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**COMMITTEES ON TOXICITY AND CARCINOGENICITY OF CHEMICALS
IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT.**

**ROYAL COMMISSION ON ENVIRONMENTAL POLLUTION (RCEP): CROP
SPRAYING AND THE HEALTH OF RESIDENTS AND BYSTANDERS**

Introduction

Background to RCEP report

1. The Department of Environment, Food and Rural Affairs (Defra) announced a public consultation on the need for buffer zones between agricultural applications of pesticides and residences in July 2003. This followed discussion in the Advisory Committee on Pesticides (ACP), taking account of some stakeholders concerns regarding risks to the health of rural residents as a result of crop spraying. Members of the ACP gave the following advice to Ministers:

'Members had concluded that on the basis of the information currently available the risk assessment for bystanders used at present provided adequate protection, even if spray is applied to the edge of a field. Nonetheless, the Committee recognised that many people may consider it socially unacceptable to spray right to the boundary of a neighbour's property. If Ministers agree, they may wish to consider options to restrict this practice.' (*Ref ACP website:*
<http://www.pesticides.gov.uk/acp.asp?id=586>)

2. The specific conditions of use for individual pesticide products are supplemented by guidance on best practice contained in the statutory Code of Practice for the Safe Use of Pesticides on Farms and Holdings (the "Green Code"). Although failure to follow the Code's guidance is not in itself an offence, it may be used in evidence against the user if prosecuted for breach of the law. The consultation documents asked for views on the risk assessment process, the Green Code and the need for buffer zones to prevent exposure. The consultation was based on the ACP's advice that the current regulatory system is adequate to protect human health but that there may be an issue of "social acceptability" in spraying right up to the boundary of someone's property. Options were presented which were i) Do nothing (i.e. risk assessment process satisfactory), or ii) Introduce buffer zones at varying distances e.g. should these be 6 m, 10m, 100m, 300 m. An estimate of the amount of land which would be excluded from agricultural use by each proposed buffer zones was calculated. The outcome was one of the highest numbers of responses to a Defra consultation in recent years (763 replies) but the responses appeared to separate into two distinct types of reply. Farmers/Growers and representative organisations opted for the *status quo* (i.e. no buffer zone). Pesticide stakeholder groups and the general public (most of whom were described by Defra as being loosely tied to the

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campaigns led by Stakeholder groups) opted for a buffer zone. Some of the replies claimed there were significant public health issues and chronic ill health attributed to pesticides. Defra concluded that it is not possible to make an accurate judgement of public opinion as a whole.

3. The Defra minister (Rt hon Alun Michael) announced (16 June 2004) that he would not introduce mandatory buffer zones but had asked the RCEP to examine the evidence on which the current system is based and the reasons for people's concerns. Mr Michael, in placing this request, was mindful of the advice from his chief scientist Professor Howard Dalton who had been asked to review the procedures used by the Pesticides Safety Directorate (PSD) for evaluating bystander risk. Professor Dalton had subsequently confirmed he was satisfied with the procedures used.

Background to current approach to Bystander risk assessment

Approach to bystander risk assessment used by PSD in approval process

4. A brief outline of the approach used for bystander risk assessment is given below. Some more information can be found in the summary appended at the end of this covering paper. Throughout this covering paper the term bystander is intended to include residents or neighbours living close to land where crop spraying takes place. Bystander exposure estimates are based on pesticide application trials conducted using spray application passes at a distance of 8m. The data included in the model uses conditions (e.g wind speeds) which exceed those recommended as the maximum acceptable standards in the Green code. The systemic doses resulting from inhalation/dermal exposure are calculated and compared to the systemic Acceptable Operator Exposure Level (AOEL). The AOEL is derived for risk assessment of prolonged use of pesticides by operators using the available toxicology data. It is considered that its application to bystander risk assessment provides a high degree of protection since the AOEL is intended to protect operators receiving repeated exposures to pesticides throughout the spraying season (which is usually a period of several months), year on year. In addition the evidence on exposure shows that bystanders will receive a substantially lower exposure in terms of dose and duration than operators. Approvals are not recommended for uses where exposures would exceed the AOEL.

5. The ACP has more recently considered modifications to the risk assessment process to include the potential for combined effects of pesticide active ingredients (using the COT report on mixture of pesticides as a basis for developing a strategy), and have also developed bystander exposure assessments to include data for 1m away from a spray boom, and information on residual air levels of pesticides. There are proposals for biological monitoring of bystanders (PSD has a research contract issued) and proposals to develop a more transparent presentation of assessment of exposures, both for UK approvals and within the EU. It is accepted by ACP that soil fumigants (i.e. which volatilise to a significant extent) required actual data on exposure

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for operators, re-entry workers and bystanders in the dossier submitted in support of an application for approval.

Request for advice

6. The ACP requested a view on the RCEP report from the COT on aspects of the RCEP report that fall within the COT's remit at its meeting of the 17 November 2005. This covering paper has been drafted for consideration by the COT and also the COC in respect of references in the RCEP report to cancer. The covering paper has not been submitted to COM as there are no specific references to mutagenicity evaluation in the RCEP report. However the covering paper and appendices have been forwarded to members of COM with a request for any written comments they wish to provide on the overall scientific content of the report.

7. A copy of the full RCEP report is appended as Annex 1 to this paper. A brief description of the approach used by the RCEP in undertaking its review, the questions posed for COT/COC, an overview of chapter 2 of the RCEP report on health related aspects of the RCEP review (with some questions on sections of this chapter) are given in this covering paper along with an overview of risk assessment for bystanders, a definition of bystander and some information on current arrangements for post market monitoring and reporting of adverse effects attributed to pesticides. A number of papers cited by the RCEP in connection with development of animal models for Chronic Fatigue Syndrome (CFS) are appended in Annex 2 to this report. Annex 3 presents the guidance provided by DH to GPs on the assessment of chronic ill health attributed by patients to pesticide exposure. An example copy of a Pesticides Incident Appraisal Panel (PIAP) report, dealing with statistical summary and incidents for 1 April 2004-31 March 2005, is appended as Annex 4 to this covering paper.

Approach of the RCEP review (*Appendix B and C to report*)

8. The RCEP initiated a consultation process on the 3 August 2004. The remit was to examine the scientific evidence on which Defra has based its decision on bystander exposure and its policy on access to information on crop spraying. The Commission also considered wider issues related to the handling and communication of risk and uncertainty, as well as public involvement, values and perceptions in this context. (ref RCEP report appendix B). The initial consultation invited comment on the intended scope of the study and recommendations for specific questions to be addressed. The COT discussed this at its September 2004 meeting, and agreed the following comments, which were submitted to the RCEP:

- "The scope of the study provided was very brief, and it was not clear whether it would be considering new data or re-examining and considering the reliability of the data that had been used to form DEFRA's decision. Additional information may be available via GP-based systems, but health outcomes of interest were not clear. The study would consider wider

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aspects of risk, uncertainty and communication. It was noted that the COT working group on uncertainty and variability in toxicology would be relevant to some of these aspects.

