on number of times an individual had something to eat, drink or smoke during the dipping session.

Table 4: Scheme for calculating exposure indices for sheep dippers

Exposure event	**Exposure to concentrate**	**Exposure to dip-wash**	**Exposure to concentrate and dip-wash by ingestion**
How scored	Total number of handling events	Photograph; time-weighted score for splashes	Total number of eat/drink/smoke events
Modifiers	Quality/presence of gloves	Quality/presence of protective clothing	Handwashing

The data were analysed by comparing uptake (increment in urinary metabolites) to exposure indices using scatter plots (to identify outliers) and multiple linear regression. Correlation was used to determine the degree of association and hence the potential for confounding among the exposure indices

Results

Twenty properties using diazinon products were surveyed with 2, 3 or 4 individuals involved on 2, 16 and 2 properties respectively. Bath volumes varied from 800 L - 4000 L (mean 1787 L). The diazinon concentration in the products used was 16% (5 properties) or 60% (15 properties). Initial dip-wash concentration varied from 0.27 - 0.44 mL/L and total concentrate used ranged from 1.8 - 9.7 L. The mean number of sheep dipped per property was 815 (range 250 - 1700), and the duration of dipping ranged from 155 - 491 minutes. The authors' summary of the observational data from the farm surveys is reported below - no raw data were provided.

Exposure to dip-concentrate

The authors state that contamination with concentrate dip on the hands or gloves occurred almost every time a concentrate container was handled in the course of filling or replenishing the dipping bath. Contamination with concentrate dip rarely occurred on other parts of the body, although on four occasions splashing was recorded on the legs or feet and on one occasion on the face. Contamination arose usually because the design of concentrate containers resulted in some residual liquid being left on the container after pouring.

Exposure to dip-wash

The authors state that the most significant source of exposure to dip wash was splashing as sheep entered the bath and were submerged below the dip wash. The extent of splashing to each individual was dependent on their proximity to the dipping bath, but working practices including speed and manner of sheep insertion, as well as the effectiveness of screens and splashboards influenced actual worker exposure. Some individuals were visibly soaked by splashing especially on the lower body, while others remained relatively dry. In general the extent of splashing to workers diminished from paddlers to chuckers to handlers. A less important source of contamination was contact with the treated fleece or aerosols from it. When sheep left the bath they were always collected in draining pens, where they usually shook their fleece vigorously to remove excess dip wash. All except one site had pens away from the workers or high sided screens to control this source of exposure. Post dipping activities (emptying and cleaning the dipping bath) did not contribute significantly to worker exposure.

Diazinon uptake

Only summary statistics of the urine analyses were provided.

The measured concentrations of urinary metabolites DEP and DEPT were summed, then corrected for creatinine levels, and Table 5 shows summary statistics for these two metabolites across individuals for the pre-dip, post-dip and next morning samples. Pre-dip urinary metabolites were low (median 5.7 nmol/mmol) with 22 out of 54 individuals having no detectable levels of DEP and DEPT. Levels were higher after dipping, with a median increment of 12.8 nmol/mmol from pre-dip to first post-dip sample, and a median increment of 9.0 nmol/mmol to the next morning sample. Five individuals recorded increments of greater than 100 nmol/mmol with 385 nmol/mmol (to first post-dip) and 127 nmol/mmol (to next morning) being the highest.

Table 5: Summary table for urinary metabolites (DEP and DEPT) (nmol/mmol creatinine)

Time[a]	N	Mean	Median	SD	Q1[b]	Q3[b]
Pre-dip	54	10.8	5.7	14.6	0.0	15.8
Post-dip	48	38.2	14.9	68.2	7.8	44.5
Next morning	52	29.3	19.2	32.0	9.5	38.1
Post-dip - pre-dip[c]	46	29.0	12.8	63.6	0.0	30.4
Next morning - pre-dip[c]	50	18.6	9.0	32.9	0.0	25.7

[a] urine samples before (pre-), after (post-) dipping and 24 h after pre-sample (next morning); [b] Q1 & Q3 are first and third quartiles respectively; [c] simple difference between samples at these times.

The authors note that analysis of uptake and exposure excluded individuals whose pre-dip urinary metabolites were >40 nmol/mmol, and this had the effect of excluding four otherwise valid individuals. This was justified on the basis that there was some evidence that uptake for those with high pre-dip levels would be underestimated using a crude increment of pre- to post-dip as the high pre-dip level might mask small increments resulting from the days dipping activities.

In a separate analysis (Table 6), pre-dip metabolite levels were compared to responses to a short questionnaire on specific activities (sheep dipping, bath cleaning or draining, use of non-SD pesticides and contact with animals) which might have resulted in exposure to OPs during the three days prior to the main observed dipping session. Those individuals (eight) who had been involved in dipping prior to the main survey recorded clearly higher mean metabolite levels than those involved in either no activity or in the other possible exposure scenarios. The numbers in these groups were small and there was considerable overlap between groups. The authors state that having adjusted for the activity of sheep dipping, none of the other three activities could explain further the variation in pre-dip urinary metabolites. Among the 34 individuals who responded that they had not participated in **any** of the four above-mentioned activities, 17 had non-detectable levels of urinary metabolites. Several of the remaining 17 had urinary levels much greater than zero, including one with a measured concentration of 57.1 nmol/mmol.

Table 6: Pre-dip urinary metabolites (DEP+DEPT) and activities 3 days prior to sample

Activity	Response					
	Yes			No		
	Mean	SE	n	Mean	SE	n
Sheep dipping	27.8	5.6	8	7.8	1.8	46
Bath cleaning	11.2	3.1	11	10.7	2.4	43
Use of pesticides[a]	11.3	4.8	11	10.6	2.2	43
Contact with animals	19.8	8.6	7	9.4	1.9	47

[a] non sheep-dip pesticides

Relationship between exposure and uptake

The exposure indices for dip-concentrate, dip-wash and ingestion were analysed in relation to individuals' uptake as measured by the increment in urinary metabolites. The subset of those with no missing urine or exposure data (n=42) was used to determine the relative importance of the routes of exposure.

Not surprisingly, the total number of dip-concentrate handling events appeared to be positively associated with uptake, and the relationship approximated to uptake of a consistent amount of concentrate at each handling event, resulting in a 4 nmol/mmol increment in urinary metabolite over a 24-hour period. This simple linear model accounted for 56% of the overall variance in uptake. Omitting one individual (code 15/1)with higher than expected uptake (noted to have had additional exposure to concentrate through the handling of contaminated clothing) increased the figure to 64% of the overall variance in uptake. The authors note that this association depends heavily on one individual (code 10/2) who recorded 22 concentrate handling events and displayed the highest increment (12.7 nmol/mmol) in urinary metabolites. Omitting this individual as well meant that the linear model accounted for only 44% of the overall variance.

The condition of the gloves worn while handling concentrate was not a good predictor of uptake, as no significant increase in explained variation was observed when the total number of handling events were categorised by the condition of the gloves worn while handling. This observation is complicated by intra-individual variation; no individuals wore gloves which afforded good protection every time they handled concentrate. Similarly, accounting for other exposure indices (exposure from dip-wash or via ingestion) offered no statistically significant improvement to the fit of the model to uptake (ignoring the outlier from handling contaminated clothing).

An analysis was conducted of uptake against the time-weighted splash score for dip-wash for those who were never observed to have handled dip-concentrate (n = 21). This model assumed that uptake increases linearly with cumulative splashing, with dip wash summed equally over all ten body regions regardless of clothing. This suggested a positive association, despite some outlying observations (codes 17/2, 23/1) with high pre-dip metabolite levels (20% of variance). With the outliers removed the linear model accounted for 32% of the variation in uptake. When another outlier (code 10/1) with inexplicably high uptake level was omitted, this model accounted for 56% of the variation in uptake in non-concentrate exposed workers. Uptake plotted against the time-weighted splash scores showed a similar positive relationship for all categories of quality of clothing (none, poor/fair, good). The authors note that individuals wore protective clothing of varying quality across the different body regions where splashing occurred most often, and also removed items of clothing as the session continued.

The exposure index for dip wash was combined into the model for the data set (n = 42) for concentrate handling events. Table 6 shows the combined data as a linear regression model. Although the effect of dip-wash was not statistically significant, the authors state that including both variables in the models gave unbiased estimates of the relative size of the coefficients of the two basic indices of exposure to concentrate and dip wash.

Table 7: Linear regression coefficients after fitting the number of dip-concentrate handling events (CONC) and the time-weighted splash score (DIP) to all data

Data used	n	intercept	CONC	DIP	R^2
All cases	42	-2.40 (5.14)[a]	3.10 (0.79)	0.39 (0.16)	62%
Omit 17/2, 23/1, 15/1	39	3.01 (4.64)	3.56 (0.70)	0.15 (0.15)	65%
Omit 10/2	38	4.25 (4.61)	2.90 (0.80)	0.15 (0.15)	45%

[a](SE)

The authors proposed a model for the uptake of OPs during a full sheep dipping session :

Uptake = a*CONC + b*DIP

Where CONC is the expected number of times concentrate is handled and DIP is the expected time-weighted splash score had an individual been observed and data recorded in a manner similar to this study. The regression analysis which jointly fitted terms for concentrate and dip wash provided estimates for the coefficients *a* and b of 3.6 and 0.2 respectively, suggesting that in terms of uptake of diazinon, exposure to concentrate is 18-times more important than exposure to dip-wash.

Predictive value of the model

A retrospective estimation of exposure will of course be unable to quantify exposure to dip-concentrate and dip-wash directly. Hence indirect methods or the use of surrogate measures will be required to produce values for CONC and DIP in the uptake model.

The model suggests that differences in diazinon uptake are strongly dependent on the principal task performed by the worker, but this itself determines the number of exposure-to-concentrate events. Thus for principal task, where paddlers experience the greatest uptake, the problem is confounding since paddlers were observed to have handled concentrate far more often than those employed in the other tasks. Moreover the number of exposure-to-concentrate events is not a simple surrogate for uptake and an attempt should be made to quantify the degree of exposure to both dip-concentrate and dip-wash separately. The authors point out that there are other unrecorded/observed factors which may result in a more acute exposure including paddlers who plunge with their hands and/or feet and incidents of falling into the bath. Data on uptake for these events in minimal or zero in the present study.

This study confirmed earlier results that, due to the nature of the work within each task and their proximity to the dipping bath, paddlers are splashed more with dip-wash than chuckers, and both are splashed a great deal more than helpers. A two-factor analysis-of-variance indicated that principal task and bath type both, independently, accounted for differences in the splash scores. As well as confirming the differences in the amount of splashing among principal tasks, this also confirmed that splashing was lower for circular baths (with or without islands) than for linear baths, with mobile baths resulting in the least amount of splashing. The authors were able to calculate mean splash scores as predicted by the fitted two-factor model with principal task and bath type as independent effects. They suggest that these scores can be used to retrospectively quantify exposure if respondents answer questions about principal tasks and bath types.

Retrospective estimates of exposure to dip-concentrate are problematic. The authors noted that the most common reason for handling concentrate was to replenish the bath during dipping (recommended by the dip manufacturers to ensure that the dipping bath remained at the correct dilution throughout the session). This practice accounted for 81% of the total of 178 handling events. This was almost always done by one person, generally the paddler, who had a mean of 7 handling events compared to a mean of 1 for chuckers and less than 1 for helpers. Among all those with principal responsibility for handling concentrate, regardless of task, there was a mean of 8 handling events throughout the dipping session. It was suggested that replenishment of the bath and hence the number of concentrate-handling events might be associated with the size of the flock to be dipped. A positive statistical relationship between handling events and flock size was apparent, and the authors suggest that for various reasons the slope of the least-squares line fitted to this data is best approximated to 1 handling event per 100 sheep.

The authors have provided a "retrospective" exposure estimation for the study population assuming one concentrate handling event every 100 sheep for the person principally responsible for handling concentrate at each farm as an estimate of CONC, and the predicted mean splash score for the correct combination of task and bath type for all individuals as an estimate of DIP. Using the complete set of 42 individuals estimates of the coefficients for CONC and DIP were 2.59 (SE 1.04) and 0.18 (SE 0.21) respectively and explained 25% of total variation in uptake. Excluding the previously defined outliers (15/1, 17/2 and 23/1), gave estimates of 2.81 (SE 0.94) for CONC and 0.01 (SE 0.22) for DIP and 28% of the variation explained. The authors viewed these results as confirmatory and proposed that for retrospective exposure estimation the values of the coefficients for CONC and DIP to be used should be the same as the values of *a* and b of 3.6 and 0.2 respectively in the model:

Uptake = a*CONC + b*DIP.

Conclusion

Implications of findings for Phase 2

In order to perform retrospective assessment of exposure it is essential that the information sought can be reliably recalled by sheep farmers. This study indicates that there are some surrogate measures of exposure which are relatively constant factors and which might be reliably recalled by farmers, these being principal task and flock size. These measures appear to be good predictors of long-term average splash score and dip-concentrate handling events which are the best predictors of long-term average uptake of OPs. These surrogates of job and flock size explain about 25% of the variation in daily measured uptake of OPs in this first phase of the study.

The phase 1 study also found that almost all items of PPE observed were classified as affording only limited protection. Therefore, there was very little scope for comparison with the protection afforded by good, even recommended, quality PPE. The authors proposed that Phase 2 questions regarding PPE should be limited to those items most commonly worn;

gloves, leggings and Wellingtons. Additional questions were to be asked on unusual incidents such as falls into the dip bath, and plunging with hands or feet.

Phase 2

Cross-Sectional Exposure-Response Study of Sheep Dippers. Pilkington A, Buchanan D, Jamal GA, Kidd M, Sewell C, Donnan P, Hansen S, Tannahill SN, Robertson A, Hurley JF, Soutar CA.

Objectives

The specific objective of Phase II was to study the relationship between cumulative exposure to OPs and clinically relevant indices of peripheral neuropathy by means of a cross-sectional field study of sheep farmers and dippers.

Methods

The study was carried out in two areas of the UK where there is a relatively high density of sheep farming. The chosen regions were Herefordshire and Worcestershire in England and the Borders, Lothians and Ayrshire in Scotland. Suitable farms were identified from databases of annual census data maintained by the MAFF for farms in England and Wales and by the Scottish Office for farms in Scotland. The study group consisted of 612 farmers with sheep-dipping experience (SD farmers) from 293 farms. These were compared to two groups with low/nil expected exposure to sheep-dip OPs, viz. a group of 53 farmers with no sheep-dipping experience (NSD farmers) recruited from pig and chicken farms, combined with 107 ceramics workers from two factories.

Exposure history questionnaire

Retrospective exposure information was obtained for the period when OP use was common (1970 onwards), using a questionnaire developed during the first phase of the study. This exposure history questionnaire was administered by trained personnel and was designed after a pilot study established that the recall of farmers and farm workers was better when questioned by job rather than by pre-determined time periods. The main features included were flock size; concentrate handling; and principal task/job; these parameters were shown to be related to OP uptake in Phase 1 of the study, and considered amenable to recall at survey in Phase 2.

The work histories were later summarised into various surrogate indices of cumulative exposure based on the Phase 1 uptake model. These variables were: total number of dipping days (DAYS); total number of concentrate handling events (CONC); exposure to dilute dip (in the form of splash score (SPLASH); and a combined index (OPEXP) which attempted to quantify cumulative daily uptake of OPs. Based on the Phase 1 findings, the use of gloves or PPE was not formally included in these indices.

Neuropathy symptoms and sensory tests

Neurological assessments were conducted by trained personnel using a modified symptoms questionnaire in conjunction with a series of quantitative sensory tests (QST). The questionnaire was based on the Mayo Clinic Methodology (Dyck et al, 1980), modified for field rather than clinical use. The authors state that the Mayo Clinic methodology supports the use of sensory testing and questionnaire as a diagnostic screening test for neuropathy.

The symptoms questionnaire focussed on symptoms occurring in the upper and lower limbs or specific organ systems, and questions on cranial nerve involvement were excluded.

Symptoms were categorised into three symptom groups relating to muscle weakness (in upper and lower limbs), sensory symptoms (eg., numbness, pain, unsteadiness in walking) and autonomic symptoms (eg. sweating, fainting, bladder or GI symptoms). An overall symptom score was derived by adding together the total scores for the three symptom groups.

The QSTs were conducted by trained personnel using portable equipment. These automated tests assess thermal sensation (hot and cold) and vibration sensation on the subjects' feet. The authors reasoned that the tests were complementary, as the hot threshold tests unmyelinated C nerve fibres, the cold threshold tests thinly myelinated Aδ fibres, while the vibration threshold tests thicker myelinated Aβ fibres. Both hot and cold thresholds and vibration thresholds increase naturally with age, so for each test the subject scored positive or negative for an abnormal age-specific threshold based on comparison with the 95th percentile results from a group of normal subjects tested in a clinic.

Identification of symptoms and signs likely to represent peripheral neuropathy was based on the questionnaire and test results according to predetermined criteria.

The neuropathy scoring system used the combined results of the symptoms score and the QST score to allocate subjects to one of four diagnostic categories viz no, possible, probable and definite neuropathy as shown in table below.

