PROCEEDINGS[1] FROM WORKSHOP ON RESEARCH ON ORGANOPHOSPHATES

Society of Chemical Industry Headquarters
14/15 Belgrave Square, London SW1X 8PS
28 March 2000

1. REGISTRATION

Agenda and Workshop delegate attendance list are attached (see Appendix 1a and 1b).

2. OPENING OF MEETING SESSION 1 (10.00)

Professor Anthony Newman-Taylor welcomed delegates to the meeting, which he chaired throughout all of its technical sessions.

3. INTRODUCTION TO SCIENTIFIC SESSION 1 (10.10)

3.1 The chairman made a brief introduction to the meeting, highlighting its evolution from the COT Report, its purpose to address relevant questions and refine those into valid research questions and its structure; comprising nominated speakers and plenary discussion.

3.2 On 20 December 1999, the Government had announced a four-point action programme in response to advice received from committees on the regulatory implications of a report on organophosphates from the Committee on Toxicity. The announcement confirmed that MAFF, HSE and the Department of Health would develop a targeted research programme to take forward the research recommendations from COT and the regulatory committees. The announcement made it clear that the wider scientific community would be involved in the process. The purpose of the Workshop was to assist in determining the scientific input and approaches required to meet research needs. Advice would be sought on what should be included in a Research Requirements Document which will invite expressions of interest in addressing specific research questions raised by COT and others. The Workshop had been designed to include research questions and issues which are being addressed by researchers but which are not included in COT's recommendations.

[1] This summary comprises views expressed at the meeting which are not necessarily those agreed by the workshop as a whole. Responsibility for the content of abstracts remains with their individual authors.

3.3 The chairman explained that speakers would include those working currently within and outside of the specific areas identified by COT as priorities. An overhead presentation of the five main areas of the COT recommendations was displayed, as shown below.

The COT Recommendations

1) **What are the most common patterns of exposure, clinical presentation and subsequent clinical course among people in the UK with chronic illnesses that they attribute to OPs?**
2) **How common is dipper's flu and what causes it?**
3) **Does low-level exposure to OPs cause disabling neurological or psychiatric disease in a small sub-group of exposed persons?**
4) **Do people with chronic disabling illness that is suspected of being related to OPs differ metabolically from the general population?**
5) **Other then acetylcholinesterase inhibition, what mechanisms play an important role in the causation of adverse health effects by OPs?**

---

4. SCIENTIFIC SESSION 1 NOMINATED KEYNOTE SPEAKERS & DISCUSSION (10.15-11.30)

Abstracts of presentations submitted by nominated speakers are given (see Appendix 2).

4.1 *COT recommendations for further research (David Coggon)*

The focus of the COT report on whether exposure to low doses of OPs can cause long term adverse health effects was reviewed, along with the research that has been published in this area. The possibility that a small sub-group of exposed persons became too unwell to continue working following exposure to OPs had not been investigated in any of the studies that were available for the COT. This gap in current knowledge, together with other areas requiring clarification, were identified by the COT. Discussion after the presentation clarified the rationale behind the COT's view that adverse neurophysiological effects due to OP exposure were rare and that exposure was not a major factor accounting for the excess of suicides in farmers. Dr Coggon recognised however the many cases of chronic ill health which were attributed to OP exposure which needed to be investigated in a systematic fashion.

4.2 *An epidemiological study of exposure to organophosphate pesticides and neuropathy among UK sheep dippers (Adele Pilkington)*

The aims, methods and results of this work were described. An empirical model developed in phase 1 was used to develop an exposure questionnaire for use in the phase 2 cross-sectional study of sheep dipping farmers and a control group. The third phase had focused on a sub-group and involved more detailed neurological and neuropsychological investigations. There were no questions after the presentation.

4.3 ***Epidemiologic design (Nicola Cherry)***

Professor Cherry described the current SCOPE study funded by HSE into genetic variation in susceptibility to chronic effects of OP. This addressed key points:

- why some people get sick and some don't after dipping sheep
- that there were alternative alloenzyme (A & B) forms of paraoxonase
- that genetic differences may determine phenotypes of A & B above
- a case-referent study (ill and unaffected dippers) using blood sampling to determine enzyme type should reveal any association between that characteristic and susceptibility
- careful means to control for exposure history and definition of patterns of illness would be needed
- 144 pairs of subjects had been analysed to date and a total of 175 would be completed by June
- report to HSE by July and peer reviewed paper by August were planned.

In discussion it was confirmed that blood samples remained available for further analysis, that the study covered different types of exposure to OPs and that it involved both genotyping and phenotyping.

4.4 ***Survey of health complaints among sheep dippers registered with sufferers' support groups (Tony Fletcher)***

The background to this proposed project was described as a systematic survey among those reporting to have suffered from ill health following exposure to OPs. It is intended to conduct a systematic survey of those registered with various organisations in order to gain a coherent overview of the consistency of the patterns of reported ill health. There were no questions.

4.5 ***Non-cholinergic neurotoxicity induced by organophosphates: elucidation of molecular targets and mechanisms (Paul Glynn)***

Research into mechanisms other than cholinesterase inhibition in the causation of adverse health effects by OPs was described. This included brain proteins involved in peptide metabolism and implicated with NTE. In discussion, the issue of whether work on NTE had been done in relation to children was raised. It was confirmed that NTE had an important development rôle but that the young were likely to be less susceptible to the effects of OPs on NTE than older people. It was agreed that there was some controversy as to whether an OP enhanced NTE effect was a causative factor or a marker of neuropathy.

4.6 ***Use of biomarkers of exposure and effect to define exposure to organophosphates in the workplace and potential toxic effect (Richard Glass/ Faith Williams)***

In discussion, examples of what might be biomarkers were given. In particular it was suggested that electrophysiological or enzyme biomarkers, such as serum cholinesterase, NTE or blood protease might be used.

5. SCIENTIFIC SESSION 2 PLENARY DISCUSSION (12.00-13.10)

5.1 The Chairman sought and received confirmation that there was a consensus among participants that the recommendations for further research made by the COT were relevant in addressing the fundamental question of a possible link between long term low level exposure to OPs and chronic symptoms which had been reported. In discussion on the meaning of low-level exposure, it was noted that COT had defined "low doses" as doses lower than those causing overt acute toxicity (i.e. symptoms and signs of acute toxicity). However, this raised the question of whether exposure not sufficient to cause cholinergic symptoms should be regarded as low level. In examining the literature it was necessary to establish whether a history of cholinergic episodes was or was not relevant to case studies. It was agreed that there could be a sub-set among those reporting chronic symptoms who had experienced cholinergic symptoms which had not been "recognised" at the time of the acute event. Such a sub-set would need to be distinguished in any further research for those who had not displayed any signs or symptoms of acute toxicity. It was noted that the existing literature had not identified a clear correlation between severity of cholinergic effects and chronic symptoms.