- “There was a need for consideration of perception of risk to include consideration of perception of exposure. People may smell solvents or non-active components of pesticide formulations and believe they are being exposed to the active pesticide with risk of adverse health consequences.
- “Members were surprised that the study was only focusing on bystander exposure from field spraying and not including other types of bystander exposure such as the spraying of pavements, golf courses and verges, which could involve a much larger sector of the population. It was considered that spraying by local authorities may be less able to take account of weather conditions than spraying on farms. Members recommended that the study should be set in the context of other sources of pesticide exposure to the public and to workers.”

There request to submit written evidence in August 2004 was followed up by a number of sessions of oral evidence. Written evidence was submitted by a number of UK Government Departments and Agencies, one devolved administration and some European and international bodies. Evidence was also submitted by a wide range of other organisations and individuals (approximately 100 are listed, and others wished to remain anonymous). During the review, four reports were commissioned including an independent review by Dr Michael Burr (Reader in epidemiology, University of Wales) of the Ontario College of Physicians report (see para 23 for reference to the Ontario report), and an estimate of the number of residents living near to arable land which could be subject to crop spraying (by the Centre for Ecology and Hydrology). The RCEP undertook visits to a Society of Chemical Industry conference, a conference on science, medicine and the law, an open meeting farm visit of the ACP and of the Advisory Committee on Hazardous Substances (ACHS) and House of Commons Environment Food and Rural Affairs committee (EFRA) to farms in Wilts, Kent, Norfolk and Cambs, visits to residents and bystanders and their families at homes in Devon, Gloucestershire, Oxfordshire, Lincolnshire, Norfolk, Essex, Hampshire, the Isle of Wight, and Cambridgeshire, a visit to the Silsoe Research Institute, and a visit to Syngenta CT Laboratory.

9. An open meeting was held on 25 September 2004 where around 50 participants attended. There were 7 presentations including one on pesticides and health and an open discussion.

Health related topics covered by RCEP review

10. These are listed in table 1.2, page 13 and in Appendix B of the report and are reproduced below.

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“What are the biological effects of bystander exposure to pesticides (what is the knowledge base)? What are the limits of toxicology and epidemiology in cases of bystander exposure to pesticides? How plausible is it that pesticides cause the health problems reported? What systems are in place to respond to and record bystander exposure and how well do they work (e.g GPs, PIAP)?

11. The RCEP published its report on the 22 September 2005 which received considerable media interest. The key recommendations with regard to health issues are given in paragraphs 6.20-6.29 (pages 108-109) of the report.

Advice requested from COT and COC.

12. The COT and COC are asked to
- i) Consider, based on members' expertise and the evidence presented in the RCEP report, whether the conclusions and recommendations reached in respect of health related topics are appropriate (see paras 6.20-6.29 of the report)
 - ii) Derive COT/COC conclusions in relation to the health related questions posed by the RCEP (para 10 above) on the basis of the evidence reviewed and members' expertise, and to consider whether these concur with those reached with RCEP.
 - iii) Consider whether any further work by COT/COC/COM should be undertaken with respect to bystander pesticide risk assessment and report any suggestions for further work to the ACP.

Overview of Chapter 2 of the RCEP report.

Introduction (paras 2.1-2.4)

13 This cites the objective of EC Directive 91/414/EEC on Plant protection products that they should have “..no harmful effect on human or animal health..” The key objective of the review has been whether the health of bystanders and residents has been adversely affected by spraying of agricultural pesticides.

Health effects attributed to pesticides (para2.5-2.9)

14 It is acknowledged that it is difficult to estimate the number of individuals who feel their health has been adversely affected by pesticides. The RCEP estimated an upper figure of 1000 down to “far fewer...” Although there is incomplete reporting it is noted in the RCEP report that the numbers are likely to be small as a proportion of the total number of people in Great

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Britain living near to sprayed fields (ca 1-1.5 million). The RCEP and secretariat visited the homes of 13 families, received oral evidence from a further 7 concerned individuals and evaluated over 50 further submissions of written and oral evidence.

Acute effects immediately following pesticide spraying. (para 2.9)

15 Well defined symptoms reported by bystanders and residents included upper/lower respiratory tract irritation, eye irritation, skin rashes, headaches, and, in susceptible individuals, asthma attacks. Less clearly defined symptoms included confusion, loss of short-term memory, impaired cognition, dizziness and shortness of breath. Several bystanders reported that these effects occurred in cycles associated with pesticide spraying.

Chronic health effects (para 2.10-2.15)

16 Residents and bystanders attributed a range of chronic ill health effects to pesticides including Parkinson-like tremors, motility problems, sensory/motor neuropathies, allergic reactions, liver disorders and asthma. There was one case each of microphthalmia and polycystic ovary syndrome in the offspring of mothers who claimed they had been exposed to pesticide spraying, although in neither case had a causal link to pesticides been established. The RCEP also reported well defined disorders such as Goodpasture's syndrome, systemic lupus erythematosus (SLE) and mixed connective tissue disease. The RCEP also reported concerns over the possibility of clusters of cancers (reference is made to lymphomas, leukaemia, and breast cancer). There were a number of cases of multisystem disorders including chronic fatigue syndrome (CFS), and multiple chemical sensitivity (MCS). There was a perception of clusters of CFS in small residential communities living near to fields. (some further information on CFS/MCS is given in Appendices F and G to the RCEP report).

17 The RECP suggest that some of these chronic ill health effects might be attributed to pesticides which have now been withdrawn.

18 Members are asked to consider whether the data base reported by the RCEP is sufficiently robust to form the basis of any conclusions regarding the plausibility of linking acute or chronic ill health to pesticide exposure.

Mechanisms of action of pesticides and possible targets in humans (Para 2.16-2.19)

19 A number of molecular effects of pesticides are reviewed which are suggested to underpin the plausibility of potential biological effects of pesticides in humans.

20. What are members views on this section?

Epidemiology (para 2.20-2.26)

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21. The RCEP reviews the difficulties in undertaking epidemiological investigations. It is noted that bystanders and residents might be a more susceptible group than individuals occupationally exposed to pesticides and that the exposure of bystanders and residents might be greater than previously recognised. It is also noted that the exposure response of the general population to nitrogen dioxide supported a lower air quality standard than the occupational exposure standard. (Secretariat comment ; AOELs are set on a more precautionary basis than other occupational standards, and are set to be protective of the general population). The RCEP suggest that investigations of alleged clusters would be valuable.

22. What are members views on this section ?

Reviews of epidemiological studies (paras 2.27-2.34)

23. The RCEP reviewed a MRC Institute of Environment and Health (IEH) review of the potential association between pesticides and Parkinson's disease commissioned for PSD, the COC reviews of prostate cancer and organochlorine insecticides and risk of breast cancer, and the Ontario college of Family Physicians review of published papers on pesticides and ill health. It is noted that the ACP were critical of this latter study and thus the RCEP commissioned an independent view from Dr Michael Burr (University of Wales College of Medicine. Dr Burr noted that it was difficult to draw definite conclusions on causality on the basis of the Ontario college but suggested a definitive study incorporating good measures of exposure would be appropriate.

24 What are members' views on this section?

Multisystem disease (paras 2.35-2.39, and Appendix F, G and H)

25 The RCEP discuss the evidence for considering CFS and MCS as defined clinical disorders. Reference is made to the CMO working group on CFS and the conclusions reached by this group in 2002 that environmental toxins were not a common or widespread trigger of CFS. An argument is presented to support the view that MCS is a defined clinical disorder. Reference is made to other disorders reported to the RCEP involving impaired cognition and memory, sleep disturbance and lack of concentration. An argument is presented that enhanced clinical investigation of these cases (a parallel with clinical investigation of Gulf War Syndrome is made). The RCEP conclude that a research programme to address the lack of knowledge of multisystem disorders is warranted.