Table 8: Neuropathy scoring system

Classification	**Criteria**
Definite neuropathy	Symptom score ≥ 2 and QST score ≥ 1
Probable neuropathy	Symptom score ≥ 1 and QST score ≥ 1
Possible neuropathy	Symptom score ≥ 1 or QST score ≥ 1
No neuropathy	Symptom score <1 and QST score = 0

The third phase of the overall study included a clinical follow up of a subgroup of subjects (n = 79) using a complete battery of tests. Subjects selected for Phase 3 were to be a sample of Phase 2 subjects stratified on the basis of the likelihood of neuropathy using field measurements. However early results found an unexpectedly high number of subjects (both ceramics workers and farmers) scoring positive for abnormal sensory thresholds in relation to clinical reference values. Clinical studies of these workers led to the conclusion that the field studies of the sensory test thresholds were not reproducible in the clinic and could not be used as the principal response variable in exposure-response analyses. The authors stated that the measured differences between clinic and field in sensory thresholds (hot - factor of two lower in the field; vibration - factor of two higher in the field) could be explained by the generally low ambient field temperatures during the field survey relative to the controlled temperature in the clinic. It was further noted however, that there was a positive correlation between the measured field and clinic thresholds, ie. a subject with a high threshold in the clinic was likely to have recorded a high threshold in the field. The authors conclude that while it is inappropriate to classify subjects into "normal" and "abnormal" groups based on QST thresholds, there is still benefit in using the actual measured thresholds as individual continuous response variables. They conclude that the cross-sectional study would not use the modified Mayo-clinic neuropathy scoring system as described above, but rather use the four distinct variables (symptom score and three QSTs) in the analysis of exposure-response relationships by performing four separate regression analyses.

Results

The study population

Following the recruitment and survey process a number of subjects from all groups were excluded from the final study group because they did not meet the predefined inclusion criteria due to disease, medications or had disqualifying exposure to sheep dip (seven ceramics workers). The final study group for analysis consisted of a total of 772 subjects. Of these, 107 were ceramics workers with no experience of sheep dipping, 53 were farmers or farm workers with no experience of sheep dipping, and 612 were farmers or farm workers with experience of sheep dipping. Raw data were not provided for analysis; the summary information is described below. There was no significant difference among the occupational groups in any of: average height (males: mean 1.78 m, SD 0.07 m); weight (males: mean 80.6 kg, SD 11.6 kg); dietary pattern; left-handedness (ca. 8%) across the groups). Variations in age, alcohol consumption, smoking status and education levels are shown in the table below.

Table 9: Summary of final Phase-2 study group

Variable[a]		**Ceramics (%)**	**NSD farmers (%)**	**SD farmers (%)**
Country	Scotland England	36 (34) 71 (66)	46 (87) 7 (13)	344 (56) 268 (44)
Age	15-24	11 (10.3)	9 (17.0)	35 (5.7)
	24-34	30 (28.0)	15 (28.3)	131 (21.4)
	35-44	40 (37.4)	7 (13.2)	142 (23.2)
	45-54	19(17.8)	17 (32.1)	149 (24.3)
	55-64	7 (6.5)	5 (9.4)	113 (18.5)
	65-74	0	0	37 (6.0)
	≥75	0	0	5 (0.8)
	Mean [SD]	38.6 [10.2]	39.2 [12.7]	45.1 [13.4]
Sex	M F	104 (97.2) 3 (2.8)	50 (94.3) 3 (5.7)	524 (85.6) 88 (14.4)
Alcohol (units/week)	None	2 (1.9)	3 (5.7)	41 (6.7)
	≤5	16 (15.0)	22 (41.5)	293 (47.9)
	5-15	35 (32.7)	16 (30.2)	176 (28.80
	15-30	34 (31.8)	10 (18.9)	78 (12.7)
	30-45	14 (13.1)	1 (1.9)	19 (3.1)
	>45	6 (5.6)	1 (1.9)	5 (0.8)
	Mean[b] [SD]	19.1 [16.2]	10.1 [12.8]	8.2 [10.2]
Smoking	Never	50 (46.7)	24 (45.3)	375 (61.3)

(cigs/day)	smoked			
	Ex-smoker	22 (20.6)	10 (18.9)	116 (19.0)
	≤10	11 (10.3)	4 (7.5)	54 (8.8)
	10-20	17 (15.9)	10 (18.9)	48 (7.8)
	20-30	6 (5.6)	2 (3.8)	15 (2.5)
	>30	1 (0.9)	3 (5.7)	4 (0.7)
Education	No quals	46 (43.0)	19 (35.8)	226 (36.9)
	Secondary	36 (33.7)	16 (30.2)	162 (26.5)
	Tertiary	25 (23.5)	18 (34.0)	224 (36.6)

[a] NSD = non-sheep dip, SD = sheep dip; [b] drinkers only

Sheep-dip farmers tended to be older with mean age of 45 years *vs* 39 years for both the NSD farmers and ceramics workers. There was also a higher proportion of female subjects among sheep-dipping farmers (14%) than among other farmers (6%) or ceramics workers (3%). Both classes of farmers tended to be better educated than the ceramics workers and drink less. A small number of subjects consumed greater than 45 units per week (n=12), with a maximum of 92 units per week recorded for one individual ceramics worker. Although the number of ex-smokers was similar among the three groups (19%), there were fewer current smokers among sheep-dipping farmers (20%) than among other farmers or ceramics workers (34%).

Estimates of exposure

The ceramics workers and NSD farmers were regarded as having no exposure to sheep dips. Four exposure indices were calculated for each subject in the sheep-dipping farmer group (Table 10). No raw data was provided. The simplest of these indices, DAYS, estimates the total number of days dipped since 1970. This variable was highly skewed, ranging up to a maximum of 1350 days, with the majority of estimates below 100 days, and a significant minority (ca. 25%) below 30 days. Variable CONC is an estimate of the number of handling events across all dipping days, and clearly there was a significant minority who handled the concentrate very little or not at all. Variable OPEXP, which is a weighted sum of the SPLASH and CONC variables is an estimate of overall OP exposure based on the phase 1 model and can be expressed as nmol.days/mmol of creatinine.

Table 10: Summary of exposure variables among SD farmers (n=612)

Statistic	DAYS	Splash ($x10^{-3}$)	CONC	OPEXP
Minimum	1	0.00	0	0.00
25th %-ile	28	1.08	9	0.35
Median	54	2.44	185	1.25
75th %-ile	102	5.00	484	2.70
Maximum	1350	75.77	9348	48.81
Mean (SD)	91 (127)	4.48 (7.26)	418 (816)	2.40 (4.28)

All four variables were correlated, with the lowest correlation (r = 0.86) between DAYS and CONC reflecting the large subset who rarely handled the concentrate. The highest correlation was between CONC and OPEXP (r = 0.99), and this is a consequence of the high weight attached to the concentrate handling component of exposure, relative to the splash score component, in the phase 1 model. The two individuals with the greatest number of days dipped also score the highest in all the other exposure variables.

The authors report that a total of 55600 dipping days were recorded across the study group. The period 1970 -1983 accounted for 42% of days dipped; 35% were estimated to have taken place between the years 1984-91 when OP sheep dips were licensed and widely used, while the period 1992-1997, accounted for 23% of days dipped. The exposure indices appeared to be consistent across these three time periods.

Exposure-response relationships

The analysis of exposure-response relationships was conducted using the four neurological response variables viz. **reported** symptoms, and the hot, cold and vibration sensory test thresholds. The main analytical approach was regression modelling. The data are presented as comparisons of responses across occupational groups both as crude estimates and after adjusting for important confounding variables (Part A). An attempt was made to quantify the relationship between the responses and the indices of cumulative exposure, also adjusting for important confounders (Part B). Some analyses of non-cumulative exposure indices and effects of other potential sources of OP exposure were also described (Part C).

<u>Part A - Occupational Groups</u>

For reasons discussed elsewhere, only the detailed analyses for the "symptoms" variable are reported here.

a. *The symptom score*

The self-reported symptom score for the occupational groupings is summarised in Table 11. Subjects responded to questions about muscle weakness including duration and parity. Negative sensory symptoms were inferred from questions relating to numbness and insensitivity to temperature or touch; positive sensory symptoms were inferred from questions relating to pain or unusual sensations; questions relating to autonomic symptoms were directed at individual organ systems. In all groups, autonomic symptoms were more frequently reported than sensory or motor symptoms.

Table 11: Prevalence of symptoms by occupational group [% affected (number)]

Symptom	Ceramics	NSD farmers	SD farmers
Muscle weakness			
Hands	0	1.9 (1)	6.4 (39)
Shoulders	0	0	2.0 (12)
Feet	0	0	2.3 (14)
Legs	0	3.8 (2)	0.8 (5)
Negative sensory			
Feet	0	3.8 (2)	5.2 (32)

Hands	0	0	2.1 (13)
Positive sensory			
Feet	1.9 (2)	5.7 (3)	10 (61)
Hands	0.9 (1)	3.8 (2)	5.4 (33)
Autonomic			
Fainting	3.7 (4)	15 (8)	14 (87)
Diarrhoea	0	0	0.7 (4)
Bladder	0	0	1.8 (11)
Impotence	0	1.9 (1)	5.6 (34)
Sweating	7.5 (8)	5.7 (3)	8.2 (50)
Group size	**107**	**53**	**612**

Table 12 shows the crude prevalence of reported symptoms broken down by age. The overall incidence was highest among SD farmers (19.1%), followed by NSD farmers (11.3%) and ceramics workers (4.7%). About one fifth of SD farmers were assigned a symptom score of 1 or more, which was almost twice the rate for NSD farmers, and almost four times the rate for ceramics workers. The consistency of these differences with age was difficult to ascertain due to the small numbers of ceramics workers and NSD farmers within specific age groups. However, there was a clear trend in reported symptoms with age among the SD farmers, that rose to a prevalence of over 30% in the oldest age group.

Table 12: Prevalence (%) of reported symptoms by age group

Symptom group	**Age**				
	<35	**35-44**	**45-54**	**≥55**	**All**
Muscle weakness					
Ceramics	0.0	0.0	0.0	0.0	0.0
NSD farmers	4.2	0.0	0.0	0.0	1.9
SD farmers	3.0	7.0	7.4	14.2	7.8
Sensory symptoms					
Ceramics	0.0	2.5	0.0	14.3	1.9
NSD farmers	0.0	14.3	5.9	20.0	5.7
SD farmers	5.4	11.3	11.4	18.7	11.6
Autonomic					
Ceramics	17.1	5.0	5.3	14.3	10.3
NSD farmers	25.0	28.6	17.6	0.0	20.8

SD farmers	26.5	24.6	26.8	35.5	28.4
Overall					
Ceramics	4.9	5.0	0.0	14.3	4.7
NSD farmers	12.5	14.3	5.9	20.0	11.3
SD farmers	9.0	16.9	20.1	31.0	19.1
Age distribution					
Ceramics	41	40	19	7	107
NSD farmers	24	7	17	5	53
SD farmers	166	142	149	155	612

The differences between the occupational groups, unadjusted for any confounders, are shown in Table 13. Symptoms were scored as a binary (yes/no) indicator variable and the effects are presented in these tables as odds ratios (OR) which are directly estimated from the parameters of the fitted model. For the three QST thresholds, the effects presented are multiplicative factors since these variables were analysed on the logarithmic scale. Table 13 shows the unadjusted ORs which compare directly the odds of symptoms among SD farmers relative to the odds among both NSD farmers and ceramics workers. Without adjustment for potential confounders, there was an almost 5-fold increase in the symptoms reporting among SD farmers compared to ceramics workers generally, and a smaller increase (approximately 2-fold) compared to NSD farmers. Table 12 also shows that before adjustment for any potential confounders, the QST thresholds for SD-farmers for hot, cold and vibration were on average higher than among NSD farmers and ceramic workers.

Table 13: Unadjusted differences between occupational groups showing multiplicative effects (x effect) and 95% confidence intervals (CI)

SD farmers v.	Symptoms		Hot threshold		Cold threshold		Vibration threshold	
	OR	CI	x effect	CI	x effect	CI	x effect	CI
NSD farmers	1.89	0.79 - 4.52	1.25	0.85 - 1.83	1.87	1.46 - 2.39	1.47	1.06 - 2.03
Ceramics	4.82	1.97 - 12.26	1.54	1.17 - 2.04	1.55	1.28 - 1.86	1.68	1.32 - 2.14

Table 14 shows an analysis of the reported symptoms score only. The occupational-group differences, adjusting for important confounding variables and interactions, are shown as Model S/1. Age was found to be an highly significant effect with, on average, a 43% increase in the odds of symptoms for every 10 years of age. There was a statistically significant higher prevalence of symptoms in England, higher by a factor of almost 2, compared to Scotland. The effect of alcohol consumption (number of units per week) was not significant. There was no evidence of any statistically significant interaction between age and either occupational group or country, or between occupational group and country. The ORs between the occupational groups show a significantly higher prevalence of symptoms in SD farmers compared to ceramic workers (OR=4.4), and a non-significant although higher prevalence in SD farmers compared to NSD farmers (OR=1.3). Therefore, in comparison with the unadjusted ORs in Table 13 the potential confounding effects of age, and country account for only a small fraction of the large difference between SD farmers and ceramics workers. A small number of subjects for whom either no response variable was recorded or for whom no relevant exposure data was recorded were omitted from the analysis.

Table 14: Odds Ratio (OR) and 95% confidence intervals (CI) for prevalence of reported symptoms between occupational groups

Terms	Model S/1		Model S/2		Model S/3		Model S/4	
	OR	CI	OR	CI	OR	CI	OR	CI
Age/10 (years)	1.42	1.22-1.66	1.42	1.22-1.66	1.41	1.21-1.65	1.40	1.19-1.65
Country (E v S)	1.76	1.18-2.64	1.93	1.27-2.92	1.90	1.26-2.88	2.05	1.34-3.12
SD farmers v								
NSD farmers	1.29	0.52-3.16	1.07	0.43-2.68	1.12	0.45-2.78	0.68	0.24-1.89
Ceramics	4.39	1.74-11.09	3.85	1.51-9.82	3.99	1.57-10.14	2.52	0.90-7.11
DAYS/IQR			1.13	1.01-1.25			1.11	1.00-1.24
OPEXP/IQR					1.11	1.01-1.23		
Av. OPEXP								
10-22 v <10							1.73	0.89-3.38
22-35 v <10							2.23	1.16-4.29
>35 v <10							1.46	0.75-2.87
Deviance (df)	637.5 (758)		633.0 (757)		633.3 (757)		626.6 (754)	

IQR = inter-quartile (74 for DAYS, 2350 for OPEXP)

b. Summary of Hot QST Threshold data

A plot of the hot QST thresholds (on a log scale) against age at survey shows wide variation among individuals. However there is a clear increasing trend with age in all three groups, but little or no separation in mean thresholds between the three occupational groups. There is some evidence, most noticeably among SD farmers, to suggest that thresholds rise more steeply after approximately age 45 years. Table 13 shows that, before adjustment for any potential confounders, thresholds among ceramics workers were, on average, lower than among both groups of farm workers.

Both age and sex but not alcohol consumption, were found to be significantly related to the hot threshold. The data predicted that 10 years of age resulted in a 63% increase on average in the hot threshold, while thresholds in males were on average over twice those in females (the majority of whom were sheep dippers). There was also a country effect present in the hot

QST data, such that although in Scotland farmers generally had lower thresholds than ceramics workers, in England, the reverse was true.

c. Summary of Cold QST Threshold data

A plot of the cold QST thresholds, on a logarithmic scale, against age at survey shows wide variation among individuals with a clear increasing trend with age in all three groups. Only among ceramics workers was there evidence of a steeper increase in later years (> 40 years). Table 13 shows that, before adjustment for any potential confounders, thresholds among SD farmers were, on average, higher than among both other groups.

Both age and sex, but not alcohol consumption or country, were found to be significantly related to the cold threshold, although the size of the effects, particularly the sex difference, were lower in relation to those for the hot threshold. The data predicted that 10 years of age resulted in an average 30% increase in the cold threshold, while thresholds among males were on average 38% higher than among females. Adjusting for these confounders, there was a significant difference among the three occupational groups such that thresholds among SD farmers were higher than among ceramics workers and higher than among NSD farmers. There was no evidence of a significant interaction of these effects with country of residence, or with the other important confounders.

d. Summary of Vibration QST Threshold data

A plot of the vibration QST thresholds, on a logarithmic scale against age at survey shows wide variation among individuals with a clear increasing trend with age in all three groups. Within all three groups was there evidence of a steeper increase in thresholds after the age of 50 years. From the figure there was no strong evidence of a difference in average vibration thresholds among the three groups. Table 13 shows that, before adjustment for any potential confounders, thresholds among SD farmers were, on average, higher than among both other groups.