5.2 The issue of whether there was a sub-group who were particularly susceptible to OPs was linked to the issue of multiple chemical sensitivity. A possible correlation between sensitisation to very low doses of OPs and the symptoms of chronic fatigue syndrome had been suggested. In this context it was explained that sensitisation was a reaction to serial exposures to very small doses or an "acquired intolerance".

5.3 The meeting noted that COT had concluded that the proposal that dippers' flu is a manifestation of acute OP toxicity remained unproven. The Committee had not, therefore, regarded it as an indicator of acute OP toxicity. The meeting agreed that it would be important for further research into dippers' flu to address the question of whether symptoms could be due to an acute cholinergic effect because, if it was, those reporting symptoms of dippers' flu might develop chronic sequelae. The possibility that dippers' flu could be caused by an allergic response to endotoxins was also raised.

5.4 There was a consensus that the possibility that chronic symptoms could be linked to low-level exposure to OPs had not been fully explored because those with symptoms sufficiently severe to take them out of work had generally not been included in previous epidemiological studies. It was agreed that there was a need to widen the population base in any future studies to include those previously exposed to OPs who were no longer fit to work.

5.5 It was noted that previous studies had not, generally, been able to provide valid quantitative data for exposure to OPs. If possible, future research should seek to establish such data and it would be important for researchers to have rapid access to exposed persons. It was pointed out that there was no certainty that the "dose to insult" curve was linear. The response could be affected by the susceptibility of individuals and the possibility that susceptibility could be changed.

5.6 It was noted that changes in the formulations of veterinary medicines and pesticides could be relevant to the question of chronic effects following low level exposure to the OP active ingredient. It was suggested that exposure to the co-formulants or additives themselves might cause or exacerbate symptoms. For example, phenols which were removed from sheep dip formulations in the early 1990s could alter the metabolic base for toxicological outcomes and this could be an important issue in relation to the possibility of sensitisation.

5.7 In turning to issues not identified by COT as those which should be addressed by further research, consideration was given to the possible immune or hormonal effects of OPs. It was noted that there had been a small number of studies including an item in the Lancet circa 1996 which had examined extensive disturbance of cellular components of immunity in a laboratory study. Reference was also made to a WHO document indicating an OP eliciting auto-immune response and, therefore, advising caution in undergoing vaccination following exposure to OPs. It was suggested that there was also a possibility of an OP impact on hormones (as endocrine disruptors) which could be synergistic or additive.

5.8 The issue of whether cholinergic conditions should be examined as a possible generic cause of Alzheimer's disease, glaucoma, ME and related Gulf War Syndromes was raised. It was noted that this symptomology could be looked out for in the examination of data held by OPIN and PEGS to be carried out by Dr Fletcher. However, it was recognised that such symptoms were not specific and could be caused by several different diseases. There was also the possibility that, if such diagnoses had been made, those with the symptoms might not have linked or reported them in relation to OP exposure.

5.9 Among other possibilities noted were : possible synergy between OPs and other agents; possible effects of OPs on gastro-intestinal disturbance, kidney disease, liver dysfunction and skeletal effects; cardiac conduction abnormalities; visual field defects. The meeting also noted the possibility, to be reviewed in the following session, that children as a group might be particularly vulnerable to OPs.

5.10 It was suggested that future research should seek to address three important areas. The first was cholinergic effects which were still not fully understood. For example Sedgwick et al had demonstrated adverse synaptic effects 30 months after a single dose administration. The second was that hypotheses of causes of Gulf War Syndrome had described disparities between in-vitro and in-vivo effects, which were possible to explain by individual differences (e.g. sodium chloride status). The third was that diagnosis of "disabling" disease should include reports of symptoms by individuals.

The Chairman concluded that there would be a further possibility of discussing additional research questions following further presentations after the lunch break.

6. INTRODUCTION TO OPEN SESSION 3 (14.00)

6.1 Baroness Hayman (MAFF Minister of State in the House of Lords) introduced the afternoon sessions, describing herself as Minister currently responsible for OP issues at MAFF. She thanked speakers and delegates who had come to the meeting in response to what was acknowledged to be a difficult issue (of the highest order). The need to listen closely to good scientific advice as well as to a broad base of opinion (scientific and non-scientific) was stressed. The Workshop was intended to allow expression of opinion in an inclusive and transparent way, through debate aimed at helping to establish an ongoing research programme to underpin developing policy in this area.

OPEN SESSION 3 NOMINATED SPEAKERS (14.05-15.15)

6.2 ***Concerns about possible effects on children of exposure to OPs, either parental or direct (Elizabeth Sigmund)***

Also cited : Early brain injury - potential risks from organophosphate compounds D A Johnson & J Clarke

In discussion it was reported that a similar cohort of children (about 12 cases) had been identified. It was suggested that it would be helpful to have evidence of the clinical characteristics of individuals in the two groups identified although it was recognised that individuals might be reluctant to expose their children to such scrutiny.

6.3 ***Occupational OP Insecticide Exposure and Reduced Proximal Femur Bone Density (Stephen Hodges)***

Dr Hodges described in vitro experiments using paraoxon and diazinon to determine their impact in altering bone reabsorption. In discussion it was confirmed that data had been age-adjusted to take account of the fact that the OP exposed group was older than the control group. It was noted that the OP exposed group and the sub-group selected for biopsies were self-selected and not, therefore, a random sample. It was pointed out that farmers would normally have high density bone stock due to hard physical work. Although it was not possible to make a link, certain symptoms of fatigue could be linked to bone atrophy.

6.4 ***Neurological effects of orgnophosphorus compounds (Goran Jamal)***

Dr Jamal described four main areas requiring further research; firstly, investigation of “dipper’s flu”, secondly, the full profile of COPIND, thirdly the effects of synergism and combination exposures with OP impurities and with other non OP compounds, and fourthly, to study the effects of both physical and psychological stress on OP toxicity.

6.5 ***Autonomic Features of Chronic Exposure to the Organophosphates in Sheep-dip (Peter Julu)***

A description was given of investigations into 40 patients who developed chronic neurological dysfunction following clear histories of several episodes of mild to moderate acute OP poisoning. A comprehensive examination of autonomic function provided evidence of patterns of autonomic lesions which were proposed as a possible basis for diagnosis of adverse health sequelae of OP poisoning.

6.6 ***Neuropsychological sequelae of organophosphate poisoning (Sarah Mackenzie-Ross)***

The place of cognitive impairment alongside physical symptoms in the diagnosis and treatment of health problems arising from OP exposure was described. Methodological problems inherent in previous work were discussed.

7. OPEN SESSION 4 PLENARY DISCUSSION (15.45-16.45)

Chair Professor Anthony Newman-Taylor

7.1 The meeting noted that, although chronic fatigue as a symptom had been recognised as an effect of pesticide exposure in a report from CDC Atlanta, it would be difficult to distinguish between OP or viral exposure as the single cause of a chronic fatigue 'syndrome'.