26 COT members will recall that the COT considered the evidence on MCS in 1999 and 2000 and concluded that this was not a clinically defined disorder which could be evaluated in further research. A literature search has identified a number of publications since 2000 which may be relevant. These

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have not yet been evaluated for quality of evidence. Do members consider that a further review of MCS should be undertaken?

27 Should a COT review of the association between chemical exposure and CFS be undertaken?

Toxicology-Introduction (paras 2.40-2.42)

28. The RCEP overview the principles of toxicological assessment of pesticides. A comparison with the approach used for pharmaceuticals is made. A brief summary of the approach used to assess bystander exposure is appended at the end of this covering paper.

Testing paradigm (paras 2.43-2.48)

29. The RCEP review the basic approach used for toxicological testing and dose-response evaluation for pesticides. They note that there are no animal models to reflect all the chronic ill health effects reported by bystanders and residents, specifically with regard to multisystem disorders such as CFS. The references cited by the RCEP to support the development of new animal models are appended as Annex 2 to this covering paper.

Uncertainty Factors (paras 2.49-2.50)

30. The RCEP provide an overview of the basic approach used to derive an AOEL (Acceptable Operator Exposure Level, see also information appended at the end of this covering paper).

New technologies and techniques (paras 2.51-2.53)

31. The RCEP make reference to the potential for use of toxicogenomics and in-vitro testing approaches to deriving information that might be relevant to chronic ill health reported by bystanders and residents. The RCEP cite the COT/COC/COM statement on the use of toxicogenomics in toxicology.

32. With regard to the sections on toxicology, what are members' views? In particular do members have any comments on the development of novel animal models for chronic ill health reported by bystanders and residents?

Monitoring Introduction, (paras 2.54-2.55)

33. The RCEP note the importance of adequate exposure assessment in monitoring for adverse effects of pesticides in humans. It is suggested that biomonitoring could help to inform assessment of risks to humans.

Biomarkers of pesticide exposure (paras 2.56-2.57)

US studies (paras 2.58-2.59)

UK projects (paras 2.60-2.64)

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34. The RCEP note that baseline biomonitoring data could be valuable with regard to assessment of risks to individuals but were surprised to note that there were no appropriate UK data with regard to pesticides.

35. The RCEP review the US National Health and Nutrition Examination Survey (NHANES) and note that data are being generated with regard to organophosphate insecticides, carbamates, organochlorines, herbicides and pest repellents. It is proposed by RCEP that the NHANES approach could be used as a model for the U.K. A reference to use of plasma cholinesterase monitoring of workers occupationally exposed to cholinesterase inhibiting insecticides is made.

36. With regard to U.K. projects, the RCEP provide an overview of the WWF sponsored survey, the research commissioned by PSD (on cypermethrin), the potential for use of the Biobank UK project, the human milk (SUREmilk) pilot study, and the Avon Longitudinal study of parents and Children (ALSPAC). The RCEP conclude that it is important to develop a national database from sample survey and large scale longitudinal studies. (It is noted that the FSA is sponsoring a number of projects on method development for biomonitoring of exposure to pesticide mixtures, in response to the recommendations in the COT report on Risk Assessment of Mixtures of Pesticides and Similar Substances. (<http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/>)

(Secretariat comment; Members will wish to note that the UK has a programme of National Diet and Nutritional Surveys (NDNS) carried out on behalf of the Food Standards Agency and Department of Health. These provide detailed information on food consumption, collected at the level of the individual, which is used to support food chemical exposure assessment as well nutritional issues. The NDNS has previously been conducted as a series of cross-sectional surveys of diet and nutrition status. In the future it will become a rolling programme in order to generate data more rapidly and to give flexibility to collect additional data at relatively short notice. There may be potential for the blood and urine samples collected in the NDNS to be analysed for biomarkers of pesticide exposure.)

37. What are members' views on this section?

Recommendations: Human health

38. These are reproduced below. What are members comments on these recommendations. Do the COT/COC concur with the RCEP? If not, what is the rationale for reaching different conclusions based on the evidence in the RCEP report? What further work would the COT/COC recommend?

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6.20 Based on the conclusions from our visits and our understanding of the biological mechanisms with which pesticides interact, it is plausible that there could be a link between resident and bystander exposure and chronic ill health. We find we are not able to rule out this possibility. We recommend a more precautionary approach is taken with passive exposure to pesticides. The existing uncertainties indicate an urgent need for research to investigate the size and nature of the problem and underlying mechanisms that link pesticide spraying to ill health. (2.65)

6.21 We recommend that a comprehensive systematic review of the literature in this field be conducted that takes account of, and avoids, the shortcomings of the Ontario study. (2.66)

6.22 We recommend that an imaginative systematic approach is taken to apply both well validated as well as novel clinical investigative methods to those with chronic symptoms linked to pesticide spraying such as magnetic resonance spectroscopy (MRS) and gene and protein profiling. (2.67)

6.23 We recommend that the Health Protection Agency and related organizations within the devolved administrations in Scotland and Wales collect population data on pesticides, their metabolites, and biomarkers of effects that would provide a sound basis for exposure assessment and could also be used to establish a national database for monitoring. (2.68)

6.24 We recommend that the private sector and universities be encouraged to develop new animal models that better reflect the chronic disorders experienced by residents and bystanders exposed to pesticide spraying (2.69).

Health Effects, monitoring and reporting (*Introduction, para 2.70*)

39. The COT/COC have had no previous involvement in the assessment of data on postmarket monitoring and reporting of adverse effects attributed to pesticides. A brief overview of the current arrangement is provided at the end of this covering paper. It is noted that the primary responsibility for postmarket monitoring and surveillance rests with the regulatory agencies responsible for the approval for pesticides (i.e the PSD (responsible for agricultural pesticides) and Biocides and Pesticides Unit of the Health and Safety Executive (HSE) (responsible for non-agricultural pesticides and biocides). An overview of the evaluation of the current arrangements was provided by the RCEP along with comments on further developments planned by the regulatory and other agencies.

Primary care (paras 2.71-2.76)

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40. An overview of the sources of advice which GPs and hospital doctors can use is provided. Para 2.72 refers to the online TOXBASE which is considered to be the first point of contact for health professionals. TOXBASE is supplemented by access to clinical toxicologists in the National Poisons Information Service (NPIS). It is noted by the RCEP that awareness of the DH handbook Pesticide Poisoning notes for the Guidance of Medical Practitioners, 2nd edition, 1996, is likely to be low. The suggested approach in the DH booklet for patients with chronic symptoms is appended to this paper as Annex 3.

Reporting Public ill health effects of exposure (paras 2.77-2.86)

41. The RCEP report that currently no single regulatory department or agency is responsible for dealing with the public health effects resulting from exposure to pesticides that are used in agriculture. A detailed overview of the working of the Pesticide Incident Appraisal Panel (PIAP) is given, which notes the time delays in reporting an incident to evaluation of available data by the panel. Reference is made by the RCEP to the overarching responsibility of the Department of Health and its Health Protection Agency (in England and Wales) and Health Protection Scotland (HPS) for protecting public health. It is noted that when the HPA had been set up the remit for pesticides had been maintained within Defra, DH, FSA and HSE.