As for the other thresholds, age and sex, but not alcohol consumption, were found to be significantly related to the vibration threshold. The data predicted that 10 years of age resulted in a 63% increase, on average, in the vibration threshold, while thresholds among males were on average 21% higher than among females. After adjusting for these confounders, there was a significant country effect. The basic pattern was a reversal of that found in the two countries for the hot threshold. In Scotland, SD farmers, and NSD farmers, had significantly higher vibration thresholds than ceramics workers, while in England, both SD farmers, and NSD farmers, were lower on average than the ceramics workers. This arose because although there was no significant difference between the Scottish and English SD farmers, there was evidence of a significant difference between the two groups of ceramics workers such that vibration thresholds among English ceramics workers were on average higher than among Scottish ceramics workers.

Part B - Analysis of cumulative exposure

a. Symptoms

The effect of cumulative exposure was investigated by sequentially adding further terms (representing estimates of cumulative exposure) to the confounder-adjusted regression models, thus allowing each term to be adjusted for all others in the model (Table 14; Models S/2 - S4). Models S/2 and S/3 in Table 14 show the estimated effects from the important confounders and occupational group differences and include as variables the two cumulative exposure indices DAYS (the total number of days dipped) in S/2, and OPEXP (cumulative exposure index) in S/3. Both these variables were scaled to show the gradient of the linear effect over the inter-quartile range (IQR) and transformed to an OR; both linear effects were statistically significant at the 5% level.

Comparison of models S/1 and S/2 and hence adjusting for cumulative exposure (DAYS), showed that the much higher symptoms prevalence among SD farmers relative to ceramics workers was only slightly reduced (OR 4.39 v OR 3.85). The higher prevalence of reported symptoms in England marginally increased however (OR 1.76 v OR 1.93), while the effect on age was negligible, reflecting the low correlation between these two variables.

The two variables DAYS and OPEXP show a high correlation; this is expected since they are both weighted sums of the same number of days dipped but using different weights. The authors note that it is very difficult to determine whether the more complex index based on the Phase 1 model did, in fact, reflect any important attribute of exposure in addition to total duration of exposure. In order to answer this question further analysis was undertaken by forming a new variable to give an estimate of the average OP exposure intensity per day dipped. This variable formed by dividing OPEXP by DAYS was grouped in four equal-sized groups by quartiles based on the observed distribution of exposure among SD farmers. This grouped variable, labelled "Ave. OPEXP" was then added to the exposure-response regression model for each variable that included the important confounders and adjusted for cumulative days dipped (Model S/4 in table 14).

Relative to the group with lowest average exposure intensity (<10 units), symptoms were estimated to be higher among those in the higher intensity groups. The difference did not appear to increase consistently with average exposure intensity, but appeared to peak at the second highest intensity group. The use of "Ave OPEXP" to adjust for average exposure intensity as well as cumulative days dipped appeared to reduce the size and significance of the difference between SD farmers and ceramics workers without affecting greatly the age and country effects (Model S/4).

b. QSTs

Due to the lack of significant findings reported, this data is presented here as a summary only. Scatter plots of the three QST thresholds against cumulative exposure, expressed as total days dipped show a large degree of inter-individual variation at all levels of exposure, but no evidence of a trend with exposure. Statistical analyses of cumulative exposure adjusted for known confounders reveal that neither index of exposure has a positive gradient with respect to the hot, cold or vibration thresholds. As the authors state, these QST findings add little support to the hypothesis of cumulative and irreversible damage to nervous tissue.

c. Other findings

- As an exposure estimate, total days spent dipping (DAYS) is as good as, or better than, the weighted estimate (OPEXP).

The variable DAYS was an estimate of the total number of days spent dipping during the research period, OPEXP was a weighted total over the same number of days, with weights for each dipping day, reflecting intensity of exposure, being determined by predicted exposure to both concentrate and dilute dip. The data show that for all four neurological responses, the simple sum of days dipped, DAYS, resulted in a marginally better fit, corresponding to a lower residual deviance, than the cumulative exposure index OPEXP. Only for symptoms was there evidence of a positive statistically significant relationship with cumulative exposure, but the significance of this effect depended on adjustment also for country. The authors state that in the context of age, 22 days of dipping was approximately equivalent to one year of aging in terms of increasing prevalence of symptoms.

• The SPLASH component in the phase I cumulative exposure model appears to be of little importance. The significant effects related to concentrate handling intensity were independent of duration of exposure.

In phase 1 concentrate handling was identified as the major route of exposure to OP sheep dips and this was reflected in the model derived for phase 2 of the study. An analysis (data not shown here) of relative importance of both the concentrate handling (CONC) and splash score components (SPLASH) of OP exposure intensity showed that for the variables symptoms and vibration threshold (but not for hot or cold thresholds), grouped average concentrate handling intensity per day (av CONC) produces a better fit to the response data than average OP exposure intensity based on the full exposure model (av OPEXP). For both the symptoms and vibration threshold variables, the inclusion of av-CONC, in addition to DAYS and the important confounders, was statistically significant at the 5% level. Importantly the analyses also showed that for none of the models fitted, was there a significant interaction between average intensity and total days dipped, indicating that the apparent effects of average intensity per day dipped were not dependent on the total number of days dipped.

• Restricting the analysis to the presumed peak exposure period of 1984-91 did not alter the findings.

The exposure history questionnaire asked specifically about dipping using OP products back to 1970. Given that peak usage is likely to have occurred between 1984 and 1991, the exposure variables (DAYS and OPEXP), for the period 1984-91 were calculated and substituted into models that included the important confounders. The results of the analyses were similar to those using the entire dataset ie. there was no additional evidence of a cumulative exposure effect when exposure was restricted to the period 1984-91 when peak usage was expected to have occurred.

• The statistical significance of the relationship between cumulative exposure and symptoms is determined by the inclusion of a very small number of highly exposed individuals.

The distribution of cumulative exposure was highly skewed with a small number of the most highly exposed individuals on the extreme upper end of distribution, and analysis showed these points had had high leverage in the models. Since the points with the highest leverage were not in the main also outliers, the models were re-fitted excluding those points which had a leverage value over 6 times the average leverage of all points. This resulted in the exclusion of 4, 17, 10, and 18 data points in the regression models of symptoms, hot, cold and vibration thresholds respectively. Exclusion of these points made little difference to the estimated exposure regression coefficients for the three QST thresholds. There was, however, a slight reduction in the size of the cumulative exposure effects for symptoms and despite excluding only four subjects from among a study group of almost 800, the gradient for cumulative exposure would no longer be deemed statistically significant.

Part C - Other aspects of exposure

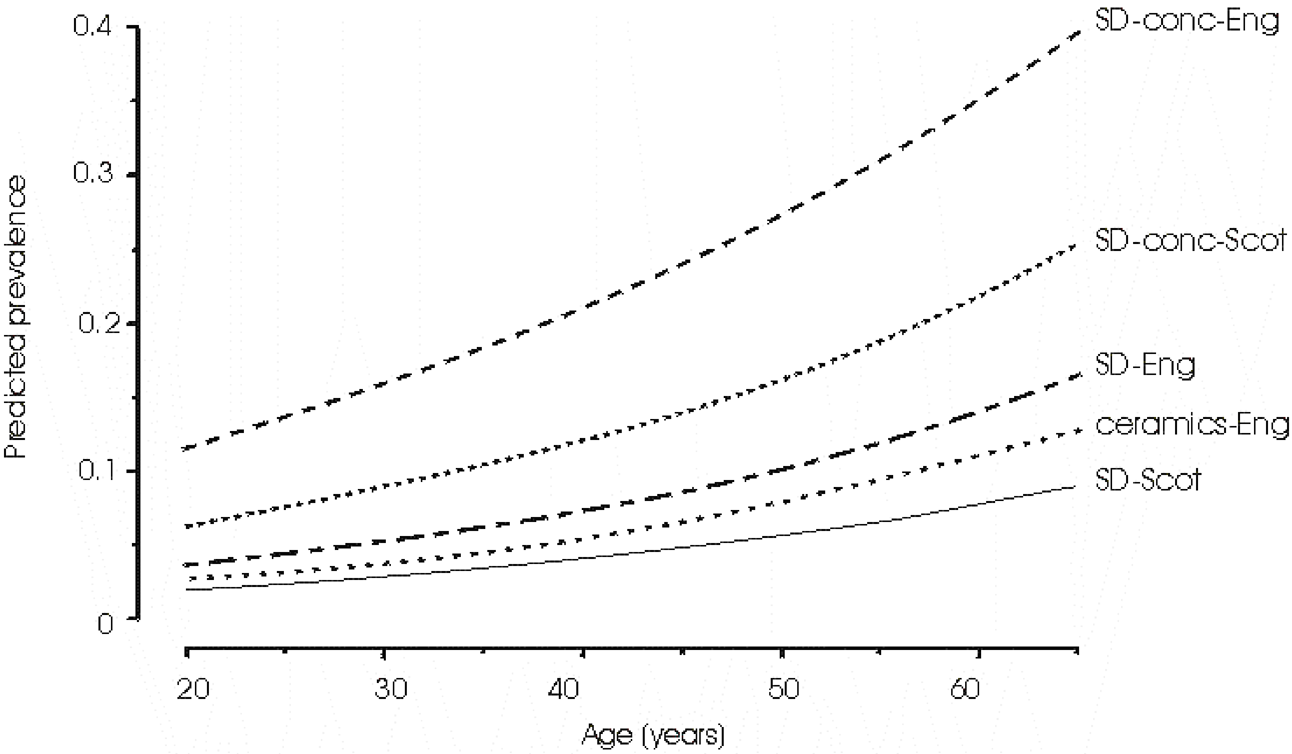
The importance of concentrate handling was investigated by including a variable which indicated those individuals who had been principal concentrate handlers into the logistic regression model of symptoms. This model included the effects of total days dipped and the important confounders, including sex, and the parameters are shown in Table 15 (Model S/5) below. The model indicates that males reported far fewer symptoms than females given the same exposure, age and country (OR = 0.34; CI: 0.17—0.70) and concentrate handlers reported far more symptoms than those who had never been concentrate handlers (OR = 3.43; CI 1.63—7.23). It is evident that this reciprocal effect is due to the fact that only 25% of females had handled concentrate compared to 87% of males. Including the effects of concentrate handling and sex in the model eliminated the statistically significance of the term for cumulative days dipped to (P = 0.08). Adjusting for concentrate handling decreased the large difference in symptoms prevalence between SD farmers and ceramics workers (OR = 1.27; 95% CI: 0.40—4.00), such that SD farmers with no experience of handling concentrate were estimated to have the same prevalence of symptoms as ceramics workers of the same age, sex and country.

Table 15: Prevalence of reported symptoms including the effects of sex and concentrate handling

Terms	Model S/5	
	OR	CI
Age/10 (years)	1.43	1.22-1.67
Country (E v S)	1.98	1.30-3.03
SD farmers v		
NSD farmers	0.37	0.12-1.15
Ceramics	1.27	0.40-4.00
DAYS/IQR	1.10	0.99-1.23
Sex (male v female)	0.34	0.17-0.70
Conc. Handler (Ever v Never)	3.43	1.63-7.23
Deviance (df)	637.5 (758)	

The prevalence of symptoms predicted by this regression model is shown in Figure 1 which graphs the predicted prevalence (or probability) of symptoms for male SD farmers aged 20 to 65 years under the four combinations of country (England or Scotland) and concentrate handler (ever or never). All predictions in Figure 1 are based on 50 days dipped. Among concentrate handlers (SD-conc-Eng and SD-conc-Scot) there is a predicted age-related increase in symptom reporting reaching 35% (95% CI: 27—43%) at age 60 years for English sheep-dippers, and the higher incidence of reportage in England vs Scotland is clear. The figure also shows the predicted prevalence among male English ceramics workers which is always marginally higher than Scottish SD farmers who had never handled concentrate.

Figure 1: Predicted prevalence of symptoms based on concentrate handling



Predicted prevalence of symptoms among male sheep dippers (SD) and ceramics workers by concentrate handling (conc) and country.

In phase 1 of the study it was found to be not possible to quantify and summarise the protection afforded by PPE worn concurrently with episodes of exposure, hence it was not anticipated that use, and quality, of PPE could be quantified adequately for individuals based solely on a retrospective questionnaire. However, questions regarding the use of waterproof trousers, footwear and gloves were included in the exposure questionnaire within sheep dipping jobs, and the authors state that the questionnaire design allowed quantitative estimates to made of the proportion of time spent wearing PPE whilst dipping within each dipping job. A weighted average of these estimates across dipping job was then calculated, weighted by the number of dipping days within each job. However the scatter plots show little relationship between the average percent use of PPE (self-reported) when plotted against average exposure intensity among all sheep dipping farmers. Additionally, when the use of gloves whilst handling concentrate was plotted against concentrate handling intensity among all those who claimed to have been principal concentrate handlers, the use of gloves was estimated to occur with a frequency of less than 50%. However, there was some evidence that those with the highest exposure to concentrate made greater use of gloves while handling and therefore may have experienced greater protection from exposure to concentrate.

The neuropathy symptoms questionnaire included questions about current exposure to vibration, both occupationally, as in the number of hours per day using different types of vibrating equipment, and at leisure, as in the numbers of hours per week spent in hobbies with potential exposure to vibration. All occupational groups had significant exposure to some sort of vibrating equipment such as tractors, saws and fork lifts, or to recreational exposures from activities such as motor cycling and mountain biking. Although the QST thresholds showed some relationship to hours/day or hours/week using vibrating equipment, no variable was confounded with the effect of concentrate handling intensity.

The exposure history questionnaire included basic questions regarding general use of pesticides and insecticides, either occupationally or domestically, during the working life of each subject. In addition, sheep dippers were asked about use of sheep dips other than in dip baths (e.g. direct application). All subjects were asked if their current jobs included working with lead, solvents or insecticides. Current work with solvents was high in all three groups, and unsurprisingly, insecticide use was much higher among the farmer groups. A majority of the sheep dipping farmers had used sheep dips other than for dipping (71%), and had treated cattle for warble fly (63%). All subjects had used insecticides domestically to some degree. None of these variables could be used as additional quantitative indices of exposure to OPs. However, each variable was analysed to determine whether there was evidence that the significant non-cumulative exposure effects estimated for OP sheep dips could be explained by simple indicators of both exposures to other sources of OPs, and other exposures which result in similar neurological responses.

This analysis showed a statistically significant effect (allowing for other confounders and cumulative exposure) for **symptom** score and use of sheep dips other than for dipping (by SD farmers). This effect was confounded with concentrate handling, the estimated OR of which reduced from 3.4 to 2.5. This reflected that relatively more concentrate handlers had used dips other than for dipping compared to non-concentrate handlers; however, even this reduced effect remained statistically significant. No other exposure variables confounded the effect of concentrate handling or, could explain the sex and country differences found earlier.

<u>Conclusions</u>

Key findings Phase2

Occupational groups

In comparing the occupational groups, ceramic workers, NSD farmers and SD farmers, the crude self-reported incidence of neurological symptoms was highest among SD farmers for all three symptom groups (autonomic, sensory, muscle weakness). For symptoms, there was also a strong regional difference, with a higher prevalence in England (OR = 1.8) compared to Scotland, among subjects of the same age and occupational group. Adjusted for age and country, prevalence of symptoms among SD farmers was similar to NSD farmers but remained high in comparison with ceramics workers (OR = 4.3).

Thermal and vibration thresholds among SD farmers were also, on average, higher than among NSD farmers and higher still (except for cold threshold) than among ceramics workers. Age was found to be strongly related to all four neurological responses, with increasing symptoms prevalence and QST thresholds with increasing age. In addition to an age effect, there was also evidence of a sex effect across the three QST thresholds, with males having higher thresholds, on average, than females. Adjusting for age and sex, there were found to be inconsistent differences among occupational groups between countries for the hot and vibration thresholds. Current alcohol consumption was not found to be a confounder.

Cumulative exposure

Symptoms was the only neurological response to show a positive relationship with cumulative exposure, whether exposure was measured by OPEXP derived from the phase-1 model, or DAYS which simply measured duration of exposure. The estimated effect predicted a 13% increase in the odds of symptoms per 74 days dipped and was consistent across the full range of exposures and consistent between the two countries. However, the statistical significance of the gradient depended on the inclusion of the small number of very highly exposed individuals. Restricting the analysis to the period 1984-91, when OP sheep dips were at peak usage, did not improve the statistical reliability.

After adjusting for cumulative exposure in addition to age and country, the odds of symptoms remained almost four times higher among SD farmers than among ceramics workers. None of the cold, hot or vibration thresholds had significant linear relationships with cumulative exposure. Adjusting for cumulative exposure in addition to age and sex, did not explain the inconsistent differences among occupational groups between countries in relation to hot and vibration thresholds, nor the higher average cold threshold among SD farmers compared to NSD farmers and ceramics workers.

Concentrate handling

The effect of concentrate handling on symptoms prevalence could be succinctly summarised as a difference between those who had, and those who had not, ever acted as principal concentrate handler (OR = 3.4; 95% CI 1.6—7.2). This effect was independent of and of greater significance than the duration of exposure. With adjustment for concentrate handling, together with the important confounders, sex was also shown to affect symptoms prevalence, with females being over three times more likely to report symptoms than males of the same exposure, age and country.