7.2 In discussion of Dr Julu's paper, the functions of the autonomic nervous system were explained. The suite of tests employed examined and characterised these functions and identified certain functions, e.g. barroreceptors and parts of the central parasympathetic nervous system, which were affected by OPs. In discussion it was confirmed that patients who had been tested (also using electrophysiological tests) had generally been exposed to OPs through the skin although in a very small number exposure had been through inhalation or ingestion. It was recognised that, although dermal exposure was most common, there could be circumstances when inhalation would also be involved so it was difficult to be certain. However, studies carried out by the IOM had established that aerosols were not found to be a significant exposure hazard. It was noted that OPs could also be absorbed through the nasal mucosa during inhalation.

7.3 Concern was expressed about recommendations for treatment with anti-depressants in cases of OP exposure or Chronic Fatigue Syndrome. There had been one case of an OP user who was given antidepressants who had committed suicide shortly after admission to a psychiatric hospital. A suggested basis for this reaction to psychotropic drugs could have been an elevation of seratonin by OPs.

7.4 It was noted that, because the COT's remit had been to look at class effects of OPs, the developmental toxicity of individual compounds had not been reviewed. It was recognised that the paper presented by Mrs Sigmund had drawn

attention to a possible link between exposure to OPs (both post and pre-natal) and subsequent cognitive impairment. As recognised when the paper had been presented, it might be possible to carry out research into this question. However, it would be important to look at consistency of symptoms and to establish whether there was any pattern. In doing so, it would be helpful to have available the clinical characteristics and history of children who had been reported as being exposed to OPs.

8. SUMMARY OF KEY POINTS (16.45-16.55)

At the invitation of the Chairman, Ray Anderson recapped on the key points of the Government's announcement of 20 December 1999, referring to a targeted programme of R&D to be funded by MAFF, HSE and DOH and to address the issues identified by COT plus such issues as were identified by this workshop. Without attempting to summarise the whole discussion, he highlighted examples of issues arising:

- dippers' flu and the possibility that it was due to cholinergic effects;
- the importance of defining what is meant by low level exposure and distinguishing between individuals who may have suffered an unrecognised acute event from those who have not;
- possible susceptible groups (including children exposed either directly or in the womb).

Explaining the further process to follow the meeting, it was confirmed that:

- the meeting had been helpful in the context of producing a specific list of R&D questions;
- these questions would be drafted into a Research Requirements Document;
- that document would be placed in the public domain;
- those research requirements would be subject to open competition (with an independent involvement in their scrutiny);
- a rapid response to addressing these questions would be sought.

The meeting was closed at 17.00 hrs.

Further copies of this document will be accessible to download from the Internet Website addresses given below:
MAFF: www.maff.gov.uk/research/publications
DH: www.doh.gov.uk/opwkshop.htm
HSE: www.hse.gov.uk/research/content/opps/index.htm

AGENDA

WORKSHOP ON RESEARCH ON ORGANOPHOSPHATES

Society of Chemical Industry Headquarters
14/15 Belgrave Square, London SW1X 8PS
28th March 2000

9.00	ARRIVAL AND REGISTRATION	
10.00	OPENING OF MEETING	Chair Prof. Anthony Newman-Taylor
10.10	INTRODUCTION TO SCIENTIFIC SESSION 1	Chair Prof. Anthony Newman-Taylor
10.15	SCIENTIFIC SESSION 1 NOMINATED KEYNOTE SPEAKERS & DISCUSSION (10 mins each including questions)	
	1	David Coggon
	2	Adele Pilkington
	3	Nicola Cherry
	4	Tony Fletcher
	5	Paul Glynn
	6	Richard Glass / Faith Williams
11.15	COFFEE	
11.45	SCIENTIFIC SESSION 2	Chair Prof. Anthony Newman-Taylor
	PLENARY DISCUSSION	
13.00	LUNCH	
14.00	INTRODUCTION TO OPEN SESSION 3	Chair Prof. Anthony Newman-Taylor
14.05	OPEN SESSION 3 NOMINATED SPEAKERS	
	1	Elizabeth Sigmund
	2	Stephen Hodges / Juliet Compston
	3	Goran Jamal / Stig Hansen / Peter Julu[2]
	4	Sarah Mackenzie-Ross
15.00	TEA	
15.30	INTRODUCTION TO SESSION 4	Chair Baroness Hayman MOS (L)
	PLENARY DISCUSSION	Chair Prof. Anthony Newman-Taylor
16.45	SUMMARY OF KEY POINTS	Ray Anderson
17.00	CLOSE	

[2] Due to lack of time presentations were made by Dr Jamal and Dr Julu only.

WORKSHOP ON RESEARCH ON ORGANOPHOSPHATES (OPs)
Tuesday, 28th March 2000
Attendee List

Dr	Robert	Abel	DETR
Mr	Paul	Adamson	Pesticides Safety Directorate
Dr	G M	Ahmed	Consultant Psychiatrist
Mr	Brian	Anderson	OPIN Scotland
Mr	Ray	Anderson	Veterinary Medicines Directorate
Dr	Peter	Barrowman	MAFF, Chief Scientist's Group
Mr	Peter	Beaumont	Pesticides Trust
Mr	Richard	Billington	Toxicology Committee, BAA
Dr	Graham	Bonwick	Chester College
Mr	Paul	Brown	"The Guardian"
Mr	Duncan	Buchanan	Institute of Occupational Medicine
Mr	Richard	Carden	MAFF
Ms	Petrina	Carmody	Veterinary Laboratories Agency
Ms	Liz	Charles	Gabb and Company
Prof	Nicola	Cherry	University of Manchester
Dr	Geraldine	Clough	Southampton General Hospital
Prof	David	Coggon	MRC, Southampton General Hospital
Mr	Gary	Coomber	
Ms	Alison	Craig	The Pesticides Trust
Mr	Michael	Day	"New Scientist" Magazine
Dr	Frank	Dewhurst	De Montfort University
Mr	Ian	Dewhurst	Pesticides Safety Directorate
Dr	Martin	Donaghy	Scottish Executive Health Department
Dr	Philippa	Edwards	Department of Health
Dr	Robin E	Ferner	Birmingham City Hospital
Dr	Robin	Fielder	Department of Health
Dr	Tony	Fletcher	London School of Hygiene and Tropical Medicine
Dr	John	Fowler	
Dr	Teg	Freer	Wonford House Hospital
Dr	H	Fullerton	
Dr	Andrew	Gilbert	Central Science Laboratory
Mr	Richard	Glass	Central Science Laboratory
Dr	Paul	Glynn	MRC Toxicology Unit, University of Leicester
Dr	Stig	Hansen	Southern General Hospital NHS Trust, Glasgow
Mr	John	Harvey	Freelance Journalist
Dr	F	Hassib PPD	ICCJ
Baroness		Hayman	House of Lords
Dr	Stephen	Hodges	University of Essex
Prof	Malcolm	Hooper	University of Sunderland
Ms	Miriam	Jacobs	University of Surrey
Dr	Goran	Jamal	Central Middlesex Hospital
Mr	Evan	Jones	Organophosphates Research Network
Mrs	Doris M	Jones	
Dr	Peter	Julu	Central Middlesex Hospital
Mr	Mark	Lang	Carlton Television
Mrs	Teresa	Layton	
Dr	Annie	Macintyre	
Dr	Sarah	MacKenzie-Ross	University College London
Dr	M I	Mackness	University of Manchester
Dr	B	Mackness	University of Manchester
Ms	Louise	Marriott	Hodge, Jones and Allen
Prof	Tim	Marrs	Department of Health
Mr	Rob	Mason	Pesticides Safety Directorate