42. The current arrangements for the approval of pesticides established under the Control of Pesticides Regulations 1986 (amended) require ministers (for DH, Defra, HSE and the devolved administrations) to act jointly to approve pesticide products. Ministers receive advice from the independent ACP. Relevant Government departments and agencies send assessors and advisors to ACP meetings. The ACP reviews papers provided by PSD and HSE on their post market monitoring activities. This includes the annual reports of PIAP and routine monitoring of TOXBASE for reports of adverse effects. The system used in the UK requires close collaboration between Government departments and agencies. The scientific advisory functions on pesticides undertaken by the Department of Health in respect of public health transferred to the HPA on 1 January 2006. An example copy of a PIAP report (for 1 April 2004-31 March 2005) is appended as Annex 4 to this paper.

Surveillance of ill health effects from pesticides (2.87-2.96)

43. The RCEP note that it is not possible to derive a precise figure for the number of people who claim their health has been affected by pesticide spraying. It is noted that PIAP is likely to underestimate the extent of bystander related ill health. Reference is made by the RCEP to the pilot Green card scheme commissioned by HSE in 1990-1993 using the NPIS Birmingham centre (appendix J to RCEP report). This was a pilot scheme based on the yellow card scheme used for medicinal products to evaluate the potential for reporting of adverse effects attributed to pesticides by GPs. The outcome was a low response over the reporting period.

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44. The RCEP also comment on the 1999 Inter-Departmental Working Group (IDWG) report on pesticide surveillance schemes for adverse health effects attributed to pesticides. This included the proposed collation of data from relevant sources (e.g the Hospital Episodes Statistics (HES), NPIS, PIAP, and the Office for National Statistics). It was noted that there was lack of information on sources of possible reports from GPs.

45. HSE has initiated research on the prevalence of pesticide ill health reports to GPs (though the IEH). The DH, Imperial College and previous ACP chairman are undertaking a retrospective evaluation of the HES database. DH/HPA are undertaking a retrospective assessment of confirmed/likely irritancy cases reported to PIAP between 1994-2004. PSD and HSE are collaborating with NPIS to improve the reporting and evaluation of cases identified through NPIS (in particular through TOXBASE). A recent report from the Edinburgh centre was reviewed by the ACP in November 2005. (Overall these data (which include deliberate/accidental ingestion of products) confirm previous evaluations of acute poisoning incidents that pesticides make up a small proportion of requests for information, most document minor symptoms with few reporting moderate symptoms.)

46. There is thus quite extensive ongoing collaborative work on post market surveillance for acute effects. One further outcome of the IDWG report was a proposal for a routine collation of data from all potential sources of incident/case reports. An example review was undertaken by HSE during the review of organophosphorus pesticides by the ACP in 2000. The outcome was that combined collation of reports were consistent with previous evaluations of separate sources of data on pesticide related acute ill health effects; i.e. a low level of mainly minor adverse effects with a high proportion of these due to accidental ingestion of products by children. The small number of major acute effects was attributed to deliberate ingestion of concentrated pesticide by adults or in rare cases attribute to occupational accidents involving pesticide products. PSD has initiated action with regard to the design (i.e. potential desirability of the packaging of pesticide products for children) and ease of access to such products by children.

47. With regard to chronic ill health, the ACP's Medical and Toxicology Panel (MTP) undertakes a routine evaluation of all published epidemiology. This action was initiated in 2000. The MTP has requested further work on the possible association between pesticides and Parkinson's disease. An IEH report has been reviewed by the ACP. It was not possible to identify any specific pesticide active ingredient for regulatory action in this review. The ACP agreed that further mechanistic research was necessary. In addition, they considered that further epidemiology could be useful where exposure to specific pesticides could be ascertained with reasonable confidence (e.g. cohort studies of pesticide production workers or long-term prospective studies of pesticides users). Research proposals have been considered by PSD. The MTP also asked for a review by the COM on the published papers on genotoxicity biomonitoring in pesticide applicators. A statement has been recently published by the COM and also reviewed by the ACP. No

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specific pesticide active ingredient was identified for regulatory action. COM is currently considering how to take forward the generic aspects relating to the assessment of background variance in indices of genotoxicity in biomonitoring studies.

Recommendations: Human Effects monitoring and reporting

48. These are reproduced below. What are members' comments on these recommendations. Do the COT/COC concur with the RCEP? If not, what is the rationale for reaching different conclusions? What further work would the COT/COC recommend?

6.25 We endorse the Department of Health's move to strengthen higher professional development in the field of toxicology within general practice. They should also ensure that professionals working in public health and specialised poisons centres have a clear awareness and understanding of how to investigate the chronic health problems related to pesticides by residents and bystanders. (2.97)

6.26 We recommend that the Royal Medical Colleges agree how patients with suspected environment-related, and in particular pesticide-related illness, should be investigated and treated, and identify a clear referral pathway from Primary Care to an appropriately trained specialist. (2.98)

6.27 We recommend that a new national reporting and monitoring mechanism for cases of ill health in bystanders associated with pesticide exposure should replace the Pesticide Incident Appraisal Panel, and should be the responsibility of the Health Protection Agency and similar organisations in the devolved administrations, as the Department of Health's agencies for protecting public health. (2.99)

6.28 We recommend that newly acquired standardised clinical, physiological and laboratory information from those who attribute their adverse health effect to passive pesticide exposure should form the basis of biological monitoring. In addition to those exposed to agricultural spraying we recommend the establishment of a system that places greater emphasis on surveillance for adverse effects of pesticides (2.100)

6.29 People are exposed to pesticides through uses other than in agriculture, such as amenity and timber treatment and these people have reported similar health concerns to the symptoms discussed in this report. Although we have not studied this in detail, the measures we recommend on health issues and monitoring human health should be extended to cover these non-agricultural pesticides. (2.10)

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COT/COC discussion.

48. The COT and COC are asked to consider the evidence reported in the RCEP report and the information in this covering paper and appendices with regard to the questions given below. Any written comments received from COM members will be forwarded to the COT/COC chairs for their consideration. It is proposed to publish a statement from COT/COC on their discussions.

49. The COT and COC are asked to

- iv) Consider based on members' expertise and the evidence presented in the RCEP report whether the conclusions and recommendations reached in respect of health related topics are appropriate (see paras 6.20-6.29 of the RCEP report)
- v) Derive COT/COC conclusions in relation to the health related questions posed by the RCEP (para 10 above) on the basis of the evidence reviewed and members' expertise and to consider whether these concur with those reached with RCEP.
- vi) Consider whether any further work by COT/COC/COM should be undertaken with respect to bystander pesticide risk assessment and report any suggestions for further work to the ACP.

Secretariat January 2006

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APPENDED SUMMARY ON APPROACH TO BYSTANDER RISK ASSESSMENT.

Who is a bystander?