Having adjusted for concentrate handling together with age, sex and occupational group, there remained a much higher prevalence of symptoms among English subjects compared to Scottish subjects (OR = 2.0). On the basis of the background information on factors such as farm size, age groups and level of education, there was nothing to suggest that the farmers from Scotland and England differ significantly other than by place of residence, nor was there any evidence to suggest a significant difference in the general pattern of OP usage between England and Scotland.

Uncertainties

- It is difficult to assess the reliability of the exposure data obtained or the degree of recall bias.

- It is also difficult to assess the impact of changes in awareness of potential health issues associated with OPs, and whether this varied across the sample of sheep dippers. It was noted that there was more media coverage of the issue in England during the period of the survey and this could in part explain the differences in reported level of symptoms between the two areas.

- Even after adjusting for exposure there was twice the reported prevalence of symptoms in the English farmers compared with Scottish farmers. However, there were no consistent or significant regional differences among the sensory threshold results.

Phase 3: Clinical neurological, neurophysiological and neuropsychological study. Report no. TM/99/02c: Pilkington A, Jamal GA, Gilham R, Hansen S, Buchanan D, Kidd M, Azis MA, Julu PO, Al-Rawas S, Ballantyne JP, Hurley JF and Soutar CA.

Objectives

The specific objectives of Phase 3 were to: classify in terms of clinical disease the subjects with abnormal indices of peripheral neuropathy identified in the Phase 2 field studies; describe any associations between neurological and neuropsychological abnormalities; and examine any evidence for a relationship between neuropsychological status and estimated cumulative OP exposure.

Methods

Recruitment of study group

A subset of subjects involved in the Phase 2 field study were invited to participate in the Phase 3 clinical studies at the Institute of Neurological Sciences (INS) in Glasgow. The neuropathy scores from the field studies were calculated and subjects placed into the categories of the "no", "possible" and "probable/definite" as shown in Table 16. The exceptionally high number of "possibles" clearly indicated a methodological problem arising from high scores for "abnormality" in the Phase 2 QST scores, especially the cold threshold. **The 247 subjects who had scored "possible neuropathy" on the basis of cold threshold were eliminated from further study**, and 80 randomly-chosen subjects from the remaining 269 subjects in the "possible neuropathy" category were invited to participate in the clinical studies. A further 80 subjects were invited from the "no neuropathy" category as were all 44 sheep farmers from the 48 "probable/definite" category.

Table 16: Neuropathy scores from Phase 2 surveys

Classification	Criteria	Phase 2 results
4 Definite neuropathy	SS ≥ 2 and QST score ≥ 1	48
3 Probable neuropathy	SS ≥ 1 and QST score ≥ 1	
2 Possible neuropathy	SS ≥ 1 or QST score ≥ 1	516
1 No neuropathy	SS <1 and QST score = 0	125

Seventy nine subjects (all were sheep farmers) attended assessments at INS. Three individuals from the 79 had potentially confounding medical conditions recorded on their Phase 2 neuropathy questionnaires and were excluded from further Phase 3 analysis. No ceramics workers were invited to attend the clinical study, and of the few non-exposed farmers invited, none in fact participated. For attendees at the clinic, the minimum number of days dipped was five days for any individual in the study group. Overall, 67% of those attending the clinic were Scottish sheep dippers.

Neurological Symptom Score questionnaire includes selected clinical symptoms known to occur in neuropathy, scored on the basis of present (1) and absent (0). The questionnaire was the same as that used during the Phase 2 epidemiological survey, but excluding details of occupation or details of relevant occupational exposure. Questions focused on symptoms occurring in the upper and lower limbs.

Neurological Disability Score was derived from a clinical examination and results were scored on the basis of severity from no deficit (0) to complete loss of function (4). The assessment was generally performed on the right side of the body (ie. reflexes, sensation, muscle power) unless otherwise indicated and both upper and lower limbs were assessed. Muscle power was assessed by applying an inverse MRC scale, where a score of zero signifies normality and a higher score signifies increasing abnormality.

Quantitative sensory testing (QST) was undertaken by measuring hot and cold thermal thresholds on the dorsum of the right foot to test for small peripheral nerve fibre function and vibration threshold over the middle of right index metacarpal and 1st metatarsal bone to test the large peripheral nerve fibre function. The equipment used was the same as in the Phase 2 field studies, with the addition of the Glasgow Vibration System (GVS).

Nerve Conduction Studies measured both sensory (sensation) and motor (muscle power) nerve function in the upper and lower limbs, focussing on large peripheral nerve fibres. Standard EMG (electromyograph) studies were carried out on a variety of muscles, while single fibre EMG studies were performed on the right extensor digitorum communis muscle. Motor nerve conduction and late response studies were carried out in both upper (motor and sensory on the right median nerve) and lower (right common peroneal motor and right sural sensory) limbs using standard techniques.

A battery of neuropsychological tests was performed to assess: General Intelligence; Psychomotor Function; Attention; Memory; Mood and Affect. The estimate of general intelligence, Verbal IQ, was used as a control variable and was measured using the National Adult Reading Test. The remaining tests were based on the CANTAB tests (Cambridge Neuropsychological Test Automated Battery) which was developed for the assessment of cognitive defects in humans with degenerative brain disease. It consists of a series of inter-related computerised tests of memory, attention and higher brain function, for which standardised data on normal volunteers were available.

<u>Results</u>

The 76 in the study group were assigned a diagnostic category based on their results for a symptoms questionnaire and QST thresholds conducted in the clinic. A further four subjects, two each from of the 'no neuropathy' and 'possible neuropathy' groups, were excluded from further analysis based on disqualifying neurophysiological findings. This left a total of 72 subjects for analysis. The group comprised 17, 36 and 23 subjects respectively assigned in the clinic to the 'no', 'possible' and 'probable/definite' categories.

Field/clinic comparability

The extremely high incidence of “possible” neuropathy subjects from the field survey dictated an analysis of reliability and validity of the field classification of subjects. A comparison of the field and clinic measurements for the initial 79 subjects who attended the clinic found that 40 (51%) were classified in the same category on both occasions; 18 (46%) of the 39 remainder classified higher in the clinic than in the field, and 21 lower. This level of agreement was only modestly better than chance, and resulted in a substantial minority of subjects (11%) being classified at opposite ends of the classification scale on each occasion. It was for this reason that the analysis of exposure-response relationships in Phase 2 was conducted using the symptom score and the three QST thresholds as individual continuous variables rather than combining them into the neuropathy categories of Table 16. The symptom score was reproducible between the clinic and field and it was used as a simple indicator (< l or > 1) of the presence or absence of reported symptoms.

The field/clinic difference in QST thresholds was attributed to lack of control of the core temperatures of the farmers who were principally surveyed during winter months. Comparison of the field and clinic QST thresholds were consistent with evidence for differences due to low core temperatures. In cold temperatures, increased sensitivity to heat might be expected to reduce hot thresholds, resulting in a bias downwards in the field compared to the clinic. Equally, cold temperatures would reduce sensitivity to both cold and vibration sensations, both of which were higher on average in the field compared to the clinic. The authors note that in a linear regression framework, a bias in the sensory test thresholds, that applied independently of exposure, would not effect the detection of a statistical exposure-response gradient whether one truly existed or not.

Neurological/neurophysiological findings

These data are summarised in Table 17 and are briefly described below.

Neurological signs: Subjects were assessed for abnormalities of reflexes, sensory signs and muscle power. E involvement of the cranial nerves.

Nerve conduction: Sural nerve was used to measure sensory function in the lower limb, and the common peroneal nerve (CPN) was used to assess motor function in the lower limb for each subject. Each subject was considered to have significant nerve conduction deficit if either sensory function or motor function in the lower limb was abnormal.

Neurological signs or Nerve conduction findings: Subjects were considered to have neuropathy if they recorded either neurological signs or abnormal nerve conduction. The authors note that as a result of the strict criteria for the analysis, there is no overlap between subjects that have neurological signs and abnormal nerve conduction, but this does not mean that these deficits do not coexist. Out of 16 subjects with abnormal nerve conduction six (3 8 %) did have one neurological sign

Electromyography (EMG): EMG recordings were scored according to predefined criteria. The table shows the number of subjects in each group with abnormal findings in the extensor digitorum brevis (EDB) muscle. Four subjects declined this investigation. Most of the sensory versus motor abnormalities abnormal scores were 1 and only one subject had a score of 2. No fibrillation or other spontaneous activity was found in any of the recordings and the abnormalities point to a remodelling of the motor unit indicating an axonal type neuropathy with chronic changes.

Single fibre EMG (SFEMG): Six subjects had SFEMG abnormalities with five of those in the possible neuropathy group. None of the individuals classified as normal on symptoms and QST had abnormal SFEMG. Of those with SFEMG abnormalities, three had one or more signs and four also had abnormal EMG.

Sensor/motor abnormality: Fifteen subjects had neurophysiological sensory abnormalities defined as abnormal sural conduction and one or more QST values. In contrast, only two subjects had abnormal motor nerve conduction and both were in the definite neuropathy group. In general there was a trend towards increasing likelihood of an abnormal QST result with progression across the neuropathy groups from no neuropathy, to possible and probable neuropathy.

Small versus large nerve fibre abnormalities: A larger proportion of subjects had abnormal small nerve fibre function (47 - 65% of 72), assessed by hot or cold sensation threshold, than had abnormal large fibre function (15 - 21% of 72), assessed by vibration threshold or sural nerve function

Summarising the findings: Twenty three (32%) out the 72 subjects had diagnosis of neuropathy by neurological signs or nerve conduction abnormality; ten (29%) of the 34 individuals classified as having "possible neuropathy" had evidence of neuropathy; twelve (52%) of the 23 subjects classified as having "probable/definite neuropathy", showed evidence of peripheral neuropathy.

Four (17% of 23) of the twelve had neurological signs and symptoms/abnormal QST and two also had abnormal EMG. Eight (35%) had abnormal nerve conduction and symptoms/abnormal QST. Six of the eight had abnormal EMG. A further three had abnormal EMG without neurological signs or abnormal nerve conduction. One (7%) of the 15 subjects from the "no neuropathy" group had abnormal nerve conduction but no clinical (signs and symptoms) or QST evidence of neuropathy.

Thirteen (18%) of the 72 subjects had sensory abnormalities defined as abnormal sural conduction and one or more abnormal QST values while only two subjects (3% of 72) had abnormal motor nerve conduction and both were in the definite neuropathy group. Forty seven subjects (65% of 72) had abnormal small nerve fibre function, assessed by hot or cold sensation threshold, while only 15 (21% of 72) had abnormal large fibre function, assessed by vibration threshold or sural nerve function. Thus, small fibre dysfunction was three times more common than large fibre dysfunction.

Table 17: Neurological/Neurophysiological findings - major

Neuropathy status Group	**Number**	**Neurological signs N (%)**	**Nerve conduction N (%)**	**N. signs or nerve conduction N (%)**
No	15	0 (0)	1 (7)	1 (7)
possible	34	3 (9)	7 (21)	10 (29)
Probable/ definite	23	4 (17)	8 (35)	12 (52)
Total	**72**	**7 (10)**	**16 (21)**	**23 (32)**

Neurological/Neurophysiological findings - minor

Neuropathy status Group	**Number**	**EMG* N (%)**	**SFEMG N (%)**	**Sensory abnorm. N (%)**	**Motor abnorm. N (%)**	**Small fibre abnorm. N (%)**	**Large fibre abnorm. N (%)**
No	15	3 (21)	0	0	0	0	1 (7)
possible	34	10 (30)	5 (15)	6 (18)	0	26 (76)	7 (21)
Probable/ definite	23	11 (52)	1 (4)	7 (30)	2 (9)	21 (91)	7 (30)
Total	**72**	**24 (35)**	**6 (8)**	**13 (18)**	**2 (3)**	**47 (65)**	**15 (21)**

* The numbers in the groups were 14, 33 and 21 for no, possible and probable/definite

The "no neuropathy" and "possible neuropathy" groups reported autonomic nervous system symptoms more commonly than peripheral nervous system. Sensory symptoms were more commonly reported than motor symptoms.

Neuropsychological analysis

The study group available for analysing neuropsychological differences numbered 74 subjects, comprising 17, 35 and 22 from the "none", "possible" and "probable/definite" clinical neuropathy categories respectively. The authors note that the clinical study group was a non-random and not truly representative sample of the wider field study group, but consisted of a stratified sample, based on the original field classification of neuropathy, with unequal sampling fractions within each of the strata.

The neuropsychological variables that were recorded were grouped into three broad categories viz. psychological symptoms (mood and affect), processing time and memory/attention. The subjects were grouped into three categories for comparison (none, possible, probable/definite neuropathy) based on their **clinical** classification of neuropathy since this was expected to be a more accurate representation of their true disease status than the field categories of phase-2. Each neuropsychological variable was compared across these groups in turn after adjustment for relevant confounders such as age, verbal IQ and alcohol consumption using multiple linear regression. A similar analysis was conducted to analyse the interaction between the neuropsychological test variables and the cumulative exposure index, OPEXP, described in the phase-2 report, again adjusting for age and verbal IQ.

Results of the neuropsychological analysis

The "possible" and "probable/definite" groups were on average older than the "no" neuropathy group, but alcohol consumption was similar. There were no significant differences in IQ between the three neuropathy groups, with mean scores close to the overall mean of 108.2 (SD 8.9). IQ scores ranged from a minimum of 88 to a maximum of 124 across the study group.

Psychological state was rated by subjects completing questionnaires derived from the Hospital Anxiety and Depression Scale (HAD) and General Health Questionnaire (GHQ). HAD assesses somatic symptoms, anxiety and insomnia, social dysfunction and severe depression, while GHQ assesses anxiety and depression. When the scores were ranked the “probable” subjects scored consistently significantly higher than the other two groups. The authors state that high scores for these variables correspond to poorer general mental health, and the adjusted mean for the “probable” group would be considered clinically significant.

Processing speed was assessed using a variety of CANTAB tests. This parameter was strongly related to both age and IQ. Allowing for these effects, there was some specific evidence of slower processing times among “probable/definite” cases of neuropathy. However, the results, across a variety of such tests, were not consistent and did not provide clear evidence of an overall slowing of processing time.

Memory was assessed using a variety of CANTAB tests. Allowing for the impairment of memory with age and for general IQ, there was no evidence of a difference in memory capability between the “probable/definite” subjects and the other groups.

Results of the neuropsychological analysis in relation to exposure

When each of the neuropsychological variables were plotted against cumulative exposure the estimates of slope were not statistically significant for 14 of the 16 tests, and the remaining two showed contradictory results with one showing improved and one showing impaired performance.

Key findings Phase-3

- Twelve (52%) of the 23 subjects classified as having "probable/definite neuropathy" showed evidence of peripheral neuropathy. Ten (29%) of the 34 individuals classified as having "possible neuropathy" had evidence of neuropathy. Small fibre populations are affected more than large fibre populations. The neuropathy described is predominantly of a sensory type both symptomatically and neurophysiologically and is characteristic of distal, chronic axonopathy with no acute features. Autonomic nervous system symptoms were commonly reported by the no neuropathy and possible neuropathy groups, but were less commonly by the probable neuropathy group.

- In general the neuropsychological tests do not show strong evidence of a direct relationship between impaired neuropsychological performance and cumulative exposure to OP sheep dips as no evidence for such a relationship was found across a wide range of indicators. It must be accepted that the sampling design of the clinical study was not optimal for this purpose.

- Subjects classified in the clinic as being "probable/definite" cases of neuropathy were more likely to self-report poorer general mental health and greater anxiety and depression than subjects classified as in the “no” or “possible” groups.

References

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Institute of Occupational Medicine, Edinburgh. Technical Memorandum Series. May 1999. Epidemiological study of the relationships between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy, and neuropsychological abnormalities in sheep farmers and dippers.

Phase 1: Development and validation of an organophosphate uptake model for sheep dippers. Report no. TM/99/02a; Sewell C, Pilkington A, Buchanan D, Tannahill SN, Kidd M, Cherrie B and Robertson A.

Phase 2: Cross-sectional exposure-response study of sheep dippers. Report no. TM/99/02b; Pilkington A, Buchanan D, Jamal GA, Kidd M, Sewell C, Donnan P, Hansen S, Tannahill SN, Robertson A, Hurley JF and Soutar CA.

Phase 3: Clinical neurological, neurophysiological and neuropsychological study. Report no. TM/99/02c: Pilkington A, Jamal GA, Gilham R, Hansen S, Buchanan D, Kidd M, Azis MA, Julu PO, Al-Rawas S, Ballantyne JP, Hurley JF and Soutar CA.

APPENDIX F A brief overview of the literature (published since 1995) on the health effects of organophosphate sheep dips.

A Brief Overview of the Literature (Published Since 1995) on the Health Effects of Organophosphorus Sheep Dips

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The Chemicals Unit of the Therapeutic Goods Administration of the Department of Health and Aged Care has prepared brief summaries of the literature relating to health effects of organophosphorus sheep dips, published since 1995.