Dr	Howard	Mason	Health and Safety Laboratory
Prof	Cecil	McMurray	DARD NI
Dr	Elaine	Mutch	University of Newcastle
Dr	Sarah	Myhill	British Society of Allergy, Environmental and Nutritional Medicine
Prof	Anthony	Newman-Taylor	National Heart & Lung Institute
Mrs	Penny	Palmer	MAFF Chief Scientist's Group
Ms	Sarah	Passingham	Ministry of Defence
Dr	Adele	Pilkington	IOM
Ms	Claire	Piper	Hodge, Jones and Allen
Mr	Andrew	Povey	University of Manchester
Ms	Sue	Rabbitt Roff	University of Dundee
Dr	K Vala	Ragnarsdottir	University of Bristol
Dr	Roger	Rawbone	Health and Safety Executive
Dr	Huw	Rees	University of Wales
Prof	Andrew	Renwick	Clinical Pharmacology
Dr	Carole	Ross	SERAD
Dr	Craig	Sams	Health and Safety Laboratory
Dr	Maurice	Sauer	Veterinary Laboratories Agency
Dr	Leah	Scott	DERA
Dr	David	Shannon	MAFF Chief Scientist's Group
Mrs	Elizabeth	Sigmund	OP Information Network
Mr	William	Sigmund	OP Information Network
Dr	A E	Smith	University of Manchester
Dr	Stuart	Smith	Health and Safety Executive
Mr	Alan	Spence	Health and Safety Executive
Prof	Mike	Taylor	Veterinary Laboratories Agency
Prof	P K	Thomas	Royal Free & University College Medical School
	Paul	Tyler	MP
Dr	Sarah	Wark	Medicines Control Agency
Mr	Stephen	Wentworth	MAFF
Mrs	Joanna	Wheatley	
Dr	Garry	Wiles	Health and Safety Executive
Dr	Faith M	Williams	University of Newcastle
Dr	John	Williams	Chester College
Ms	Frances	Wolferstan	
Prof	H F	Woods	University of Sheffield

SUMMARIES AVAILABLE FROM NOMINATED SPEAKERS - SESSION 1

1. David Coggon

COT RECOMMENDATIONS FOR FURTHER RESEARCH

The COT report focuses on whether exposure to low doses of OPs can cause long-term adverse neurological or neuropsychiatric health effects. Quite a lot of research has now been published in this area and from this the report draws several useful conclusions. However, a major gap in current knowledge was identified.

This relates to the possibility that low doses of OPs might cause important disabling neurological or neuropsychiatic disease in a small sub-group of exposed persons.
As well as research to address this question directly, the report identifies four other questions, 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?
- 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?

---

2. Adele Pilkington

An epidemiological study of exposure to organophosphate pesticides and neuropathy among UK sheep dippers

Pilkington A, Buchanan D, Jamal GA*, Gillham R**, Hansen S**, Julu PO*, Kidd M, Al-Rawas SF *, Abdel-Azis M ***Hurley JF, Soutar CA. Institute of Occupational Medicine (IOM), Edinburgh, *Imperial College, London (formerly at INS, Glasgow), **Institute of Neurological Sciences (INS), Glasgow, *** Leicester Royal Infirmary

Aims

The broad aim of the study was to investigate whether cumulative exposure to organophosphates (OPs) in sheep dips is related to clinically detectable measures of polyneuropathy.

Methods

The study was completed in three main phases. The first phase sought to develop an empirical model for the uptake of OPs during different activities involved in dipping. This involved observing dipping sessions at twenty farms, and measuring OP metabolites in urine samples of sheep dippers both before and after dipping. This information was then used to develop an exposure questionnaire which was used in the second phase of the study, and applied retrospectively over a working life.

The second phase was a cross-sectional field study of 612 sheep dipping farmers, together with control groups of farmers with no sheep dipping experience and ceramics workers. Neurological assessments were based on a standard neuropathy symptoms questionnaire, and thermal and vibration quantitative sensory tests.

The third phase of the study involved more detailed neurological and neuropsychological investigations of a subgroup of 79 exposed sheep farmers from phase two. The questionnaire and sensory tests used in the cross-sectional study were repeated. Additional tests included nerve conduction, electromyography and clinical assessment. Neuropsychological assessment included the CANTAB battery and standard measures of anxiety and depression.

Results

The results from Phase 1 suggested that the most important source of exposure to OPs was contact with concentrate dip. Levels of urinary metabolites increased with increased handling of the concentrate containers. Increased splashing with dip wash was also found to be positively associated with increment in urinary metabolites.

In phase 2 after adjusting for confounders there was a weak positive association between cumulative exposure to OPs and neurological symptoms, the significance of which was dependent on the inclusion of a few individuals with extremely high exposure. There was no evidence of an association between cumulative exposure and the thermal or vibration sensory thresholds. However, separating the effects of exposure intensity and duration, revealed a higher prevalence of symptoms, primarily sensory, among sheep dippers who handled the OP concentrate. There was also evidence that thermal and vibration thresholds were higher among concentrate handlers.

More detailed clinical assessments during phase 3, also suggested that the pattern of changes found was consistent with a sensory neuropathy. Individuals classified with a probable clinical neuropathy were also more likely to report symptoms of anxiety and depression.

Conclusion

The findings suggest an association between exposure to OPs, predominantly the concentrate, and sensory neurological symptoms, and to a lesser extent, sensory thresholds .This suggests that long term health effects may occur in at least some sheep dippers exposed to OPs over a working life and is consistent with results from earlier studies.

---

3. Nicola Cherry

No abstract is yet available, but Prof. Cherry spoke about epidemiologic design and why we need to study those who are sick. See 4.3 for notes from the presentation.

---

4. Tony Fletcher
Outline of presentation to MAFF workshop 28/3/00

"Survey of health complaints among sheep dippers registered with sufferers' support groups"

Tony Fletcher
Environmental Epidemiology Unit
London School of Hygiene & Tropical Medicine
Keppel Street, London WC1 7HT

Background
Substantial numbers of individuals with a history of repeated exposure to organophosphates used in sheep dipping, have complained of a variety of symptoms, above all neurological and neuro-psychiatric. They attribute these to their organophosphate exposure and have sought or are seeking, treatment, recognition and in some cases financial compensation for their illness. Some of them are sufficiently disabled to be unable to work. Many report frustration at the scepticism that they face, including from medical professionals, that their conditions are indeed attributable to their exposure to sheep dip chemicals. A number of support organisations have sprung up who provide information and moral support to these sufferers, in particular OPIN, PEGS and NIOPSA (respectively the Organophosphate Pesticide Information Network, the Pesticide Exposure Group of Sufferers and the Northern Ireland Organophosphorous Sufferers' Association).