1. The legislation introduced in the UK in 1986 to regulate pesticides (Control of Pesticides Regulations 1986) and the EU Directive 91/414/EEC do not provide a definition of a “bystander”. All of the legislation has generic references to protecting human health from unacceptable risks associated with exposure to pesticides. A reference to bystander exposure assessment is included in the Uniform Principles (EU Directive 97/57/EC), which state ‘Member States shall evaluate the possibility of exposure of other humans (bystanders or workers exposed after the application of the plant protection product)...to the active substance and/or to other toxicologically relevant compounds...’ (general principle 2.4.1.4) and ‘Waiting and re-entry safety periods or other precautions must be such that the exposure of bystanders or workers exposed after the application of the plant protection product does not exceed the AOEL...’ (specific principle 2.4.1.4). PSD were the first EU regulatory group to start to model bystander exposure (using data on tracer exposure during tractor passes near to a volunteer bystander 8 m away) during application. Concerted discussions within the EU on approaches to bystander exposure assessment began in 1996. A working understanding of bystanders has been developed (see bullet points below) ‘Bystanders’ covers persons;

- who are located within or directly adjacent to an area where pesticide treatment is in process or has taken place;
- whose presence is quite incidental and unrelated to work involving pesticides but whose position may put them at risk of exposures;
- who take no action to avoid or control exposure.

2. There have been differences of opinion in the U.K. regarding the scope of bystander risk assessment. Some stakeholders have argued that bystander should be formally defined to include the term “neighbour” or “resident”, i.e. permanent residence near to agricultural spraying implying permanent low level exposure. The ACP held an open meeting on bystander risk assessment in July 2002. The approach used has been refined following subsequent ACP discussions in 2003/4 to allow for closer passes of spray machines (ca 1 m) and to consider potential for long term exposures (e.g. residual air levels).

3. The evidence used in risk assessment that the highest levels of bystander exposure will be to very low transient levels of pesticides is much disputed by the pesticide stakeholder groups who view bystander exposure in terms of a “neighbour” model where there is persistent exposure which results in chronic ill health.

The Toxicology Evaluation of pesticides (for Bystanders)

4. The data requirements are outlined in detail in the EU Directive (91/414/EEC). The approach given below is used in all EU member states.

5. In brief, the key reference dose used for bystander risk assessment, the AOEL, is derived as follows. The AOEL is derived from the extensive toxicology database on pesticides (these are amongst the most highly evaluated chemicals in the world) considered by the ACP which covers all durations of exposures, specific end points (such as mutagenicity, carcinogenicity, reproduction, teratogenicity (two species), neurotoxicity (a specific requirement for pesticides using acute and repeat dose schedules usually in the rat and specialist investigations and may include neurotoxicological evaluation during reproduction testing) and in vulnerable groups (such as foetuses, neonates and during the development of offspring) and specialised end points such as immunotoxicity where indicated. The use of multiple species in the toxicological testing regime (most actives will have repeat dosing data for at least three species (rat, mouse, non rodent (usually dog)) provides additional reassurance. Information on kinetics (Absorption, Distribution, Metabolism and

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Excretion, ADME) is usually provided in the rat but may be extended to cover more than one species and possibly *in-vitro* information using human tissue when needed to evaluate possible species differences in mechanisms of toxicity. Uncertainty Factors (UFs) are applied to the lowest relevant No Observed Adverse Effect Level (NOAEL) derived from the most appropriate and sensitive end point in the toxicology database. Most AOELs are termed systemic AOELs and are derived from oral toxicology studies and use an adjustment factor to allow for the extent of oral absorption (if this is below approximately 80%). This allows the AOEL to be compared to the estimates of exposure and in particular the estimate of absorbed dose in bystanders and operators. The UF may vary with the severity of effects documented or uncertainty in the toxicology evaluation, but is at least 100-fold when applied to animal data.

6. The key question when using animal toxicology data to undertake human risk assessment is what is the probability of an effect being missed when estimated exposures are 1000-10,000 times below the NOAELs derived from studies in three species.

Some comparisons with pharmaceuticals

7. In general the toxicology test databases for pesticides and pharmaceuticals are similar, although data requirements are determined on a case by case basis and the duration of some subacute/subchronic studies have been traditionally different (e.g use of rodent 3 month and 6 month studies). The main difference is that the animal toxicology is used to aid in decisions on clinical trials in humans for pharmaceuticals whereas for pesticides there are no premarketing studies in volunteers. This aspect has been raised by the RCEP who note that one in five drugs do not pass the clinical trial phase.

8. There have been a relatively limited number of studies which looked at the prediction rate of animal toxicology tests for human pharmaceuticals. Olson H *et al.* (Regulatory Toxicology and Pharmacology, vol 32, 56-67, 2000) reported the results of a large multinational pharmaceutical company survey. Overall rodent and non rodent species showed a true positive concordance rate of 71% for pharmaceuticals where human toxicity was identified in clinical trials. (compiled for 150 compounds where 221 human toxicity events were described). 94% of the concordant effects were identified from studies of one month or less in duration, i.e. relatively acute effects. This approach doesn't investigate the value of animal tests to screen out chemicals which then are never developed or taken into clinical trials or investigate all the reasons why pharmaceuticals might fail in clinical trials (e.g limited efficacy). It may be important to distinguish between the different stages of drug development i.e. Phase I, which is the first time the test compound is administered to humans (usually volunteers, but for certain types of drugs such as anti-cancer drugs into patients); Phase II, exploratory use in therapeutic indication in a small number of patients; Phase III, large scale clinical trials for safety and efficacy. Medicines may fail at each stage. The main reasons for failure are both adverse effects and lack of efficacy. These two findings may be linked; a drug that had efficacy in an animal model may not show efficacy in humans if the dose that can be administered to humans is limited by unacceptable toxicity.

9. One point that can be made regarding a comparison of pharmaceuticals and pesticides is that medicines are developed to have biological effects in humans at the doses used whereas modern pesticides are developed to have no effects in humans. This is evidenced for example by the development trend away from broad spectrum organophosphate insecticides which inhibit cholinesterase in mammals and insects to more selective pesticides (such as move from the rather general toxicity exhibited by some of the earlier herbicides to the more specific action of the ALS inhibitors) designed to predominantly affect insects. A further point is that pesticide exposures are not deliberate and are usually very much lower than for pharmaceuticals.

Approach to mixtures of pesticides

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10. In response to consumer concern about mixtures of pesticides (the so-called “cocktail effect”), the Food Standards Agency asked the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) to consider the risk assessment of multiple residues of pesticides and veterinary medicines in food, and of multiple sources of exposure to these substances. The COT report was issued in 2002. It concluded that the nature and extent of combined exposure, together with the likelihood of any adverse effects, which might result, should be evaluated when carrying out risk assessment. Default assumptions should be that chemicals with different toxic actions will act independently, and those with the same toxic action will act additively. Thus if bystander exposures for each active ingredient in a mixture are acceptable there is no unacceptable risk provided the mechanism of action of the pesticides are independent. Where there is evidence for combined action (e.g for cholinesterase inhibitors) then the default assumption recommended by the COT working group was to assume additivity. Convincing evidence of synergistic/potential effects in toxicology used for human health risk assessment was not found by the COT.

11. The ACP recently adopted procedures for combined risk assessment of pesticide mixtures using the approaches suggested by the COT. These are applied to applications for approval of products containing more than one pesticide active substance. The ACP and the MTP has also considered the risk of additivity of toxicity of multiple pesticides applied at the same time in a tank mix and has concluded that the mixes that are commonly used pose a low risk of enhanced toxicity.