The major published reports identified were as follows:-

1. Epidemiological study of the relationships between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy, and neuropsychological abnormalities in sheep farmers and dippers. Technical Memorandum Series. Phase 1, Development and validation of an organophosphate uptake model for sheep dippers. Report no. TM/99/02a; Phase 2, Cross-sectional exposure-response study of sheep dippers. Report no. TM/99/02b; *and* Phase 3, Clinical neurological, neurophysiological and neuropsychological study. Report no. TM/99/02c: Institute of Occupational Medicine, Edinburgh. May 1999.

2. Official Group on OPs: Report to Ministers. MAFF Publications, London. 1998

3. ECETOC Technical Report No. 75. Organophosphorus pesticides and long-term effects on the nervous system. December 1998 (ISSN-0773-8072-75)

4. Organophosphorus esters: An evaluation of chronic neurotoxic effects. Ray, David. MRC Institute for Environment and Health, May 1998.

5. An investigation into the possible chronic neuropsychological and neurological effects of occupational exposure to organophosphates in sheep farmers. Stephens R, Spurgeon A, Beach J, Calvert I, Levy LS, Berry H & Harrington JM. Institute of Occupational Health, University of Birmingham, UK. HSE Contract Research Report No. 74/1995. (ISBN 0 7176 0929 4)

In addition, abstracts of several published papers have been reproduced.

In an accompanying paper, the Chemicals Unit has reported on the 1999 paper from the Institute of Occupational Medicine (paper no. 1) in some detail.

Epidemiological study of the relationships between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy, and neuropsychological abnormalities in sheep farmers and dippers. Technical Memorandum Series. Phase 1, Development and validation of an organophosphate uptake model for sheep dippers. Report no. TM/99/02a; Phase 2, Cross-sectional exposure-response study of sheep dippers. Report no. TM/99/02b; *and* Phase 3, Clinical neurological, neurophysiological and neuropsychological study. Report no. TM/99/02c: Institute of Occupational Medicine, Edinburgh. May 1999.

Brief Summary

Study Aim: Is cumulative exposure to OP sheep dips related to clinically-detectable measures of neuropathy?

(1) The most important source of OP exposure (measured by urinary metabolites) was contact with concentrate. (Increased splashing with dip wash was positively correlated with increased urinary metabolites.)

(2) Higher rates of reported symptoms were seen in OP-exposed sheep dippers as cf. non-exposed farmers or ceramic workers (see Table 1).

In at least some farmers/farm workers, reported symptoms were associated with exposure to sheep-dip chemicals; sensory symptoms were more commonly reported than motor symptoms by sheep dippers.

Markedly higher rates of symptoms were reported by those who had at some time been concentrate handlers. (In dippers who had not principally handled concentrate, there was no apparent difference from non-exposed workers.)

Average concentrate handling intensity, independent of duration of exposure, could explain the difference between sheep-dip farmers and non-exposed (ceramics) workers in relation to reported symptoms and one of the sensory threshold measures (cold sensory threshold).

There was a much higher prevalence of symptoms amongst English study subjects as cf. Scottish subjects (see Figure).

(3) No evidence was adduced to indicate that cumulative exposure to OPs was associated with impairment of measured sensory thresholds.

(4) Increasing likelihood of neuropathy was associated with neuropsychological findings (anxiety and depression). The results did not show that neuropsychological findings were related to cumulative exposure to OPs (limited power of study).

Conclusions: Study suggestive of an association between OP exposure, predominantly the concentrate, and evidence of chronic peripheral neuropathy. Possible that exposures to concentrated forms of OPs above a certain threshold, on a repeated basis, even over a relatively short time-scale, could be associated with long-term health effects.

Table 1: Prevalence of symptoms by occupational group [% affected (number)]

Symptom	Ceramics	NSD farmers	SD farmers
Muscle weakness			
Hands	0	1.9 (1)	6.4 (39)
Shoulders	0	0	2.0 (12)
Feet	0	0	2.3 (14)
Legs	0	3.8 (2)	0.8 (5)
Negative sensory(1)			
Feet	0	3.8 (2)	5.2 (32)
Hands	0	0	2.1 (13)
Positive sensory(2)			
Feet	1.9 (2)	5.7 (3)	10 (61)
Hands	0.9 (1)	3.8 (2)	5.4 (33)
Autonomic			
Fainting	3.7 (4)	15 (8)	14 (87)
Diarrhoea	0	0	0.7 (4)
Bladder	0	0	1.8 (11)
Impotence	0	1.9 (1)	5.6 (34)
Sweating	7.5 (8)	5.7 (3)	8.2 (50)
Group size	**107**	**53**	**612**

(1) reduction in sensory function

(2) altered sensation eg. numbness or pain

Official Group on OPs: Report to Ministers. MAFF Publications, London. 1998

Brief Summary

In the face of continuing public debate over whether organophosphate products damage human health, a meeting of UK Government Ministers in 1997 established a high-level group of officials to examine the government policies relating to OP products and arrangements for administering them. The terms of reference for the group included: monitoring the flow of OP-related information between relevant Government Departments; evaluating all available scientific evidence, defining any data gaps and proposing how they might be addressed; examining the licensing procedures for OPs. The committee was chaired by MAFF and membership was drawn from over ten UK Ministries and Agencies.

The group found that selected OP compounds are widely used in the UK and throughout the world as pesticides, both agricultural and in the home and as human and veterinary medicines. Most health concerns expressed by the UK public focused on their use as sheep dips. Most OPs act as acetylcholinesterase (AChE) inhibitors. In humans, the acute effects of OP exposure are generally rapidly reversible, although a number of delayed or chronic syndromes are related to severe acute OP poisoning. Development of delayed neuropathy, which can result from exposure to some OPs but does not correlate with AChE inhibition, would not be expected to be caused by the OPs in sheep dips. The potential of OPs to cause ill health following long-term low-level exposure remains unknown. The group conducted a review of the current OP literature and stated that the data were difficult to interpret and no firm conclusions could be drawn; however they did establish a list of 16 questions for consideration by an expert committee.

The group recommended that the views of the various advisory committees dealing with various aspects of OPs should be placed in the public domain. Authoritative reviews of the potential effects of OP compounds on other bodily systems (bone marrow, immune system) should be considered.

The group found thirteen government Departments and Agencies involved in OP-related issues and recommended careful co-ordination between them. The group identified necessary areas of co-ordination including routine policy making and the need to share scientific data and expert advice in relation to safety assessments and suspected adverse reactions. The group further recommended a legislative change to allow exchange of documents between Departments and greater disclosure to the public.

The group reviewed relevant aspects of the regulatory system. There are three advisory committees relevant to the licensing of OP products viz. the Advisory Committee on Pesticides (ACP); the Veterinary Products Committee (VCP); and the Committee on Safety of Medicines (CSM). The group made recommendations on the membership and remit of these committees. The group analysed the definitions and use of the Precautionary Principle in the regulation of OP products and concluded that the current application of this Principle was appropriate and consistent with current legislation.

The group reviewed the means of control of OP products other than by licensing. A register of individuals with OP-sensitivity was not recommended. A licensing system currently exists for the sale and supply of OP dips and the group recommended the license be extended to non-OP dips such as synthetic pyrethroids (SPs). The group presented arguments for and against extending current licensing for purchasers of pesticides to also cover all users of pesticides.

The group reviewed the three adverse reaction schemes relating to different uses of OP products viz. The Pesticide Incidents Appraisal Panel (PIAP) covering both agricultural and non-agricultural pesticides; for veterinary medicines the Suspected Adverse Reaction Surveillance Scheme (SARSS) including the human Suspected Adverse Reactions (SARs); for human medicines the spontaneous suspected adverse drug reaction reporting scheme, known as the Yellow Card Scheme. While recommending some changes be implemented, the group did not recommend harmonisation of the three schemes because their aims have such different origins and purposes that their operational differences were justified.

The report contains summaries of four recent court judgements relating to exposure to OP products; no firm legal precedents relevant to long-term exposure to OP sheep dips were found.

The group reviewed the purpose and impact of relevant legislation and non-legislative measures. They recommended various changes to control OP exposure including modification of containers, disposable packaging and mandatory PPE, all designed to minimise skin contact for concentrate-handlers. Various other possibilities for minimising risk included encouraging: veterinary injectibles; use of non-OP compounds; and the use of contract dippers. The group finally and briefly reviewed the impact of changes in relevant environmental regulations.

Appendices include:-

- A comprehensive information brochure for sheep-dippers entitled “AS29 Sheep-Dipping” a leaflet in the Agricultural Safety Series published by the Health and Safety Executive (HSE)
- A Research and Development catalogue for current research (last ten years) funded by government.

Organophosphorus esters: An evaluation of chronic neurotoxic effects. Ray, David. MRC Institute for Environment and Health, May 1998.

Brief Summary

This report, prepared by David Ray of the IEH under contact to the Department of Health, reviewed the available scientific and medical literature to evaluate the possibility that chronic neurotoxicity could result from exposure to organophosphorus (OP) pesticides.

The report noted that the only OPs currently approved for use as sheep dips in the UK are propetamphos and diazinon, with a number of others removed from the market in recent years.

Agent	Year of licence expiry
bromophos	1988
chlorpyrifos	1989
iodophenfos	1990
coumaphos	1991
chlorfenvinphos	1994

Summary and Conclusions of the Report

There is good evidence that OPs cause three syndromes of poisoning in humans and experimental animals viz. acute pharmacological toxicity, the intermediate syndrome, and delayed polyneuropathy.

Mammalian resistance to the OPs is "almost wholly" a function of detoxification capacity rather than any inherent resistance of mammalian target proteins ie. metabolic and pharmacokinetic factors dominate the toxicology of these compounds.

The efficacy, low environmental persistence, and low production costs will probably ensure that OPs have a continuing use well into the future.

It appears that, for the majority of sheep farmers and farm workers, exposures associated with normal sheep-dipping are 'low-dose' exposures (defined here as levels low enough not to produce any externally-visible cholinergic signs).

Ray provided a tabular summary of the effects seen in 19 epidemiological and/or clinical studies of low level OP exposure (reproduced on the following page). Comparison of these studies is difficult; in some the effects of hard work and OP exposure are closely linked, while in others exposures may be a mixture of high and low level exposure. While the effects reported in these studies range from small to negative, a number of studies do report indications of toxicity associated with low-level exposure.

"Although there is at present insufficient evidence to eliminate the possibility that subtle (ie. not subjectively apparent) effects may be produced by low-level exposure to organophosphorus pesticides, based on the balance of published evidence it can be concluded that such exposures are not likely to be responsible, in themselves, for any adverse health effects large enough to be subjectively apparent."

"Attention in the UK could be more usefully directed to examining agent-specific effects in this country, and class effects could most usefully be evaluated in a prospective study of cases of higher exposure elsewhere". Were a clear effect identified under conditions of high exposure, the information obtained could then be applied in the UK to study more threshold effects. It should be recognised that a UK population with only low exposure is a poor choice for any investigation designed to identify a novel effect. Although UK populations do differ from others in the pattern of use and the specific spectrum of pesticides, it would be remarkable if the UK population with low exposure were to suffer an adverse effect not seen more clearly in more highly exposed populations elsewhere in the world". [The report focussed on the high incidence of poisoning reports and frank intoxication in tropical and developing countries eg. China, Nicaragua, Poland, Pakistan.]

Problems seen in previous neurotoxicity studies on OPs in humans included:-

- lack of definition of exposed groups in epidemiological studies;
- the restricted use of some of the more sensitive neurobehavioural tests in clinical studies;
- lack of use of the same indices across a number of otherwise good neurobehavioural studies, these preventing the drawing of definitive conclusions;
- the non-specific nature of low-level signs of OP intoxication;
- common lack of estimation of known individual and societal factors that are liable to influence reporting rates; and
- the absence of a clear theoretical or mechanistic framework to explain long-term effects.

Interesting observations which would be useful to follow-up include:-

- the incidence of suicide and depression;
- adaptation to signs of toxicity which could lead to increased occupational exposure due to lack of warning signs;
- the possibility of novel protein targets for OPs in the brain;
- individual disposition to OP neurotoxicity, based on variation in blood or liver metabolic capacity etc;
- an evaluation of central cholinergic excitotoxicity (death of cells as a result of prolonged excitatory drive).

Summary of effects seen with low-level exposure[a] (ranked by group size)

Exposed sample size & study type	Measures	Effect
73 clinical[b]	EEG	increased β
37 clinical	postural sway	performance ↓*
20 clinical	neurological	sensory ↓*
158 epidemiological	neuropsychological	reaction time ↓ symbol-digit ↓* syntactic reason ↓* learning/memory →
118 epidemiological[b]	demographic	suicide increased mood disorders ↑*
105 epidemiological	symptom reports	tremor ↑*+
90 epidemiological	neuropsychological	reaction time ↓+ symbol-digit ↓+ dexterity ↓*+ anger ↓*+ anger ↑*
90 epidemiological	neuromuscular	vibration sense ↓*
57 epidemiological	neurobehavioural	reaction time ↓* symbol-digit → visual memory → verbal memory → verbal ability → dexterity ↓
56 epidemiological[b]	EEG, pyschological	EEG (more θ) subjective memory ↓* fatigue ↓*
53 epidemiological	neuropsychological	slower performance
49 epidemiological	neurobehavioural	pattern memory → symbol-digit → tapping → Coordination → Continuous performance →
45 epidemiological	neurological, neuropsychological	nerve conduction → vibration sense → mood → serial digit score ↑*
36 epidemiological	neuromuscular	EMG decrement *
36 epidemiological[b]	neurobehavioural	dexterity ↓*
24 epidemiological	psychological	tension ↓* sleep disturbance ↓* depression →
23 epidemiological	neuropsychological	reaction time → vigilance → linguistic skill → proprioception →
16 epidemiological	EEG, neuropsychological	EEG (decreased α)* visual/motor ↓*
11 epidemiological	neuromuscular	EMG → nerve conduction → tendon reflex ↓*
11 epidemiological	neuromuscular	EMG → nerve cond. (motor) → nerve cond. (sens.) ↓* jitter →

[a] Low-level exposure is here defined as a level insufficient to cause acute cholinergic signs
[b] Group may have included some people with acute intoxication

↓, worse performance; ↑, better performance; →, unchanged performance;
+, only during exposure; *, statistically significant

ECETOC Technical Report No. 75. Organophosphorus pesticides and long-term effects on the nervous system. December 1998 (ISSN-0773-8072-75)

Brief Summary

Introduction

This report was commissioned by the European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium. Its purpose was to review evidence for neurotoxicity arising from chronic, low-level organophosphate (OP) exposure. The report was produced by a task force named "Organophosphorus pesticides and long-term health effects", consisting of G Krinke [Novartis] (Chairman), M Butler [ECETOC] (Secretary) and 5 other members. An interim version of the report was critiqued by Professor M Lotti and Drs MK Johnson and D Ray. There was also a 15-member peer review committee chaired by W Tordoir [Shell International]. Most of the task force and peer review committee members are current employees of the drug/chemical manufacturing industry.

The task force's terms of reference were to:

1. Review the characteristics of classical neurotoxicity (acetylcholinesterase [AchE] inhibition and organophosphorus-induced delayed neuropathy [OPIDN]) associated with OP pesticides;
2. Review the clinical and pathophysiological characteristics of the "chronic neurotoxic syndrome" recently alleged to occur in humans and the exposure situation in which it has been described;
3. Review the commonly-used testing protocols in respect of their sensitivity to the characteristics of this "syndrome", and the extent to which existing experimental data can contribute to an assessment of the organic nature of the "syndrome"; and
4. Suggest an experimental approach for the investigation of the "syndrome" and/or prediction of a potential to cause it.

Summary of the Report

This summary concentrates mainly on item 2 above.

The task force carried out a review of the scientific literature on the effects of chronic (months or years) low-level, apparently asymptomatic exposure to OPs. In all, some 10 epidemiological studies (dating between 1961 and 1997) were summarised, in which the authors had reported psychiatric, neuropsychological or neurophysiological effects among persons exposed occupationally to OP pesticides, or residing in districts where there was extensive use of these chemicals. The alleged sequelae of repeated, asymptomatic exposure in humans comprised adverse effects on <u>cognition</u> (reduced attention/vigilance, memory disturbance, impaired information processing), <u>sensorimotor domain</u> (reduced reaction speed, impaired dexterity, slowness of language function, disturbed visual function), <u>mood</u> (anxiety, irritability, depression), <u>sleep</u> (disturbances, fatigue) and <u>sexual function</u>. The assessment included the studies of UK sheep farmers by Stephens *et al* (1995, 1996). Also reviewed, were 4 epidemiological studies (1975-1995) involving chronic exposure to OP pesticides *without* findings of adverse effects.

Nine published reviews of the epidemiological literature were examined by the task force. Some of the data contained in these reviews were derived from persons who were allegedly exposed to OPs in settings such as manufacture/handling of chemical warfare agents, or agricultural aviation accidents. Four of the reviews had concluded there were indeed prolonged health effects arising from OP exposure, ranging from psychological to neurological disturbances, with symptoms including impaired memory or concentration, malaise, ataxia, muscle weakness or aching, headache and dizziness. However, in 3 reviews the authors had concluded there was insufficient evidence of causal association between OP exposure and prolonged effects in humans, while the remaining 2 reviews were equivocal in their findings.