Members of and subscribers to these three organisations with symptoms and OP exposure add up to approximately 1000 individuals across the UK. It is likely that that individuals who have left sheep farming through ill-health and are included among these 1000, would not be picked up by cross-sectional studies of farmers such as those recently published. These registers therefore offer a unique route to assembling information on this potentially sizeable population. However systematic data are not available across this populations and so we were asked by them to design and carry out a systematic survey of these sufferers., so the scope of the potential health burden could be assessed. This project is proposed as a collaborative exercise between LSHTM and IOM and funding is being discussed with MAFF.

Survey
It is proposed to undertake an interview-based survey of all the individuals in these registers, with detailed clinical examination of a sample of them to validate their answers. This latter group will be provided with a detailed diagnostic report as well as advice on treatment. As this population is self-selected, and there is no control group, it will be impossible to establish the cause of their conditions on an individual basis to the survey participants. However it was judged to be of value to gain an overview of the consistency and coherence (or not) of the patterns of exposure and symptomatology. The survey, for the first phase is thus principally descriptive, though once the population is surveyed and described may well be that useful nested studies will be identified. This and other aspects of the project will be overseen by an Advisory Group including representatives of the government departments, support organisations and scientific advisers. It is expected that the main outcome will be a description of the patterns of reported ill-health and exposure history, and their inter-relationships, from which the size of the health burden which might conceivably be attributed to OPs in this population, can be given.

---

5. Paul Glynn

Non-cholinergic neurotoxicity induced by organophosphates: elucidation of molecular targets and mechanisms. Paul Glynn, MRC Toxicology Unit, University of Leicester, UK.

Recommendations of the COT Report* (1999) included the need for further research into mechanisms, other then acetylcholinesterase (AChE) inhibition, in the causation of adverse health effects by OPs. Recently we have begun to identify brain proteins more sensitive to commonly-used OPs than AChE itself: one of these is an enzyme involved in peptide metabolism. The basic methodology in this new project, using a proteomic approach, is an updated version of that used by our laboratory to identify NTE, the target for OP-induced neuropathy. By cloning the NTE gene we have gained insights into the structure of this unusual protein and into the molecular consequences of its reaction with neuropathic OPs. Our studies with NTE transgenic mice are allowing an assessment of the possibility that the mechanism of OP-induced neuropathy involves not simply an inhibition of NTE's enzyme activity, but instead a toxic gain of function in the protein. Increased mechanistic understanding is vital for hazard assessment and prediction of health risks in man, and to provide epidemiologists with more specific indices of effect.

* ORGANOPHOSPHATES: Committee on toxicity of chemicals in food, consumer products and the environment. (Chairman, H.F. Woods). Department of Health, 1999.

---

6. Richard Glass / Faith Williams

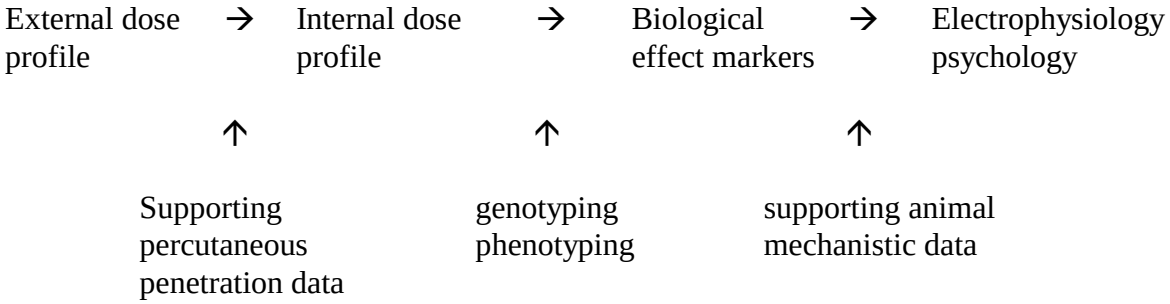
JOINT PROJECT BETWEEN CENTRAL SCIENCE LABORATORY AND NEUROTOXICOLOGY UNIT, NEWCASTLE UNIVERSITY

USE OF BIOMARKERS OF EXPOSURE AND EFFECT TO DEFINE EXPOSURE TO ORGANOPHOSPHATES IN THE WORKPLACE AND POTENTIAL TOXIC EFFECT

Background

There is currently limited information relating exposure history to biomarkers of internal exposure or to biomarkers of effect other than acetylcholinesterase inhibition, which is generally low and recovers soon after exposure. There is a requirement for a more sensitive biomarker of effect.

Worker study



Scientific Approach

Selected distinct types of exposure scenarios in volunteer workers using normal working practice, which will include repeat exposures. To investigate the same workers on more than one occasion to define the effects of multiple exposures associated with each type of exposure pattern.

1. Evaluation of worker exposure. Using existing in-house protocols to determine potential dermal and inhalation exposure, and estimate skin deposition and stratum corneum reservoir by tape stripping. Contamination of protective clothing and rates of its penetration by OP's will be an essential part of this evaluation.
2. Internal dose profile. Blood levels of parent OP and active oxon metabolite (if sufficiently sensitive assay can be developed) for levels immediately post exposure. Full urinary metabolite profile up to 48 hours after dose to define uptake.
3. Biomarkers of effect. Serial blood samples for monitoring of red blood cell acetylcholinesterase, serum cholinesterase, neuropathy target esterase (if appropriate), blood protease, other markers of CNS integrity and function
4. Genotyping and phenotyping of individuals
5. Markers of effects on neurotransmission. Use of the electrophysiological technique (SFEMG) as used in Newcastle and psychological measurements both short term after the exposure and longer term.

Parallel approaches to define organophosphate effects in man that Newcastle University would propose:

Mechanism of organophosphate toxicity
Experimental animal studies of repeated low-level exposure to OPs has demonstrated long-term neurotoxic effects. Electrophysiological measurements in the mouse phrenic nerve-diaphragm preparation have shown that multiple low-level doses of OPs can cause changes in neurotransmission (an increase in the variability of latency of evoked end-plate potentials (EPP jitter)). This effect on nerve function was delayed and occurred when acetylcholinesterase activity had returned to normal levels

The aims would be

- to determine the site and mechanism of the increase in EPP jitter in the mouse. Are these pre-junctional effects related to changes in conduction along the motor nerve, changes in end-plate morphology or caused by nerve-terminal regeneration ?
- to establish if there is any histological evidence in the mouse of nerve damage in the brain, spinal cord or peripheral axons after repeated low-level dosing with OPs.
- to determine the effects of repeated low-level dosing with OPs on the function of the neuromuscular junction in the mouse.