Bystander Exposure assessment undertaken by PSD.

12. The bystander exposure model used by PSD uses tracer studies to predict exposure. Tracer studies are acceptable for non-volatile pesticides. Studies involved collecting airborne tracer in the breathing zone and tracer that would impinge on clothing or uncovered skin on a bystander positioned 8 metres downwind. Trials (arable crops) were conducted at wind speeds from 7-24 km/h (mean 16 km/h). These were relatively high wind speeds (cf Green code indicates that pesticide application in wind speeds of 9.6-14.5 km/h is inadvisable). The mean potential dermal exposure was 0.1 ml/spray/single pass. Typical mean inhalation concentration was reported to be 0.02 ml spray/m³. Maximum values were about 5 times the mean value. In estimating dermal exposure no reduction from clothing was assumed. In converting air levels a heavy work respiratory rate of 3.6 m³/h (= an adult running, ca 10x resting rate). A duration of 5 minutes inhalation with 100% retention/absorption was assumed. The total inhalation is 0.006 ml/spray/person. It is assumed that the bystander remains in the same position downwind.

[It is worthwhile noting that HSE have reported that many of the environmental incident cases investigated by inspectors involve application of pesticides either under inappropriate wind conditions or where there is a dispute over the weather conditions under which application took place.]

13. The further estimates of exposure evaluated in July 2003 for 1m distance from the spray application both in respect of dermal and inhalation exposure were found to be up to 7 times higher the mean of the data derived for 8 m (highest value was 0.69ml cf 0.1 ml which was the mean at 8m). However most of the data for 1m were within the range of estimates (i.e. the upper end of the 8 m data) used for routine risk assessment. Residual air concentrations were very low (see extract from PSD report below). There were a few estimates of relatively high exposure (i.e exceedences of AOELs) when exposure of children playing in areas subject to drift fall out was further modelled. Dermal absorption for the active ingredients involved would have been considerably below the assumed values of 100% and most likely below 10% . Using more likely values for dermal absorption the estimates of exposure were expected to be below the AOEL and thus the situation has been resolved.

14. However there is a lack of UK data on long-term air levels and hence estimates of long-term bystander exposures. There are useful data on long-term air levels from studies

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done in California. These data suggest that in the 72 hours following application maximum peak air levels of most pesticides are very low (i.e. around 1 µg/m³ or less). At this level daily exposure would be about 0.0003 mg/kg bw/day, which indicates that exposures of most pesticides would be well within acceptable levels. Apart from the soil fumigants for which are outside the scope of the approach discussed in this paper, chlorpyrifos appears to be the worst case compound with levels a clear order of magnitude greater. However, exposures estimated using these data do not suggest the current approach is not protective.

15. PSD have provided a breakdown of bystander exposure estimates compared to respective systemic AOELs. The information given below provides considerable confidence that exposures will be well below the AOEL. It is possible to say that most bystander exposures will be a tiny fraction of the systemic AOEL.

Table 1 Bystander exposure as percentage of AOELs

Active Substance	Approved for use in UK on field crops or where a field crop sprayer would be used (Yes or No)	Realistic worst case bystander exposure as a percentage of the lowest AOEL
1-Methylcyclopropene	No -fumigant	18
Azamethiphos	No – animal housing	24
Benthiavalicarb-isopropyl	Yes	0.3
Boscalid	Yes	0.1
Chlorpyrifos	Yes	24
Clomazone	Yes	0.12
Clothianidin	No-seed treatment	2
Cyazofamid	Yes	0.02
Cyflufenamid	Yes	0.09
Dimoxystrobin	Yes	0.5
Ethephon	Yes	100
Fenamidone	Yes	0.05
Fenpropimorph	Yes	0.2
Fonicamid	Yes	4
Flufenacet	Yes	2
Fluoxastrobin	Yes	1.4
Iodosulfuron-methyl-sodium	Yes	0.0004
Malathion	No- indoor, hand-held or ULV for food storage, pigeon loft, ornamental production and watercress	1
Mepanipyrim	Yes	0.3
Mesosulfuron-methyl	Yes	0.007
Methiocarb	Yes	68
Methoxyfenozide	No -orchards	0.02
Metrafenone	Yes	2.5
Oxadiazon	Yes-herbicide in fruit/ornamental crops	0.58
Peroxyacetic acid	No-seed potato treatment	negligible
Picolinafen	Yes	0.007
Pinoxaden	Yes	0.07
Pirimicarb	Yes	28
Propoxycarbazone-sodium	Yes	0.05
Prothioconazole	Yes	0.7

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Prothioconazole metabolite MO4	Yes as a metabolite found in spray	18
Pyraclostrobin	Yes	0.5
Quizalofop-P-tefuryl	Yes	1.5
Silthiofam	No –cereal seed treatment	2
Sulfuryl fluoride	No- fumigant	100
Tolclofos-methyl	No –drench or seed potato treatment	5*
Tolyfluanid	Yes	22
Zoxamide	Yes	0.002

Table 2 Detailed information on bystander risk assessment for pesticides.

Active substance where realistic worst case bystander exposure >10% AOEL	Comments
1-MCP	1-MCP is a fumigant product for treating apples in store. Estimated bystander exposure is 18% of AOEL, and reflects exposure to 1-MCP as the store is ventilated after treatment, rather than exposure following spraying. This exposure estimate is not therefore derived from the standard ‘sprayer’ model. The AOEL, 0.009 mg/kg bw/day, is derived from the NOAEL in a 90 day rat inhalation study of 9.0 mg/kg bw/day with a 100 fold assessment factor. Each batch of stored apples is only treated once per year, so will thus only be ventilated once per year. (<i>Estimated consumer exposure is of the same order of magnitude at about 15% of ADI. Operator exposure estimates are unusually lower than other exposure estimates for 1-MCP as the product is formulated in granules which only release the 1-MCP vapour when water is added by use of a dispensing machine designed for the purpose. The operator leaves the store before the 1-MCP is generated. Engineering controls thus significantly reduce exposure for the operators.</i>)
Azamethaphos	Azamethaphos is an OP insecticide for use in animal and poultry houses. Application is by brush and roller or by spray. Estimated bystander exposure is compared to a short term AOEL, 0.01mg/kgbw/d (derived from the full recovery of cholinesterase after 14 days seen in a single dose neurotoxicity study in the rat) and accounts for 24% of the AOEL. Given that this use takes place inside animal housing, bystander exposure is unlikely.
Chlorpyrifos	Chlorpyrifos is an OP insecticide with a number of uses on a range of crops. It has been under review in UK for some years, and data are currently awaited on actual levels of environmental exposure. Estimated bystander exposure is 24% of AOEL. The AOEL for chlorpyrifos 0.01mg/kgbw/d is derived from the NOAEL for inhibition of brain cholinesterase in dogs, with a 100 fold assessment factor. This bystander exposure estimate is based on an orchard application using the standard POEM based model. Estimated exposure from a field spray would be lower but was not specifically calculated in the review.
Ethephon	Ethephon is an OP growth regulator generating the plant hormone ethylene. It is used in horticultural and cereal crops. Estimated bystander exposure calculated as part of the UK review was 100% of the AOEL. Further data on exposure levels was requested. The estimates have assumed 50% dermal