Most of the above studies were criticised because of methodological deficiencies, relating to poorly characterised exposure to the chemicals, failure to consider agent-specific effects or interactions between different agents, reliance on anecdotal data, small group sizes and lack of appropriate controls.

A series of tolerability studies in human volunteers was also reviewed by the task force. In these, the subjects received low oral or inhalational doses of OP pesticides for up to several weeks. Even at doses/concentrations high enough to cause plasma or erythrocyte AchE depression, the only other evidence of toxicity was respiratory tract irritation during inhalation exposure. However, while these studies overcame some of the limitations noted previously, psychological tests were not performed.

Finally, the task force assessed studies on peripheral nerve function, carried out by electrophysiological measurement using needles or surface electrodes. The subjects were mainly exposed to OP pesticides in an occupational setting. All studies using needle electromyography were stated to be negative. Studies using the less reliable surface electrodes showed inconsistent evidence of impaired nerve conduction, which was dismissed by the task force. The task force pointed out, however, that most measurements had been made in the upper limbs despite the fact that neurotoxicity is more likely to occur first in the longer axons in the legs.

Findings with respect to “chronic neurotoxic syndrome”

- The task force found no pharmacokinetic evidence for cumulative effects of chronic exposure to OPs at levels that were below the threshold for acute toxicity.
- Tolerability studies with several OPs in human volunteers had not revealed any sequelae from daily, low-level asymptomatic exposure lasting for several weeks.
- The described features of the “chronic syndrome” were found to resemble complaints and changes seen in the general population and known to be linked to other societal and socio-economic factors.
- There was insufficient evidence in the epidemiological literature to convince the task force that there is a “chronic syndrome” resulting from chronic, apparently asymptomatic exposure to OPs.
- To resolve whether or not such a syndrome does exist, the task force considered that continued surveillance of the exposed populations is the most appropriate course of action.

An investigation into the possible chronic neuropsychological and neurological effects of occupational exposure to organophosphates in sheep farmers. Stephens R, Spurgeon A, Beach J, Calvert I, Levy LS, Berry H & Harrington JM. Institute of Occupational Health, University of Birmingham, UK. HSE Contract Research Report No. 74/1995. (ISBN 0 7176 0929 4)

Brief Summary

This report (107 pages, plus 13 un-numbered appendices) raised concerns in Australia when it was published in 1995. The acute effects of over-exposure to organophosphate-based pesticides, widely used throughout the world, are well known. This study was designed to investigate concerns that long-term exposure to OP sheep dips may result in damage to the nervous system. In a cross-sectional study, neuropsychological performance in 146 sheep farmers who were exposed to OPs in the course of sheep dipping was compared with 143 non-exposed quarry workers (controls). A range of outcome measures which assessed mood and symptom reporting after acute exposure, and cognitive functioning, psychiatric state and neurological symptoms in the absence of recent exposure. OPs involved included diazinon, chlorfenvinfos and propetamphos.

The farmers performed significantly worse than controls in tests to assess sustained attention and speed of information processing. These effects remained after adjustment for covariates. The farmers also showed greater vulnerability to psychiatric disorder than did the controls as measured by the General Health Questionnaire. There were no observed effects on short-term memory and learning. Repeated exposure to organophosphate-based pesticides appears to be associated with subtle changes in the nervous system. Analysis of dose-effect relationships in respect of one test indicated that these effects occurred in the lowest-exposure group, which included individuals with only two years of exposure.

The results suggested that further work is required to (1) investigate the suggestion that those reporting a high level of acute symptoms immediately following exposure may experience effects identifiable by the presence of neurological signs; (2) define more precisely the levels of exposure at which the identified effects occur.

Although the effects observed were not severe, it was concluded that measures should be taken to reduce exposure to organophosphates as far as possible during agricultural operations, particularly in terms of identifying the most appropriate clothing and dipping equipment during sheep-dipping.

Results from this study were also published in the medical literature, as follows:-

Neuropsychological effects of long-term exposure to organophosphates in sheep dip. (1995) Stephens R, Spurgeon A, Calvert IA, Beach J, Levy LS, Berry H & Harrington JM. Institute of Occupational Health, University of Birmingham, UK. The Lancet (May 6) 345(8958):1135-1139

Organophosphates: The relationship between chronic and acute exposure effects. (1996) Stephens R, Spurgeon A & Berry H. Health and Safety Laboratory, Sheffield, UK. Occup Environ Med 53(8): 520-525 (Aug.)

Abnormalities on neurological examination among sheep farmers exposed to organophosphorous pesticides. (1996) Beach JR, Spurgeon A, Stephens R, Heafield T, Calvert IA, Levy LS & Harrington JM. Institute of Occupational Health, University of Birmingham. Occup Environ Med 53(4):258-63 (Apr.)

In addition, comments on 'The Lancet' paper (Neuropsychological effects of long-term exposure to organophosphates in sheep dip) were published as follows:-

Davies DR (1995) Lancet 345(8965):1631 (Jun 24)

Watt AH (1995) Lancet 345(8965):1631-1632 (Jun 24)

O'Brien SJ, Campbell DM & Morris GP (1995) Lancet 345(8958):1631-1632 (Jun 24)

Neuropsycholopathological changes by organophosphorus compounds - a review. Eyer P. Human Exp Toxicol 14: 857 - 864 (1995).

Brief Summary

This review, from the Walther-Straub Institut für Pharmakologie und Toxicologie at the University of Munich considered the available literature on neuropsychopathological changes after exposure to OP insecticides. It was concluded that subacute neurological sequelae following acute intoxication include intermediate syndrome and OPIDN (organophosphate-induced delayed neuropathy), the latter caused by particular OPs which inhibit the so-called neuropathy target esterase (NTE) enzyme. Long-term toxic effects affecting behaviour as well as mental and visual functions appear to be occasionally observed after exposure to high doses, if there are repeated clinically-significant intoxications. The available data do not indicate that asymptomatic exposure to OPs is connected with an increased risk of delayed or permanent neuropsychiatric effects. Nevertheless, the available studies cannot rule out the possibility of hitherto unknown toxic mechanisms of OP action ie. inhibition of AchE may not always be a pre-requisite for long-term neuropsychopathological effects.

It was unclear from the review whether individual pre-disposition, particular OPs, and/or other additional influences of other chemicals, nutrition, alcohol, or intercurrent disorders may play an additional role.

Abstracts of papers published in the literature on the effects of exposure to OP sheep dips

The following are abstracts of papers published between 1995 and the present on the effects of exposure to OP sheep dips.

Neuropsychological effects of long-term exposure to organophosphates in sheep dip. (1995) Stephens R, Spurgeon A, Calvert IA, Beach J, Levy LS, Berry H & Harrington JM. Institute of Occupational Health, University of Birmingham, UK. The Lancet (May 6) 345(8958):1135-1139

Organophosphate-based pesticides are widely used throughout the world. The acute effects of over-exposure to such compounds are well known. Concern has also been expressed that long-term exposure may result in damage to the nervous system. In a cross-sectional study, we compared neuropsychological performance in 146 sheep farmers who were exposed to organophosphates in the course of sheep dipping with 143 non-exposed quarry workers (controls). The farmers performed significantly worse than controls in tests to assess sustained attention and speed of information processing. These effects remained after adjustment for covariates. The farmers also showed greater vulnerability to psychiatric disorder than did the controls as measured by the General Health Questionnaire. There were no observed effects on short-term memory and learning. Repeated exposure to organophosphate-based pesticides appears to be associated with subtle changes in the nervous system. Measures should be taken to reduce exposure to organophosphates as far as possible during agricultural operations.

Organophosphates: The relationship between chronic and acute exposure effects. (1996) Stephens R, Spurgeon A & Berry H. Health and Safety Laboratory, Sheffield, UK. Occup Environ Med 53(8): 520-525 (Aug.)

The relationship between chronic (non-reversing) neuropsychological effects and acute exposure effects was investigated in 77 organophosphate exposed male sheep-dippers. Acute exposure effects were assessed prospectively using a purpose-constructed symptoms questionnaire administered pre-, and 24 h post-exposure. Urine was analysed for dialkylphosphate levels to confirm recent exposure. Chronic effects were assessed in a cross-sectional neuropsychological study in the absence of recent exposure using computerised neuropsychological tests, the General Health Questionnaire, and the Subjective Memory Questionnaire. Simple correlation and multiple linear regression analyses (adjusting for confounders) were used to assess relationships between the change in total symptom reporting from baseline to 24 h after exposure and chronic effect outcomes. There was no evidence of any association between reported symptom levels and chronic neuropsychological effects. This suggests that chronic effects of OP exposure appear to occur independently of symptoms that might immediately follow acute OP exposure. This has implications for exposure control: individuals may experience chronic effects without the benefit of earlier warning signs of toxic effects during acute exposures.

Abnormalities on neurological examination among sheep farmers exposed to organophosphorous pesticides. (1996) Beach JR, Spurgeon A, Stephens R, Heafield T, Calvert IA, Levy LS & Harrington JM. Institute of Occupational Health, University of Birmingham. Occup Environ Med 53(4):258-63 (Apr.)

Organophosphates are effective pesticides which are frequently used in several agricultural settings. Although their acute effects are well characterised, it remains unclear whether long term exposure can damage the human nervous system. This study sought to investigate their long term effects
by comparing abnormalities on neurological examination between groups of workers exposed to organophosphates and an unexposed group.

146 exposed sheep farmers and 143 unexposed quarry workers were recruited into a cross sectional study of symptoms and neuropsychological effects of long term exposure to organophosphates in sheep dip. From a symptom questionnaire given immediately after dipping the 10 most symptomatic and 10 least symptomatic farmers were selected. Several months later each of these, along with 10 of the unexposed quarry workers, underwent a standardised neurological examination similar to that which might be used in clinical practice, at a time as remote as possible from recent exposure to organophosphates, so as to exclude any acute effects.

All 30 selected subjects agreed to participate. The components of the examination which showed a significant difference were two point discrimination on the dorsum of the hand (symptomatic farmers 22 mm; asymptomatic farmers 13 mm; quarry workers 8 mm) and the dorsum of the foot (symptomatic farmers 34 mm; asymptomatic farmers 10 mm; quarry workers 11 mm), and mean calf circumference (symptomatic farmers 35.0 cm; asymptomatic farmers 36.3 cm; quarry workers 38.6 cm). Overall the prevalence of neurological abnormalities was low.

The differences in neurological examination detected between groups were subtle and their clinical significance was unclear. However, they do suggest evidence of an adverse neurological effect from exposure to organophosphates. Further larger scale studies will be required before it is possible to confirm or refute the differences detected.

Exposure to sheep dip and the incidence of acute symptoms in a group of Welsh sheep farmers.
Rees H (1996) Occupational Health Department, University Hospital of Wales, Cardiff. Occup-Environ-Med. 53(4): 258-263 (Apr)

The objective of the study was to measure the exposure of a group of farmers to organophosphate
pesticide in sheep dip, and to record the incidence of symptoms after exposure. A prospective study of the autumn 1992 dipping period. Working methods were assessed by questionnaire. Absorption of organophosphate pesticide was estimated before, immediately after, and six weeks after dipping by measuring plasma cholinesterase, erythrocyte cholinesterase, and dialkylphosphate urinary metabolites of organophosphates. Symptoms were recorded by questionnaire at the same time as

biological monitoring. Possible confounding factors were identified by medical examination of the subjects. The study was carried out on 38 men engaged in sheep dipping, living in in three community council electoral wards in Powys, typical of hill sheep farming areas in Wales.

Twenty three (23) sheep farmers and one dipping contractor completed the study - a response rate of 63%. A sample of seven men who refused to enter the full study had similar working practices to the 24 subjects. Subjects reported inadequate handling precautions, and significant skin contamination with dip. Two men reported under diluting dip concentrate for use. Both had significant depression of erythrocyte cholinesterase after dipping. This indicated some absorption of organophosphate pesticide - but this did not reach levels usually associated with toxicity. It was not clear whether the symptoms of these two mens were caused by organophosphate exposure. Measurement of dialkylphosphate urinary metabolites in a single specimen of urine voided shortly after the end of dipping could not be correlated with individual exposure.

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.

Watterson AE (1999) Regulating pesticides in the UK: a case study of risk management problems relating to the organophosphate diazinon. Centre for Occupational and Environmental Health, De Montfort University, Leicester, UK. Toxicol Lett 107(1-3): 241-248 (Jun 30)

The objectives of the study were (1) to assess aspects of occupational and related environmental health risk assessment and risk management decisions of UK regulatory bodies on diazinon used in sheep dip; and (2) to benchmark those decisions against 'the public health precautionary approach'.

Diazinon health and safety data available within Government Departments, industry and from users in animal husbandry practice were analysed. Results were reported as follows: (1) data on diazinon produced by the manufacturing companies for the UK pesticide regulatory agencies are not fully transparent; (2) UK regulatory health and safety processes assume accuracy of manufacturer's data and information provided on personal protective equipment (PPE) and application effectiveness; (3) data available reveal gaps and problems with diazinon toxicity, PPE and application methods; and (4) little published evidence shows that industry followed up the health of dippers after product registration or that government departments adopted a public health approach to regulation. It was concluded that diazinon sheep dip illustrates the need for the application of a rigorous precautionary principle in both initial registration and later monitoring of chemicals.

The following papers relate to the usage of OP sheep dips in the UK, and their potential to contaminate waterways.

French NP, Wall R & Morgan KL (1994) Ectoparasite control on sheep farms in England and Wales: the method, type and timing of insecticidal treatment. Department of Clinical Veterinary Science, University of Bristol, UK. Vet Rec 135(2): 35-8 (Jul 9)

The chemical control of sheep ectoparasites raises important environmental, health and welfare issues. There is increasing concern about the possible harmful effects of pesticides on human ealth and the role of dipping in the contamination of natural watercourses. A longitudinal survey was conducted in 1991, the last year of compulsory dipping for the control of sheep scab, to obtain information about the chemical control of ectoparasites on 485 farms in England and Wales. Organophosphate insecticides were the most commonly used for both summer and compulsory dipping and for spraying sheep, although many of the products used for spraying sheep were not licensed for this purpose. The early pattern of dipping and spraying appeared to follow the pattern of incidence of blowfly strike although more than 40 per cent of sheep were dipped during the first two weeks of the compulsory dipping period. Compulsory dipping for the control of sheep scab was reduced from two dips to one dip between 1988 and 1989 and removed altogether in 1992. The results from the survey were compared with the results of a previous survey and showed an apparent decline in the use of dipping and an increase in the use of alternative methods of control between 1988 and 1991.

Virtue WA & Clayton JW (1997) Sheep dip chemicals and water pollution. Scottish Environment Protection Agency (formerly Tweed River Purification Board), Burnbrae, Galashiels, UK. Sci Total Environ; 194-195: 207-217 (Feb 24)

The Tweed River Purification Board's objective of reducing the numbers and significance of water pollution incidents by a proactive approach based on persuasion and education is described. This has consisted of prioritising potential pollutant sources which have then been investigated in detail followed by discussion and agreement with dischargers as to remedial measures. The paper describes in detail the Board's investigation of pollution from the organophosphate (OP) sheep dips, diazinon and propetamphos, and their effects on surface waters throughout its area. Examination of historical incidents and a preliminary survey of sheep farms in the Ettrick Water catchment in 1989 confirmed the potential for serious pollution. Comparison of OP concentrations in the Ettrick with strategic sites throughout the catchment confirmed the widespread nature of the problem and led to visits to every sheep farmer in the Board's area in 1990 and 1991, when 795 dippers were investigated. The study involved risk assessments of the location of dippers and the spent dip disposal practice which confirmed that poor siting, inadequate disposal and particularly poor management of the dipping operation were responsible for the pollution problems observed. Practical advice on the management of dipping and disposal of spent dip was given individually to farmers. The success of the project in reducing pollution is reflected in a significant and sustained reduction in OP concentrations in environmental samples. The future of ectoparasitic treatments for sheep, the potential for antidotes to spent sheep dip and legal obligations relating to its safe disposal is also considered.

APPENDIX G Use pattern information provided in grower performance questionnaires to diazinon review.

The information provided by sheep farmers has been extracted for the purposes of the NRA Expert Panel review. Numbers cited in tables may represent uses other than ectoparasite treatment, but have been retained as supporting information.

SECTION I - CHEMICAL MANAGEMENT - DIAZINON

1. How long have you been using the chemical?

	Counts
1 - 3 Years	2
3 - 5 Years	1
More than 5 yrs	15

3 (a) Is it used every season/year?
(b) What factors determine this? Please describe the factors.