Inter-individual differences in susceptibility
It has been suggested that a small sub-group of the population may be more susceptible to the effects of OPs than others. Few reasons have been put forward as to why this should be, but variability may be influenced by the individual's capacity to metabolise these compounds. Most organophosphates require activation by cytochromes P450 (CYPs) for toxicity and are detoxified by the A-esterases (PON1) and carboxylesterases. Interindividual differences in activation and detoxification may be different for different compounds and contribute to differences in susceptibility to toxicity

Our approach would be to genotype and phenotype a group of over 60 individuals who have been referred to Professor Peter Blain reporting adverse effects following chronic exposure to organophosphates and compare to the control population

Clinical picture
Clinical experience (Professor Blain) of over 60 patients, referred for an expert medical opinion has failed to identify a specific set of symptoms and signs that could define a syndrome. The clinical features in these patients are not consistent nor is the causative agent easily determined, although organophosphates in sheep dips are most commonly implicated. Clinical investigation of these cases is difficult without a clear case definition or a diagnostic marker and in most cases there are poor historical data on exposure.

The aim of this study would be to compare a series of specific variables in this group of patients with a comparable control group. The protocol adopted for the study will enable us: (I)to determine the health profiles of the patient and control groups using a General Health Questionnaire (2) to determine the differences in neurobehavioural parameters between the patient group and the control group (3) to determine the differences in neurophysiological parameters (including single fibre electromyography (SFEMG)) between the patient group and the control group and (4) to assess the patient group genotypically and phenotypically for the enzymes involved in the metabolism and toxicity of organophosphates and to compare this profile to that of the control group.

SUMMARIES AVAILABLE FROM NOMINATED SPEAKERS - SESSION 3

1. Elizabeth Sigmund

Contribution to the OP Workshop
28/3/2000

Concerns about possible effects on children of exposure to OPs, either parental or direct

In September 1998 members of OPIN, accompanied by Dr Vyvyan Howard of the Foetal and Infant ToxicoPathology Unit, Liverpool University, presented evidence to members of the HSE at Rose Court, Southwark Bridge, London, relating to twenty two cases of severe cognitive impairment among children of families with direct occupational exposure to OP sheep dips. In each case one or other parent has been personally affected.

Members of HSE present were: Dr Stuart Smith, Senior doctor in the Health Policy Directorate of HSE; Glynne Jones, from HPD, HSE; Julia O'Hara, head of Human Health Effects Section, of the HSE Pesticide Registration Section, Bootle. Also present for part of the meeting was Margaret Clare, the newly-appointed Head of Physical and Biological Agents Division of HSE Health Policy Directorate. Dr Roger Rawbone of the HSE, whose update on MS 17 is published tomorrow, informed me two weeks ago that he was never informed of this meeting, either before or since. He was not happy.

On October 9 1998 Dr Stuart Smith wrote to OPIN, saying that the points made at the September meeting were "weighty", and that the HSE members present "will need to put the argument more formally to our scientific advisers, both Governmental and independent, before deciding what to do", he said that they had found themselves "handicapped by our need to rely on our unaided recollection of what was said". It would seem to us that such senior representatives of HSE would have provided a secretary to take detailed notes of such a meeting in which "weighty" matters of health were to be discussed.

What follows is a list of five questions to us, which would be the suitable basis for a formal scientific enquiry ie:

> "The evidence for thinking that pre-natal or post natal exposure takes place at high enough levels to cause the effects in question",
>
> "The reasons for thinking that the abnormalities referred to are caused by the exposures referred to,"
>
> "The reasons for thinking that the behavioural and other developmental disorders suffered by the children whose cases you described are linked to morphological abnormalities referred to " (by Dr Howard),
>
> and "Why these effects, or correlates of them, would not be expected to emerge during assembly of the pre-approved data package for the products involved".

The latter question,is, of course, of great significance, and one to which we would all like to see detailed answers.

His letter ended by saying: " I am sorry if this seems a rather lengthy list, but to do your concerns justice I think that it is important that we cover all the links in the chain of cause and effect".

We considered this letter in detail, and Dr Howard forwarded several scientific papers to Dr Smith, but no further action was taken. OPIN is a small, modestly funded support-group for people who contact us, with evidence of occupational exposure to OPs; we are not - and have never pretended to be - a scientific body, and see our role as having a duty to raise issues with the relevant Governmental department, as and when they come to our attention. Having conferred with several specialists, and taken note of a number of scientific papers relating to the effects of OP exposure on children, we considered that we had taken the appropriate action in taking the matter to the HSE. It seems anomalous that we should then be asked to supply detailed scientific proof of the "links in the chain of cause and effect", that is what we had hoped that the HSE might undertake. It still seems to us that research in this area of concern should be undertaken.

As you will be hearing (have heard) directly of Dr Howard's concerns I will not attempt to repeat his words. [SEE EDITORIAL NOTE BELOW]

I have been asked to read a short paper from David Johnson, a paediatric neuropsychologist from the Ainslie Hospital, Edinburgh. As David is unfortunately unable to be present in person he asked me to deliver this paper on his behalf.

(To be forwarded later).

As you will see there are very real concerns about possible central nervous system damage to the foetus or infant, whose nervous system is extremely vulnerable to nerve toxins such as OPs. All the reports received by OPIN show strikingly similar symptoms - ie cognitive impairment involving short term memory loss, language deficits, sequencing, both of numbers and letters, and lack of the ability to order information - all leading in the older child to lack of confidence and self esteem, which causes outbreaks of depression and anger.

Two young children from Cornwall have been seen by a leading London-based paediatric neurologist, who gave a written report which confirmed that both children were suffering severe neurological imbalances, but owing to the consultant knowing nothing about the possible effects of OP exposure he could not comment on the possibility that exposure to OPs might have contributed to their condition. He recommended genetic investigation, which after a three year waiting time, has not yet transpired!

As this audience will know, none of the Government funded studies undertaken in Britain have ever considered possible damage to children, despite OPIN's appeal to the HSE, and to the COT committee in 1998. We find this insupportable, and recommend that a research programme, conducted by experienced experts, be set up as soon as possible. This is obviously an extremely important area of research, as there are many thousands of children involved in agriculture and horticulture world wide, and therefore potentially exposed to OPs. It is surely the responsibility of the developed nations to make sure that such detailed research is carried out.

(A list of references to papers on the subject of foetal and infant cognitive and neurological damage is appended, also a copy of Dr Smith's letter to me).

END

Elizabeth Sigmund

12/3/2000

[EDITORIAL NOTE: in view of Dr Howard's non-attendance at the Workshop, Mrs Sigmund has requested by telephone to Dr A Gilbert CSL on 30th March 2000 that her specific references to Dr Howard's views in this paper be not regarded as strictly authoritative.]

References

"Clinical and experimental toxicology of OPs and carbamates" (Ed. By Dr TC Marrs and Dr B Ballantyne) Butterworth Heinemann.