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	<p>absorption. The AOEL, 0.05mg/kgbw/d, is derived from clinical symptoms recorded in human volunteer studies, with a 10-fold assessment factor. The estimated bystander exposure is based on orchard application.</p> <p>Since the UK review was completed the EU review has progressed. An AOEL of 0.03mg/kgbw/d and dermal absorption of 1.5% for the in use dilution have been agreed by EU expert groups. These values would result in an estimate of bystander exposure of <10% of the AOEL.</p>
Methiocarb	<p>Methiocarb is a carbamate molluscicide and insecticide, and is usually applied in pelleted formulations. There is an approved liquid formulation – ‘Provado Ultimate Bug Killer’, an aerosol product for use by amateurs. The highest bystander exposure estimate for this compound was based on estimated exposure of a child eating soil from ornamental potted plants in the home that have been treated with this formulation, and estimated exposure was 68% of AOEL. The AOEL, 0.013mg/kgbw/d, was derived from NOAEL from a 90-day dog dietary study. Effect at the next highest dose was reduction in erythrocyte and retinal cholinesterase activities and increased incidence of vomiting. An assessment factor of 100 was applied. Bystander exposure to the field applications of methiocarb would be considered negligible as the formulations are pellets. (<i>Consumer exposure estimates through more usual dietary exposure routes are 21.5% of ARfD</i>).</p>
Pirimicarb	<p>Pirimicarb is a carbamate insecticide used on a wide range of agricultural and horticultural crops. Estimated bystander exposure is based on orchard application and accounts for 28% of AOEL. The AOEL, 0.035mg/kgbw/d, is derived from the NOAEL for reduced brain cholinesterase activity, tremours and increased haemosiderin deposition in a 12 month dog study.</p>
Prothioconazole	<p>Prothioconazole is a triazole fungicide. It forms a triazole metabolite MO4, which is more toxic than the parent compound, so this drives most of the risk assessments. This bystander risk assessment for MO4 unrealistically assumes that 100% of the exposure following a spray of prothioconazole being applied is present as MO4. Estimated exposures would then account for 18% of the AOEL for MO4 (0.01mg/kgbw/d). When the same level of exposure is compared to the AOEL for the parent compound prothioconazole (0.25mg/kgbw/d), estimates of exposure are less than 1% AOEL – the more usual situation for bystander risk assessment. The true level of exposure to MO4 is difficult to ascertain, but it would certainly be less than 100% of exposure for the bystander. Data provided in the operator exposure study indicate that exposure to MO4 is unlikely to be > 60% of the total exposure from spraying prothioconazole.</p>
Sulfuryl fluoride	<p>Sulfuryl fluoride is a fumigant. The estimated bystander exposure for this compound is compared to an Acceptable Operator Exposure Concentration (AOEC) of 3ppm, rather than an AOEL. The Systemic AOEC is derived from the NOEL for evoked potentials of 300ppm in an acute neurotoxicity study in the rat and applying a 100 fold assessment factor. An exclusion zone for bystanders around buildings being treated is required as a condition of approval, monitored to ensure that air levels remain below 3ppm. This is below the Occupational Exposure Standard (OES) of 5ppm for sulfurlyl fluoride, and has been shown to be achievable. Thus a bystander at the edge of this exclusion zone could be exposed to a maximum of 100% of the AOEC during the ventilation of a treated flour mill.</p>
Tolyfluanid	<p>Tolyfluanid is a fungicide approved for use on a range of fruit crops. Estimated bystander exposure is at 22% of the AOEL 0.36mg/kgbw/d. Data were derived from an application for agreement of a short term AOEL, so the evaluation considered did not include the full range of human risk assessments. The long term AOEL is derived from NOAEL of 15 mg/kgbw/day for maternal bodyweight effects in a two generation study in the rat. There was no correction for oral absorption. A 100 fold assessment factor was used. The short term AOEL was derived from the NOAEL of 36 mg/kgbw/day based on body weight, clinical chemistry, liver weight and</p>

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histopathology effects in a 3 month study in the dog. Bystander exposure estimates are based on orchard spray.
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Approaches to post market surveillance

Surveillance for acute effects

15. The MTP/ACP have reviewed the value of these approaches on a number of occasions (the most recent being 2001 and 2003). They have concluded that there is a low incidence of adverse effects associated with pesticides but little is known about the nature of the exposures. This is one of the reasons for the suggested research from DH on the HSE database and the likely/confirmed incidents in the PIAP database. It has not been possible to derive any conclusions regarding individual pesticide active ingredients from these data. The ACP considered the evidence for all organophosphate insecticides in 2000 and reached a similar conclusion. An Interdepartmental working group reported on monitoring schemes in 1998 and concluded that an annual exercise should be undertaken to bring together the data from all the available sources. The ACP recommended that this would not be a useful exercise after it had reviewed a report of the combined data on OPs. The Interdepartmental group also recommended that further research be conducted to see if any additional information on pesticide incidents might be collected from GPs. The HSE is currently funding a three year project to fulfil this suggestion. The MTP did not think additional research into cases of acute pesticide poisoning identified by GPs would be valuable. However the main concern of RCEP has been the post market surveillance for chronic effects.

Pesticide Incidents Appraisal Panel (PIAP)

16. Incidents of poisoning involving operators and the public are investigated by the Health and Safety Executive (HSE). Their Pesticide Incidents Appraisal Panel was established to consider all investigated incidents where the use of a pesticide at work may have affected the health of the user or someone nearby. During 2003/4 HSE investigated 204 incidents, of which 62 alleged ill health. A copy of the 2003/4 PIAP report is appended as Annex 6 which shows the trends for reported incidents.

17. The Panel is chaired by a doctor from HSE's Health Directorate. It consists of representatives from HSE's Field Operations Directorate (including the Employment Medical Advisory Service), a Department of Health toxicologist, and external specialists from the National Poisons Information Service.

18. The Panel assesses documentary evidence compiled from investigations by HSE and local authorities into cases of alleged pesticide related illness. It provides an overview of these cases in order to inform the pesticides approvals process. The Panel may also have the results of any examinations or investigations carried out by the National Health Service and others involved in the care of individuals. Each case is carefully considered on the basis of the investigation reports and the known or suspected adverse effects of the chemicals involved.

19. The Panel classifies cases according to pre-defined criteria. Its assessment and the details (pesticide, nature of activity etc.) of individual cases are recorded on a database which is used to provide annually updated analyses and statistics.

20. **DH/HPA** have a proposal to follow up confirmed/likely cases of irritancy (skin/eye/respiratory). It is expected that within this category there are a small number of bystander cases. It is proposed to consider the exposure scenarios in these cases and draft a

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report. A questionnaire has been agreed by panel members. DH/HPA have recently received the relevant data which is being anonymised before a blind evaluation is undertaken.

21. One of the potential problems with the PIAP system is possible under reporting by Local Authority (LA) Inspectors. There is evidence that this may be true as very few LA incidents are ever seen by PIAP. HSE continue to try to encourage reporting from LA inspectors (Trading Standards Officers/Environmental Health Officers).