- (Sheep) The presence of fly struck sheep, almost every year. The presence of lice in sheep, only as needed, once in last 11 yrs.
- (Sheep) use for lice control only when evident, have used twice in last 15 yrs
- (Sheep) used twice in 20 yrs to jet sheep (and still have nearly full container)
- (Sheep) blowfly strike and lice control
- (Sheep) fly numbers and nos of stock affected
- Flystrike, lice control, mulesing

4. Are there alternative chemicals available?
If yes what are they?

- (Sheep) various
- (Sheep) cyromazine, propetamfos
- (Sheep) Vetrazin and Jetamec (no longer available) for fly treatment, lice treatments not as effective
- Vetrazin for fly strike, a whole range of licicides (I use Fleececare on my sale rams each year as a sales promotion factor, - no lice present)
- (Sheep) flystrike chlorfenvinphos, propetamphos (Coopers Dead Mag)

5. Why do you continue to use this chemical and not an alternative?

- (Sheep) cheaper and effective
- (Sheep) much more reliable on lice and cheaper
- (Sheep) price, and it is effective at killing maggots immediately and has some repellent effect. Some of the others eg IGRs don't do this
- Cost effective, does the job
- (Sheep) get effective results with powder, less mess than liquids

- (Sheep) I have used chlorfenvinphos before and do not like it because of side effects. I have only recently been aware of Dead Mag, however I have assumed that any treatment products are similar in terms of safety and residue.

6. Have you altered your farming methods or practices in relation to this chemical since you started using it?

	Counts
Yes	12
No	6

If Yes What do you now do differently?
- (Sheep) use safety gear
- (Sheep) use safer chemicals for treating fly blown sheep, have bred sheep fly resistant so no longer jet for protection
- more careful
- don't use it on the board, use gloves, don't use it for prevention

7. Is this chemical an essential part of an Integrated Pest Management (IPM) strategy?
If Yes how is it used in IPM?

- For lice control (eradication) I run a closed flock – don't introduce sheep. Use AI for rams. For fly control, use strategic timing of crutching and mulesing to minimise fly strike

8. Do you mix this chemical with other chemicals in your pest control program?
If yes what other chemicals do you mix this chemical with?

- Vetrazin (sheep)
- (sheep) jetting with cyromazine

<u>SECTION II CHEMICAL APPLICATION</u>

1. In your experience, are the current label directions for use clear, unambiguous and still applicable?

If no what aspects of labelling need clarification?.
- WHP details need to be much larger so that they can be easily seen by people who have forgotten their glasses

2. Do you use any specific strategies to minimise residues of this chemical in your produce?

If yes what strategies do you use?

- Use as little as possible and only when lice are found to exist
- (Sheep) don't sell treated stock until fully recovered

- (Sheep) use management and breeding to reduce chemical use, only rams are jetted each year now (heads)
- Avoid application close to shearing
- Make sure only treat affected areas and only use on individual animals
- Don't sell until well after use/WHP

3. Do you use the same product for all your applications of this chemical or do you use other types of formulations and/or products?
Same=14, different=3

4. Have you experienced any difficulties in disposing of containers or unwanted chemical in accordance with label instructions?

	Counts
Yes	5
No	15

If yes please list any specific difficulties you have experienced?

- Container pourer has spout not easily pulled out for use
- Nowhere to dispose of them legally. No recycle collection of Dept. depot for chemical containers
- Have to dig pit. Store empty containers until it warrants digging.
- Disposal of chemical containers is generally too difficult, they end to lie about in a heap until there are sufficient to justify removal to a centre (which may be far away)
- Round drums are hard to squash

5. Have you experienced any difficulty in handling the concentrate because of the containers in which the chemical is packed?

	Counts
Yes	9
No	9

If yes what difficulties have you experienced?

- For the liquid (EC) formulation not all manufacturers containers have as easy pour attachment. This is more user friendly. We have tried screw-on pouring attachments but they are not always compatible. Ease of handling for the operator is of concern because it is the most hazardous step in our operation.
- Need pouring spout to avoid splashing, "glugging" as poured out of drum
- Very hard to pour from 20L container without spilling. Kleendok burns face if windy when using spray container.
- Cap on container is extremely difficult to remove on occasions, metal can is not ideal
- Pourers (and air vents) should be compulsory on all liquid containers

- Metal containers rust lid on. Paper labels come off. Needs name of product permanently on container
- Dispenser should accompany every liquid container. There is too much chance of spillage when using small containers, especially tins
- Pouring out the required amount of concentrate (often miniscule amounts)

6. Use Patterns:

For each target situation:
a) Please provide information on the use pattern using the table provided at Attachment A

b) **What mixing and application equipment is used? Please give details of the equipment and include any specialised application methods. See also part (g) below.**

- Safety gear for workers, eg gloves, masks etc. Measuring apparatus into spray tank with pump mixing, high volume spray in a boom spray.
- Mixing equipment – graduated 1L and 5L chemical resistant measuring jugs. Applicator equipment – Silvan Turbomiser (low volume), Silvan 1000L trailed tank (high volume) fitted with 2 handheld hoses.
- For treating fly strike, hand spray. For lice, a plunge dip and contractor
- Measuring container from chemical drum, pour into boomspray, pumped out onto sheep either spraydip or jetting, Kleendok sprayed directly onto sheep
- (Sheep) usual jetting wand used for application. A sponge with handle is used to apply to strike area
- (Sheep) pour measured amount into plunge dip. Mix with long handled broom.
-

c) What is/are likely to be the most common application method/s? Do you prefer any particular application methods/equipment? Are there any application methods/equipment that you avoid using?. Please give reasons.

- Hand jetting of sheep
- (Sheep) special powder dispensers
- Sheep jetting by hand, dipping by shower dip, mulesing application by spray pressure container
- (Sheep) plunge dip may be used
- (Sheep) pour on wounds out of 5L tin

d) What is the likely seasonal use of the chemical? Please record the amount of chemical required for an average season.

- Fly strike – autumn, spring – 250mL (max); lice – enough to do 2500 sheep at label rec.
- (Sheep) Use about twice a year, 20L
- (Sheep) 2kg
- (Sheep) normally Feb/Mar after rain in summer, a little in Dec. Depends on season, in 1996 used 10L, in 1997 less than 1L
- (Sheep) 150 mL`

- (Sheep) 10-20L/yr
- Sheep – 20L Jetdip (diazinon), 5L Kleendok, 5L KFM
- (Sheep) use approx 80L when treatment reqd

e) Are there any climatic or other conditions that you think may increase worker exposure, or alternatively reduce the likelihood of exposure? Consider such things as any product uses in commercial pest control, pet parlours, by mobile hydrobath operators and facilities such as catteries, kennels or within intensive animal industries etc. Please describe.

- Confined space on shearing board in shed
- Hot weather increases the fumes that are given off, protective clothing and breathing apparatus need to be used
- Hot weather makes it too uncomfortable to wear protective gear all the time

f) How do you conduct your spraying operations? For example do you spray all day until you have finished, do you spray on consecutive days until it is finished, do you employ spray contractors, is the whole farm sprayed etc? How often do you spray in this way with this chemical??

- 300 sheep/hr
- 20-30 sheep
- 200 sheep/hr
- Jetting 200 sheep/hr
- 400 sheep per hour in a jetting operation
- 300 sheep/hr in plunge dip
- flystrike treatment, max of 30/hr if sheep are separated and the wool cllipped off prior to use

g) Are there any particular mixing methods or packaging that are relevant to occupational exposure; for example, water soluble packaging or enclosed mixing or transfer systems, such as containers with inbuilt measuring devices? Please describe.

- Mixing and transfer systems are excellent. Containers with inbuilt measuring devices would ensure that all operators were at the same level

- (Sheep) Need an applicator built into the container which allows for small amounts to be delivered into a hand sprayer – 10-20mL at a time.
- Need pouring spouts and graduated container measure quantity pouted out eg fluid level on side of can
- Inbuilt measuring helps
- Mixing by boom in boomspray vat
- A good dispenser which ideally delivers measured quantity of concentrate directly to water container is what I'd like
- A spout on the container would make mixing safer and easier. Also a measure in the lid or attached.

h) Please supply details of equipment you use including size of tank and type of agitation, type of pump and operating pressures, type of nozzles, size of booms, number of nozzles etc

i) 7.Do you have any other information on factors that may affect worker exposure during use of this chemical, such as the re-entry period into crops or premises after the use of the product or the re-handling of treated animals? If so, please give details.

- Don't handle freshly jetted sheep
- Need to be set up so sheep can exit well away from operators
- I do not treat sheep in the shed at shearing nor within a week of shearing, where possible I remove the wool from infested areas during this period
- Prolonged use of the powder during mulesing is unpleasant if there is any breeze. If I have to use an insecticide again I shall choose another chemical, liquid and less toxic to humans

SECTION III CHEMICAL PERFORMANCE

1. Do you achieve the same control/results as you did when you first used this chemical?

	Counts
Yes	19
No	3

If no do you have any specific reasons to support your conclusion?

- Blowflies striking sheep within about a six week period, used to get 8-10 weeks protection

2. Do you have any reason to suspect that there may be resistance to this chemical in your area?

	Counts
Yes	6
No	12

If yes please supply details of any specific instances where resistance has been identified.
Are you aware of any formal investigations carried out in relation to these instances? If so please supply details.

- Others say flies are becoming resistant to diazinon, I still get 4 weeks protection
- When routine prevention used to be carried out (10 yrs ago), the prevention time before restrike was getting less

3. Have you noticed any change in the effectiveness of your pest control program using this chemical (e.g. adverse effects, reduced effectiveness) associated with:

(i) changes in application technology?

	Counts
Yes	0
No	19

(ii) changes in formulation type used?

	Counts
Yes	1
No	17

(iii) changes in crop varieties, species/breeds or use situations?

	Counts
Yes	0
No	17

If 'Yes' to any of the above, please supply details.

4. Do you believe that the recommended timing of application is still appropriate?

	Counts
Yes	17
No	0

5. Have you noticed any variation of effectiveness or safety of this chemical when used as directed, associated with environmental conditions such as humidity, temperature, prolonged wet or dry conditions etc.

	Counts
Yes	2
No	14

If yes what variations have you observed and under what conditions?

- If you have a period of rain ie 1-2 inches soon after application length of period of protection from fly strike is reduced

6.Have you noticed any differences in effectiveness or safety when using:

(i) different products of the same formulation type?

	Counts
Yes	0
No	16

(ii) products with different formulation types?

	Counts

Yes	1
No	14

If 'Yes', what is the basis for your assessment?

- Not 100% effective kill with Clout S

7. Have you experienced any difficulties with the stability of either the concentrate or the spray mixture?

	Counts
Yes	2
No	16

- Tends to hang in the air when using powder in shed or sheltered area
- It is volatile in hot windy conditions

Use pattern table for Question 2 Section 1 Chemical Management

Chemical: Diazinon

PQ No.	Crop, Species or Situation	Pest/disease/weed/purpose	Rate(s)	No. of applications	Timing of applications	Method of application	Region/location
7	Sheep	Blowfly	Ad hoc	Before the affected sheep dies	Hand activated sprayer followiing clipping affected area		WA
	Sheep	Body lice				Plunge dip	WA
12	Sheep	Fly dressing	Treat affected area	1	When flies or larvae are present	Powder puffer	
13	Sheep	Lice	100mL/100L	1	Feb	Spraydip	NSW Central tableland
	Sheep	Flystrike prevention	1L/1000L	1	Nov	Hand jetting	NSW
	Sheep	Mulesing	Undiluted	1	Sept	Hand spray	
19	Sheep	Lice	Label	1	Within 4 weeks shearing	Plunge dip	WA
20	Sheep	Blowfly strike	Label	As reqd		Pour on soution to cover infested region and a margin beyond	Mid N SA
	Sheep	Powder form at mulesing about once every 5 yrs	Liberal sprinkle of exposed area	1	Aug		
21	Sheep	Flystrike	5 mL/L	1	When maggots appear on sheep	Pour on affected part of sheep	S Tas
22	Sheep	Lice	Small	1	After shearing	Dip shower	WA
23	Sheep	Lice	Grown sheep 2.5-3L/head Lambs 1.5-2 L/head	1	No more than 6 weeks off shears	Plunge dip	S Tas

APPENDIX H Hand Jetting Sheep - Agnote DAI/72

First Edition – Electronic January 1999

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When the decision has been made that sheep must be treated with insecticide to prevent or control flystrike or louse infestations, woolgrowers must also decide which product to use and how to apply that product. The decisions they make will depend on:

- whether the target pest is blowfly or lice,
- whether the pest is resistant to any insecticide group,
- what products are registered for the purpose,
- their cost, availability.

Whichever product is chosen, it is generally considered that thoroughness of application is crucial to getting the most out of the insecticide. Correct hand jetting has been shown to be the most thorough method of application but is relatively slow, hard work requiring good quality, comfortable protective clothing, access to water, a race, and proper jetting equipment.

A consequence of the laborious nature of the work and the frequent problem of badly designed facilities is that many producers do a poor job. Moreover, thoroughness of jetting diminishes as the operator tires.

Poor hand jetting reduces flystrike protection and can necessitate the need to retreat sheep. It is better to choose a product capable of providing long term flystrike protection and applying it properly to maximise the benefit of the treatment. Producers unwilling to hand jet properly - or who waste product by fire hosing yarded sheep - would be better off using an automatic jetting race (AJR), preferably of an improved design, or one of the new backline applications.

Occupational health and safety

Producers should protect themselves by wearing the appropriate protective equipment when preparing jetting fluid and jetting sheep. To properly jet sheep the operator must be in the race with the sheep. They should be wearing waterproof long pants, steel capped gum boots and long sleeve waterproof gauntlets. Thin, inexpensive cotton inner gloves worn inside the gauntlets make it easier to don and doff the gauntlets.

When preparing the jetting fluid a respirator and face shield should be worn for protection from fumes and splash. At the end of jetting this equipment should be washed, dried and stored ready for next time. Soap, water and a towel should be available to wash pesticide splashes, and a change of clothes should be ready for the operator to change into, if contaminated with insecticide or at the end of jetting.

Equipment

Jetting is best done in a concrete-floored race with adequate drainage to prevent puddles and mud forming. Trees or a roof covering to shade the operator will provide more comfortable conditions. The jetting pump should be located away from the sheep so that its noise during operations does not bother the sheep or inhibit filling the race.

The pump should be checked prior to use to ensure it is operating efficiently. Adequate fuel should be available. The pump must be capable of delivering 700kPa (100 psi) at the handpiece while still returning enough jetting fluid via the recirculating hose to provide sufficient mixing in the sump. When the jetting fluid has been mixed, the pump should be started and the handpieces held below the surface of the fluid in the sump in the "on" position for about five minutes. This will provide thorough mixing and ensure the hoses are full of jetting fluid, not just water. If two operators are jetting in side-by-side races the pump must be able to deliver 700kPa at each handpiece and still provide recirculation.

Inexpensive pressure gauges fitted in-line at the handpiece provide a convenient way of monitoring pressure at the handpiece.

It is impossible to see a gauge at the pump while jetting sheep in the race and the reading may bear no resemblance to the pressure at the handpiece anyway. There should be sufficient length of hose attached to the jetting wand to comfortably reach from one end of the race to the other.

Fly control

The handpiece selected should be matched to the wool length of the sheep. For wool less that 4-5cm the traditional sickle shaped wand with the five protruding nozzles (Figure 1 right) is a good choice. When it is combed through the fleece it will not snag. In longer wool the nozzles will catch in the wool and make the job difficult.

Figure 1

For protection from body strike three passes of the sickle shaped wand are required. The first is along the backline from the poll to the tail. Further blows are made on either side, but overlapping the first blow. The nozzles must be held in the fleece to ensure penetration to skin level.

In longer wool the wand may be "pumped" up and down in the fleece to ensure fluid pools in the fleece along the backline. As a rule of thumb, for body strike protection, aim to apply a minimum of 0.5L of jetting fluid per month of wool growth. Calculate this volume and time how long it takes to jet this volume into a graduated container. This is the minimum time that should be spent treating the backline of each sheep.

For wool longer than 5cm the Dutjet® wand (Figure 1- right) is a better choice. This wand has a metal shroud covering the T-shaped delivery tube. The tube has three big bore jets. The shroud has an angled back edge which opens the staple and the wand is drawn along the back of the sheep. This places the jets directly over the opening in the wool so that fluid is directed onto the skin.

Again, about 700kPa pressure at the handpiece is required. There is no need to push the Dutjet as firmly into the fleece. Slight downwards pressure is sufficient. A single blow from poll to tail is all that is usually required. The wand must be drawn along the back of the sheep at a rate such that fluid pools at the trailing edge of the shroud. Any faster than this does not provide a thorough treatment. Any slower will result in the excess fluid running over the outside of the wool and being wasted. Again, apply a minimum of 0.5L/month of fleece growth.

Thorough jetting of the back of sheep, irrespective of which wand is used, should ensure sufficient fluid is held in the fleece to penetrate to skin level. The addition of a scourable food dye such as Permicol Blue®, or the use of an indelible pencil can be used to check wetting.

Fluid will run around the body and drip from the belly of thoroughly treated sheep. Proper jetting for bodystrike protection should provide coverage for the belly, but rams and wethers may require direct treatment of the pizzle area.

Similarly, the poll of horned rams may need to be treated. If protection of the crutch is required, extra blows up the inside of each leg from the hock up to, and over the tail, are necessary (Figure 2 at right). With increasing concern about insecticide residues, producers may consider only jetting flystrike prone sites on their susceptible sheep.