"Accumulation of chlorpyrifos on residential surfaces and toys accessible to children". (Gurunathan, Robson, Freeman, Buckley, Roy, Meyer, Bukowski and Lioy) Environment Health Perspectives - Vol. 106. No.1 January 1998.

"An anthropological approach to the evaluation of preschool children exposed to pesticides in Mexico". (Guilette, Meza, Aquilar, Soto and Garcia). Ibid. June 1998.

"Central nervous system plasticity and exposure to OP pesticides". (Overstreet and Schiller). The Vulnerable Brain and Environmental Risks. Vol 2 "Toxins in Food", Plenum Press, New York 1992.

"Neurobehavioural effects of prenatal exposure to the OP - Diazinon - in mice".
(Spiker and Avery, Department of Pharmocology , University of Arkansas for Medical Scientists, little Rock, Arkansas). Journal of Toxicology and Environmental Health, 3:989-1002, 1977. Hemisphere Pub. Co.

"Amygdala kindling in immature rats: proconvulsant effect of the OP insecticide - chlorpyrifos". (Wurpel, Hirt and Bidanset. Department of Pharmaceutical Science, College of Pharmacy and Allied Health Professions, St.John's University, Jamaica, New York 11439). Neurotoxicology 14(4). 429-436. 1993, Intox Press Inc.

Letters from Professor Brian Neville, Professor of Paediatric Neurology, Great Ormond St. Hospital for Children, NHS Trust. Copies held, with parental permission, by OPIN.

ADDENDUM

Paper by David Johnson forwarded as fax.

DRAFT

EARLY BRAIN INJURY – POTENTIAL RISKS FROM ORGANOPHOSPHATE COMPOUNDS

David A Johnson
Consultant Paediatric Neuropsychologist

Julia Clarke
Consultant Clinical Neuropsychologist

There is increasing concern that organophosphate compounds (OPCs) may cause impaired neurological functioning in adults.

The physiological immaturity of a child's brain renders it correspondingly more vulnerable to the effects of any insult. Generally, the younger the brain then the greater its vulnerability.

The foetal brain is uniquely sensitive to toxic insult by a number of mechanisms. Far from being well protected from the ravages of the outside world the foetus is particularly vulnerable because of its physiological immaturity and placental dependency. Toxic insult may occur in acute or chronic form by placental-foetal exchange, storage into fat or amniotic fluid, or immature metabolism. Hepatic immaturity, for example may create a substantially lower threshold for insult than at maturity. The effects of toxins may be transmitted via parental sperm, creating the earliest stage of insult to the foetus. Similarly, toxic substances may continue to adversely effect the child after birth, via breast transmission.

It is readily acknowledged that there is an absence of appropriate scientific investigation in this field. There is an urgent need for well designed and carefully controlled prospective studies. One should urge caution in extrapolating from adult studies or from studies on the effects of other toxic insults upon the foetal brain. However, the unique vulnerability of the foetal and immature brain also urges concern. Early brain injury precludes completely normal development. Neuro-developmental delays and deficits may result from underlying anomalous or absent growth. The full effects may not be seen until maturity, in the late teenage years when the critical periods for cognitive and behavioural development have passed. There is no reasonable basis for a policy of wait and see.

END

---

2. Stephen Hodges

Occupational Organophosphate Insecticide Exposure and Reduced Proximal Femur Bone Density

Introduction

Organic compounds incorporating a phosphate group have the innate possibility to interact with skeletal metabolism. This is true for the bisphosphonate class of drugs, which have been designed specifically to target metabolic bone disease and as agents to counter the skeleton eroding secondary effects associated with some tumours. There is no reason to suspect that organophosphate insecticides would not also have some effects on the skeleton. This issue has not been thoroughly investigated.

In vitro experiments using the specific organophosphate insecticides paraoxon and diazinon, which are said to be greatly different from a lethal-dose$_{50}$ perspective, were found to be equipotent in altering bone resorption in a tissue culture experiment using mouse calvaria. At 'high' concentrations (10^{-6} M) these chemicals inhibited 1,25$(OH)_2$ vitamin D_3 initiated bone resorption. However, at 'low' concentrations (10^{-8} - 10^{-9} M) these chemicals augmented bone resorption by some 15%. The fact that the compounds had very similar activities suggests that the sulphur atom in diazinon, which is thought to confer the greater safety to the chemical, does not have to be converted to an oxygen atom to exert an effect on the skeleton. This conversion is considered to be a function of hepatic metabolism.

Methods

The clinical investigation that was initiated to investigate the possibility of skeletal effects in humans exposed to organophosphate insecticides recruited men with documented occupational long-term, low-level exposure to these chemicals. Only men were investigated in this study in order to limit the possibility of confounding factors imposed by women experiencing the menopause, which is a known risk factor for osteoporosis. The exposure group men were self-reporting as suffering from health problems, allegedly from exposure to organophosphate insecticides. There were 88 men in the exposure group and these were compared to 43 men in the control group. The latter were drawn from an urban environment and none of these men had an overt exposure to organophosphate insecticides. All the men recruited into the study were subjected to rigorous exclusion criteria for the possibility of any factors known to interfere with skeletal metabolism. All the men had bone mineral density measurements assessed at the proximal femur, lumbar spine and distal radius. They had a plain radiography and bloods were drawn for routine clinical chemistry analyses. Blood and urine samples were also collected for specific assays for biochemical markers of skeletal metabolism and for genetic susceptibility studies. From the strictness of the exclusion criteria, on examination these men should have presented with very healthy skeletons.

A subset of the men (n=24) who were undergoing litigation had an iliac crest biopsy for the assessment of tissue levels of organophosphate insecticides and for specific histomorphometric analyses.

Results

The men in the control groups and the exposure groups had similar mean body mass, but the exposure group were slightly older (50.5 ± 10.8 vs 43.9 ± 11.1, P=0.002). Bone mineral density decreases as a function of age, therefore the bone mineral densities were adjusted to account for this using a linear regression analysis (Statgraphics Plus V4, Manugistics) to generate parameters to correct for age differences on bone mineral densities. Distribution characteristics structured the statistical comparisons, log transformation of the data was necessary in some analyses and unequal variances were accounted for.

All the men had similar bone mineral densities at the lumbar spine and the distal radius. However, there were statistically significant differences between the control and exposure group with respect to the bone mineral densities at all regions of the proximal femur.

The histomorphometry data on the iliac crest biopsy samples showed clear and distinct differences between the organophosphate insecticide exposure group and archived control samples for specific bone cell activity parameters. The same operator conducted all the measurements in the histomorphometric study in order to reduce errors. These data have been published in *The Lancet* (Vol. 354 pp1791 – 1792 [1999]).

Discussion

The current methodologies used to measure bone mineral density have a well-documented history of reliability, accuracy and precision. The differences observed in the proximal femur between the control group and the organophosphate group are therefore of interest. This difference amounts to approximately 0.4 standard deviation units. A recent consensus document from a leading group of clinical experts has suggested that men with a one standard deviation unit difference from age matched controls should be considered for possible intervention. For the proximal femur, and under normal circumstances, it is not considered that men would present with reduced bone mass until their mid-late sixties onwards. Epidemiological studies suggest that for men about 50 years there is an approximate 6% chance of presenting with a fracture of the proximal femur. The men from our exposure group would have a predicted risk of up to 9%. This finding gives cause for concern as the exposure group were highly selected against presenting with low bone mineral density through other factors such as steroid use or hypogonadal status. Furthermore, exercise is well known to increase bone mass; the nature of the employment of the men in our study suggested that their skeleton should have benefited from their work practice and that they would have been expected to have banked a respectable bone stock. It could be argued that a control group of more physically active men would have given a more accurate reflection on the likely bone mineral density status of the men exposed to organophosphate insecticides.

A central problem is that using cross sectional data, as in this study, there is no information on what is going to happen to the skeleton of the organophosphate insecticide exposed men. Indeed, just as the bone mineral density data of the skeleton may be a witness to past insult, the histomorphometric data suggests that

the *current* skeletal status of these men may be deteriorating at an alarming rate. Further studies are urgently required to define and understand the full impact of skeletal toxicity induced by occupational long-term, low-level exposure to organophosphate insecticides.

It is of concern that the *in vitro* studies cannot show a distinction between the two forms of organophosphate insecticide on skeletal metabolism. This data strongly suggests that there does not need to be hepatic conversion of the sulphur containing organophosphate insecticides to inflict skeletal damage. This is alarming as, in the treatment of headlice, organophosphates are left in contact with the child for several hours. Re-infection, or incomplete clearance of the infestation, often means that the same children can be exposed to multiple doses of these chemicals. The skeletal toxicity issue of these organophosphate compounds needs to be addressed as the adult histomorphometry study suggests that there are potentially, long-term skeletal health problems, as the men that were examined had not been overtly exposed to organophosphate insecticides for several years.

As a footnote it is worth mentioning, as it arose in the question session following the presentation, that the histomorphometric tissue samples cannot, in themselves, be considered to carry bias due to the fact that the subjects were proceeding with litigation. This is too subjective an issue for scientific debate, but I suggest that litigation does not, in this case, carry the sub-clause ‘most ill’, but may reflect more the fact that these subject were possibly the ‘most committed’ to resolving their claims for ill-health.

---

3. Goran Jamal

NEUROLOGICAL EFFECTS OF ORGNOPHOSPHORUS COMPOUNDS

GORAN A. JAMAL, ***MB ChB MD PhD FRCP***
Imperial College School of Medicine

In addition to the acute cholinergic poisoning, organophosphorus (OP) compounds are capable of producing intermediate syndrome, delayed OPIND and chronic neurological, neurobehavioural and psychiatric disorder (COPIND). The concept of the neuropathy target esterase (NTE) inhibition and ageing as a marker of OPIDN and the use of the hen test as an exclusive screening test for neurotoxicity of Ops is flawed. COPIND syndrome can be produced either following one or more episodes of acute cholinergic effect (phenomenon 1) or following repeated prolonged exposure to relatively small quantities of OP which do not produce cholinergic manifestations (phenomenon 2). The chronic effects on children is serious under recognised and may be more incapacitating.

There are four main important areas which require further research; Firstly, investigation of "dipper's flu" as these may well represent cholinergic episodes and if so then they could be causing COPIND through phenomenon 1 in large numbers of farmers. Secondly, the full profile of COPIND and the extent of the overlap between its various components needs further research. Thirdly, to study the effects of synergism and combination exposures with OP impurities and with other non OP compounds. Fourthly, to study the effects of both physical and psychological stress on OP toxicity.

4. Peter Julu

Abstract:

Autonomic Features of Chronic Exposure to the Organophosphates in Sheep-dip

Peter O.O.Julu, Stig Hansen[1] and Goran A. Jamal

Peripheral Nerve and Autonomic Unit, Imperial College of Science, Technology and Medicine, Department of Neurology, Central Middlesex Hospital, Acton Lane, Park Royal, London NW10 7N and [1]Department of Clinical Physics, Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF.

We investigated 40 patients who developed chronic neurological dysfunction following clear histories of several episodes of mild to moderate acute organophosphate poisoning. Extensive failure of the cutaneous thermoregulatory vasomotor function was found in 38 patients (95%), but emotional sudomotor function was absent in only 11 patients (27%). There was failure of the cardioaccelerator function in 28 patients (70%), failure of the sympathetic control of blood vessels in the skeletal muscles was found in 18 patients (46%). Twenty patients (50%), some with clear history of oral ingestion of organophosphates had failure of the sympathetic control of the splanchnic vascular bed. We saw disturbances of the baroreflex function in 33 patients (83%). Nearly all patients in this group had lower than normal resting cardiac vagal tones. Despite the sympathetic failures, there was either none, or very mild postural hypotension in these patients, contrary to this being the common effect of other causes of autonomic failure like diabetes mellitus and pure idiopathic autonomic failure.

Our finding support existing evidence that long-term neurological sequelae follows acute organophosphate intoxication and repetitive low level exposure to these compounds. Autonomic target-organs in the skin, large blood vessels and the heart including central parasympathetic functions are most affected. This pattern of autonomic lesions is unique to chronic organophosphate poisoning and could be diagnostic of the condition. This is the first detailed study of autonomic dysfunction in the neurological disorders associated with organophosphate exposure to our knowledge.

---

5. Sarah MacKenzie-Ross

Neuropsychological sequelae of organophosphate poisoning

ABSTRACT

Much has been written about the physical symptoms of acute organophosphate poisoning and possible mechanisms of damage. Cognitive impairment has often been looked at in rather a limited way, which is unfortunate as it can be severe and disabling in some individuals. Methodological problems inherent in previous research are discussed, for example: (1) The lack of epidemiological studies on the prevalence and severity of neurological problems in farmers exposed to organophosphates. This makes it difficult to determine if organophosphates are equally toxic to all individuals or if certain individuals are vulnerable. (2) The majority of studies have examined individuals with a history of acute poisoning. Less is known about the effects of long-term low level exposure. Agreement about the nature of 'dippers flu' is lacking, so it is difficult to know whether it represents acute mild poisoning. If it does then individuals with and without a history of 'dippers flu' should be examined separately. To date, studies have not made this distinction and have combined both groups of farmers in their analysis. (3) Many researchers have only included a small number of cognitive tests in their protocols which may lack sensitivity and produce false negative results. Through the course of clinical work, the author has carried out in-depth psychometric testing on a small number of farmers with a history of exposure to organophosphates (and 'dippers flu'). These farmers show evidence of significant mental and motor slowing, impaired memory, executive dysfunction and emotional changes (anxiety and depression). Further studies are needed to determine the mechanism of damage; and whether these farmers are particularly vulnerable to the effects of organophosphates (and if so, why ?).