Figure 2

Woolgrowers should aim to use a number of different strategies to control flystrike. Insecticides should not be used where another management strategy can be just as effective. For example, jetting the crutch should not be considered a substitute for proper worm control and crutching. The objective with hand jetting is saturate the whole staple so that jetting fluid reaches skin level where maggots feed. Although not all chemicals behave in the same way, the fleece and the skin act as reservoirs of insecticide that meter out insecticide into new wool growth. Water soluble compounds like cyromazine are washed down the staple during rain

Hand jetting verses Automatic jetting races

With greater emphasis now being placed on residues in wool, some recent work compared the performances of hand jetting and two Automatic Jetting Race configurations. On average, hand jetting applied 3.1L of jetting fluid per sheep, the standard HarringtonR AJR 1.7L/sheep and a modified AJR 4.5L/sheep. Sheep in that trial carried eight months wool growth. Importantly, results indicated that hand jetting left significantly higher insecticide residues than the standard AJR and residues at least as high as the modified AJR.

The same trial showed that hand jetting sheep with eight months wool using diazinon or cyromazine left residues at shearing 4-5 times higher than the present industry target level of 10mg/kg.

Lice treatment

Jetting long wool sheep to reduce louse infestations is only a stop gap measure to minimise wool damage before shearing and a thorough off-shears, or short wool treatment. Moreover, jetting woolly sheep will cause high insecticide residues in the wool at shearing.

Depending on the time of year, early shearing may be a more economic and more practical option. Nevertheless, because lice are more likely to be present all over the sheep treatment must target more areas than simply the back. Jetting fluid needs to penetrate to skin level around the neck and sides of infested sheep. Lice numbers will be reduced but the infestation will not be eradicated.

At the present time only two products are registered and can be used for long wool lice treatment. (See Agnote DAI78 - Pesticides Registered to Control Lice and Fly in NSW - December 1998 under development). Irrespective of what pest you are targeting and which product you are jetting, always read the label thoroughly and make sure you understand it. If in doubt, ask the reseller, company representative, Rural Lands Protection Board Ranger or Veterinarian, NSW Agriculture officer or consultant for advice. Adhere to the Withholding Period (WHP) and be aware that the Export Slaughter Interval (ESI) may be longer than the WHP.

Further Reading

Sheep blowflies - Agnote DAI/70

Dressing for Flystrike and wounds - Agnote DAI/71

Chemicals registered for lice and fly control - April 1999 - Agnote DAI78

Mulesing: accredited contractors - January 1999 - Agnote SW101

Disclaimer

between equivalent products is intended and that the inclusion of a product name does not imply endorsement by NSW Agriculture over any equivalent product from another manufacturer.

Always read the label

Users of agricultural or veterinary chemical products must always read the label and any permit, before using the product, and strictly comply with the directions on the label and the conditions of any permit. Users are not absolved from compliance with the directions on the label or the conditions of the permit by reason of any statement made or not made in this publication.

Document 204, submitted 06 July 1999

APPENDIX I Organophosphates: Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

ORGANOPHOSPHATES

Chairman & Chairman of the Working Group on Organophosphates: Professor H F Woods

Executive Summary

Downloading

The full report is available in Portable Document Format (PDF) as two files: the chapters and the appendices. These files may take some time to download, as they are 372 KB and 479 KB respectively.

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Executive Summary

1.1 This report of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment considers whether single, prolonged or repeated exposure to low doses of organophosphate compounds (OPs) can cause long-term adverse health effects. Low doses were defined as those which do not produce overt acute (short-term) toxicity accompanied by recognised clinical symptoms or signs of acute toxicity. The report was drafted by a specially constituted Working Group of the Committee.

1.2 For practical reasons the Working Group concentrated on effects on human health suspected of being common to OPs in general (i.e. class effects) rather than considering compound-specific effects. In particular, they focused on neurotoxic effects. Most of the relevant scientific evidence concerned possible neurological, psychological or psychiatric effects and these were the types of illness most frequently attributed to OP exposure by those who made submissions to the Working Group. The composition of the Working Group reflected the need for a detailed investigation of this subject and the Working Group sought expert advice on psychiatric issues.

1.3 The Working Group held a total of fourteen meetings between May 1998 and September 1999 and a draft report was submitted to the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment for endorsement in October 1999. Details of the background to the establishment of the Working Group and its methods of working are given in Chapter 2 of the report.

1.4 Chapter 3 describes the nature of OPs, their chemical structures and biological properties. For the purpose of their deliberations, the Working Group defined OPs as organophosphorus compounds that inhibit the enzyme acetylcholinesterase. Their mode of action as inhibitors of this enzyme is described and consideration is then given to the various uses of OPs as pesticides and veterinary medicines, the co-formulants used in such products, and the regulatory process for approval and licensing these products in the United Kingdom.

1.5 Chapter 4 summarises the various ways in which individuals may be exposed to OPs.

These include exposure to trace amounts in food and water, through the use of household or garden insecticides, and in the treatment of headlice. Consideration is also given to occupational exposure such as that during orchard spraying and, in particular, sheep dipping. The fate of OPs in the body is described, with sections on their absorption, metabolism and excretion.

1.6 The toxicology of OPs and the mechanisms involved in their acute cholinergic effects and in the induction of delayed polyneuropathy are considered in Chapter 5. The value of the hen test for screening compounds that induce delayed polyneuropathy is discussed. This chapter also examines the scope for potentiation of toxic effects through concomitant exposure to other compounds and individual variations in susceptibility to the effects of OPs.

1.7 The report then considers the sources of data that were relevant to the Working Group's remit. In Chapter 6 information provided by individuals in personal testimony, and relating to data held by the OP Information Network and the Pesticide Exposure Group of Sufferers, is described. Many individuals reported long-term illness, often severely impairing normal life, which they believed to be caused by exposure to OPs. Data available from adverse reaction schemes (the Health and Safety Executive's Pesticides Incidents Appraisal Panel; the Veterinary Medicines Directorate's Suspected Adverse Reaction Surveillance Scheme; the Medicines Control Agency's Yellow Card Scheme) and data from the National Poisons Information Service were also considered. However, these were found to be of very limited value in relation to the remit of the Working Group. The consequence was that the Working Group were unable to draw on any substantial body of clinical data. The Working Group were thus faced with a major problem. Although many of the individuals who submitted evidence reported very real, distressing illness, often distinguished by unusual combinations of symptoms, few could provide long-term medical observations or supporting clinical data. Many felt that their problems had been inadequately monitored and investigated. Individual case reports were informative but could not be used to make any assessment of cause and effect.

1.8 Chapter 7 consists of a review of the scientific evidence, largely derived from published scientific papers, describing epidemiological studies that were relevant to the deliberations of the Working Group. The Working Group identified 27 reports of such studies as being the most informative with regard to the potential toxicity of low-level exposure to OPs. These are summarised in detail in Appendix 4, with the Working Group's critique of each. Some of them concern the late sequelae of acute poisoning episodes rather than low-level exposure as defined by the Working Group. These were relevant because any chronic health effects that could be shown to result from acute poisoning might also occur with lower exposures and thus would merit special attention. The Working Group also considered the full report of a major study by the Institute of Occupational Medicine published in July 1999. In view of the importance of this study, which investigated an occupational group of particular concern, namely sheep dippers in Britain, it is summarised in detail in Appendix 5 together with a critique by the Working Group.

1.9 The review in Chapter 7 is divided into five sections covering different types of health outcome relating to the nervous system, namely: neuropsychological abnormalities, electroencephalographic abnormalities, peripheral neuropathy and neuromuscular dysfunction, psychiatric illness, and effects on the autonomic nervous system. Within each section consideration is first given to long-term effects following acute OP poisoning. This is followed by consideration of the effects of exposure to OPs in the absence of any recognised acute poisoning episode. It was, in the main, the Working Group's analysis of these studies that underlay the conclusions set out in Chapter 8.

Conclusions

1.10 Chapter 8 gives the Working Group's considered response to the question posed in their remit, namely to advise on whether prolonged or repeated low-level exposure to OPs, or acute exposure at a dose level lower than that causing overt toxicity, can cause chronic ill health. As noted earlier, the Working Group considered not only the evidence relating to low-dose exposures (i.e. those insufficient to cause overt toxicity) but also studies on the long-term sequelae of recognised acute poisoning episodes. The rationale for this is described in paragraph 1.8.

1.11 Although it has been proposed that dipper's flu is a manifestation of acute OP toxicity, the Working Group concluded that this is unproven. Thus, for the purpose of this report it was not regarded as an indicator of acute OP toxicity.

1.12 In reviewing the scientific evidence the Working Group focused on the five different health outcomes relating to the nervous system that are listed in paragraph 1.9. Of these, the data on EEG abnormalities and effects on the autonomic nervous system were insufficient to allow any firm conclusions to be drawn. The conclusions, which are those of the Committee, regarding the other endpoints are given below.

Long-term sequelae of acute poisoning

Neuropsychological outcomes
1.13 The balance of evidence supports the view that neuropsychological abnormalities can occur as a long-term complication of acute OP poisoning, particularly if the poisoning is severe. Such abnormalities have been most evident in neuropsychological tests involving sustained attention and speeded flexible cognitive processing ("mental agility"). In contrast, current evidence suggests that long-term memory is not affected after acute poisoning.

Peripheral neuropathy
1.14 Peripheral neuropathy, as one feature of OP-induced delayed polyneuropathy, is a well-established complication of poisoning by OPs that inhibit the enzyme neuropathy target esterase. The neuropathy is predominantly motor but possibly also sensory. Compounds that produce more than 70% inhibition of neuropathy target esterase give positive results in the hen test. Compounds evaluated as giving a positive response in the hen test are not used in the United Kingdom and have not been approved or licensed by regulatory agencies (i.e. the Veterinary Medicines Directorate or the Pesticides Safety Directorate).

1.15 The balance of evidence indicates that acute poisoning by other OPs, which do not inhibit neuropathy target esterase, can also lead to persistent peripheral neuropathy detectable by neurophysiological tests. If this occurs, most cases are not at a level that would give rise to symptoms.

Psychiatric illness
1.16 The limited evidence available does not allow any firm conclusions to be drawn regarding the risk of developing psychiatric illness in the long term as a consequence of acute poisoning by OPs.

Prolonged low-level exposure

1.17 In comparison with the positive neurological and neuropsychological findings following recognised poisoning incidents, the evidence relating to chronic low-level exposure to OPs, insufficient to cause overt acute toxicity, is less convincing.

Neuropsychological outcomes
1.18 Although some studies suggest impairment in the same tests that are affected after acute poisoning, others do not. The balance of evidence does not support the existence of clinically significant effects on performance in neuropsychological tests from low-level exposures to OPs. If such effects do occur, they must either be relatively uncommon or so small that they are not consistently detectable by standard methods of testing.

Peripheral neuropathy
1.19 The balance of evidence indicates that low-level exposure to OPs does not cause peripheral neuropathy. If effects on peripheral nerve function sufficient to cause severe disability do occur, they must be rare.

Psychiatric illness
1.20 The available data indicate that exposure to OP sheep dips is not a major factor in the excess mortality from suicide among British farmers. However, in general, the evidence relating psychiatric illness to OPs is insufficient to allow useful conclusions.

Acute exposure to OPs at a lower dose than causes frank toxicity

1.21 No studies have examined the long-term effects of a single exposure to OPs insufficient to cause acute toxicity. However, the findings in individuals with prolonged and repeated low-dose exposures, and in those who have suffered recognised acute poisoning, together indicate that any risk of serious health effects from such limited exposure must be small.

Questions posed to the Working Group by the Official Group on OPs

1.22 In addition to addressing the central question stated in the remit of the Working Group, consideration was given to the specific questions (listed in Appendix 2) posed to the Working Group by the Official Group on OPs. These were modified for clarity and as a result of the evolution of the thinking of the Group over time. Answers to these questions, as modified, are given in Appendix 3.

Monitoring of human adverse effects

1.23 It was a matter of particular concern to some members of the Working Group that the present schemes for monitoring human adverse effects had yielded so few relevant data and that little progress had been made in establishing a relevant clinical database.

Outstanding issues

1.24 In addition to drawing the above conclusions the Working Group identified outstanding issues, which need to be addressed by further research.

1.25 The major gap in current knowledge relates to the possibility that OPs cause disabling neurological or neuropsychiatric disease in a small sub-group of exposed persons. Most research has focused on people who were in work at the time of investigation, and therefore by definition were sufficiently fit for employment. Moreover, the available published studies have generally been designed to look for effects on the mean level of quantitative health indices in the exposed population, rather than exploring the possibility that only a small proportion of subjects may be at increased risk of clinically significant disease. Thus, although the substantial body of evidence that has now accumulated gives little support to the hypothesis that low-level exposure to OPs can cause chronic disease of the nervous system, it does not exclude the possibility that at least some of the illnesses that were described to the Working Group as following such exposure are indeed a manifestation of toxicity.

1.26 Further investigation, using suitably designed studies, is needed to establish whether the risk of more severe neurological or neuropsychiatric disease is increased by low-level exposure to OPs.

1.27 In view of the widespread public concern about OPs, evident from the response to the Working Group's inquiry, there is an urgent need for further research targeted at the issues set out above.

Recommendations for further research

1.28 The Working Group recommended further research to address the outstanding issues. These were grouped around the following questions, the answers to which would help to clarify the remaining uncertainties:

- What are the most common patterns of exposure, clinical presentation and subsequent clinical course among people in the United Kingdom with chronic illnesses that they attribute to OPs?

- How common is dipper's flu, and what causes it?

- Does low-level exposure to OPs cause disabling neurological or psychiatric disease in a small subgroup of exposed persons?

- Do people with chronic disabling illness that is suspected of being related to OPs differ metabolically from the general population?

- Other than acetylcholinesterase inhibition, what mechanisms play an important role in the causation of adverse health effects by OPs?

APPENDIX J Summary of NRA Review Activities relevant to organophosphate sheep dips

Introduction

In reviewing a chemical that is currently in the market place, the NRA must be satisfied that the continuing use of a chemical meets legislative requirements prescribed by the Agricultural and Veterinary Chemicals Code (scheduled to the *Agricultural and Veterinary Chemicals Act 1994*). These requirements mean that the use of an active constituent or product, in accordance with the recommendations for its use would not:

- be an undue hazard to the safety of people exposed to it during handling or people using/consuming anything containing its residues;
- be likely to have an effect that is harmful to human beings;
- be likely to have an unintended effect that is harmful to animals, plants or things or to the environment; and
- unduly prejudice trade or commerce between Australia and places outside Australia.

Outcomes of review of chemicals can include confirmation that registered use patterns are acceptable, cancellation of registration, removal of use patterns, requirements for additional data, label changes and other risk management measures. A registrant also has the option of withdrawing a product from sale during the review process.

Recent Reviews

A number of organophosphates have been prioritised for review in the NRA Existing Chemicals Review Program, since the program's inception in 1994. In total, the NRA either has reviewed or is currently reviewing 13 different organophosphate compounds contained in many registered products. As a result of the reviews completed at the time of this report, registration of two chemicals has been cancelled (parathion-ethyl and monocrotophos), two have been voluntarily withdrawn (demeton-S-methyl and azinphos-ethyl) and two have had registration severely restricted (mevinphos and parathion-methyl). None of these chemicals have been used as sheep dips.

Of the organophosphate compounds used as sheep dips, the NRA has taken a number of recent initiatives in the review of uses:

- Chlorfenvinphos and diazinon are currently under review as part of the Existing Chemicals Review Program (ECRP). In the case of chlorfenvinphos, proposed requirements for additional data include dermal and inhalational exposure data for mixer/loaders and applicators using plunge dips, automatic spray races and hand jetting equipment used in sheep. Review recommendations have not yet been developed for diazinon, but they are expected to include occupational exposure data requirements.

- Propetamphos was listed in the original 80 chemicals identified for priority review in the ECRP in 1995. The time of its review has not been scheduled.

- A report for The Woolmark Company was released in November 1998 titled "The Residue Implications of Sheep Ectoparasiticides". The Executive Summary of this report is below. In addition to environmental and trade issues, the report addressed concerns about pesticide residues on wool arising from use of registered sheep ectoparasiticides in relation to occupational hazard to shearers and other wool handlers. The report suggested a number of options for addressing the identified concerns and recommended a series of regulatory actions, a number of which had implications for worker safety.

  - In response to the Woolmark Report, the NRA has initiated a special review of the registration and associated label approval of certain sheep ectoparasiticide products. The review will assess the occupational health and safety, environmental safety and overseas trade implication aspects of using these products.

  - New occupational health and safety requirements were prepared by the National Occupational Health and Safety Commission (NOHSC) and are described in the document *Guidelines for Conducting a Health Risk Assessment of Sheep Ectoparasiticides for Wool and Sheep Handlers.*

- The registration requirements for veterinary products including ectoparasiticides were updated in 1999. The new data requirements are available on the NRA web site (http://www.dpie.gov.au/welcome.html) and have been incorporated into the NRA Requirements Manual.