Hospital Episodes Statistics

22. The Hospital Episodes Statistics, gathered centrally by the Department of Health, enable the identification of numbers of 'finished consultant episodes' in England, and include cases where the cause is accidental poisoning by agricultural and horticultural chemicals other than plant foods and fertilisers. A finished consultant episode is defined as 'a period of patient care under one consultant within one hospital provider'. The statistics are compiled from information provided by all NHS hospitals in England. Between 1 April 2002 and 31 March 2003 there were 163 'finished consultant episodes' involving accidental pesticide poisoning and 77 involving intentional self-poisoning (out of a total of 12,757,656). DH has proposed an evaluation of the HES database for cases of accidental pesticide poisoning (aged 16-64) from 1998-2003. This should provide information on the exposure scenarios that occurred.

23. The equivalent system in Scotland is the Scottish Morbidity Records Scheme 'SMR1', which covers acute inpatient care statistics. In Wales, the Patient Episode Database for Wales fulfils a similar role.

The National Poisons Information Service (NPIS)

24. There are six NPIS centres in the UK (in Belfast, Birmingham, Cardiff, Edinburgh, London and Newcastle). They provide advice to health care professionals including GPs about the management of cases where poisoning is suspected or has occurred. Each Centre produces an annual report for the Department of Health and the statistics reflect the number and the nature of enquiries received. The level of detail recorded varies, but most Centres document basic information on the pesticide involved and how the poisoning occurred. However, much will depend on the information provided by the caller. In 2002, 2,047 telephone queries to NPIS involved agrochemicals out of a total of 178,246 enquiries.

25. The ACP has recently reviewed some detailed evaluations of NPIS data generated by the Edinburgh office. This provides new information on a number of enquiries and is consistent with all previous evaluations of acute incidents reviewed by the ACP.

Mortality data from the Office of the National Statistics

26. In England and Wales, data on deaths from acute poisoning are collected by the Office of National Statistics, based on returns from Coroners in England and Wales. Similar data is provided by the Registrars General for Scotland and Northern Ireland. Deaths are classified by Coroners (or the Procurator Fiscal in Scotland) as an accident, suicide, homicide or undetermined. In 2002, 533,527 deaths were recorded. Seven deaths were recorded as being from pesticide poisoning of which five were from intentional poisoning.

27. Data used to also be collected by the Department of Trade and Industry (the Home Accident Surveillance Scheme). (A survey of A&E attendances at a selected number of departments) This was discontinued in 2002 and the databank transferred to the Royal Society for the Prevention of Accidents (ROSPA). Evaluation shows a similar low level of reporting.

28. PSD have also collated data from pesticide manufacturers.

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PSD questionnaire on the possible effects of pesticides on human health.

29. Extract from paper presented to November 2004 ACP meeting (para 30-32 below). The paper has been seen by PIAP who considered that it was not possible to derive definite conclusions from these data as the extent of follow-up of cases was limited.

30 Approval holders are under an on-going obligation to submit immediately any new information on the potentially dangerous effects of a product or of residues of an active substance contained in a product, on human or animal health, ground water or the environment. This requirement is intended to provide information in addition to the other methods employed by PSD such as literature searches. In order to check whether this adverse data reporting system is functioning as effectively as it should, PSD carried out a survey of all human health incidents reported to Approval Holders in 2002.

31 All Approval Holder Letters No's 30 and 35 of 2003, requested that Approval Holders submit details of all human ill-health incidents involving their pesticide products reported to them by users in 2002. The information submitted has now been examined and the results and conclusions are set out below;

Results:

- 171 Approval Holders submitted responses to the survey. This represents 99.98% of total turnover declared for PSD's 2003/2004 levy exercise.
- Regulatory action has been undertaken against those approval holders who did not respond, in that their products have had approvals either suspended or revoked. The survey also established that a small number of companies are no longer trading.
- Approval Holders reported 137 possible human health incidents involving pesticides.

Of these 137 incidents (from the information supplied),

- 17 were as a result of accidental use (e.g. accidental spillage), 28 were as a result of mis-use or abuse of the product, and 92 may have involved approved use.
- We have made an assessment that 76 of these incidents merit further investigation.

Of these 76 incidents, we have established that

- 34 involved amateur products (home garden products),
- 40 involved professional products (agricultural products),
- 2 were not classifiable from the information supplied.
- 55 different active ingredients were involved.

Conclusions:

1. The results of the survey give no cause for immediate concern. While none of the 76 incidents have yet been confirmed as directly attributable to pesticide exposure, approximately 50 of these either reported no symptoms, or relatively minor symptoms such as rashes, itching, sore throats, nausea, blistering or headaches.
2. PSD has written to the companies whose products were involved in each of the 76 incidents, to request further information in order to determine what if any action is necessary.
3. PSD has also written to Approval Holders reminding them of their responsibilities concerning the reporting of human health incidents. This exercise has prompted further consideration of the effectiveness of the current reporting system as a whole. PSD have tightened up reporting procedures in order to ensure that all incidents are

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fully reported. PSD are also considering the wording of the current system and will inform companies of their obligation to report as soon, and as fully as possible, any incidents that come to their attention.

4. PSD has repeated the exercise in order to ensure that approval holders are meeting their requirements with respect to reporting adverse human health incidents, to ensure that developments to our procedures have been fully implemented and to ensure that we remain vigilant in the case of any emerging patterns.

32. PSD initiated a call for data for 2003/4. Deadline for submission is 15 April 2005. these data were evaluated and considered by the ACP on 22 Sept (Ref ACP 22/1 (315/2005)).

Surveillance for chronic effects

33. The RCEP was predominantly concerned about chronic fatigue syndrome, multiple chemical sensitivity and cancer. The RCEP have also made specific reference to a review prepared by the Ontario College of Physicians which has received considerable media attention.

34. The ACP/MTP have recommended that surveys of the epidemiological literature and targeted investigations is the most appropriate approach. Monitoring schemes are only of value for acute effects.

35. Previous MTP/ACP reviews have identified a need for further investigation of the potential association with Parkinsons disease and genotoxicity in pesticide applicators. Both initial projects have now been completed. Short briefing notes on the chronic effects identified by ACP are given followed by those identified by RCEP and issues raised in the Ontario College review.

Parkinson's Disease.

36. The ACP recommended a detailed epidemiological review at its September 2001 meeting. The ACP reached some conclusions at its November 2004 meeting following consideration of a report from the Institute for Environmental Health (IEH).

37. Parkinson's disease (PD) is a neurodegenerative disorder characterised by the loss of dopaminergic neurons in the nigra striata and the formation of intraneuronal inclusions called Lewy bodies in different brain regions. PD is idiopathic. However, there are related syndromes, which have similar symptoms, generally referred to as parkinsonism. There have been several epidemiological studies that reported conflicting findings as to whether pesticide exposure is a risk factor for developing PD and/or parkinsonism. Toxicological studies have shown that pesticides may be involved in the development of some features of parkinsonism in animal models. However, these studies have generally used routes of administration and dose levels that are not comparable to the routes and levels of exposure experienced by humans. Some authors have suggested a genetic component to the susceptibility of individuals to pesticide exposure and the development of PD and/or parkinsonism. Overall, the question of whether pesticides are involved in the development of PD and/or parkinsonism is complex and would benefit from a critical review of the literature to consolidate current understanding.

38. The Medical and Toxicology Panel had considered the report of a Defra funded review of the scientific literature on links between Parkinson's Disease and pesticide exposure in some detail at their October 2004 meeting. The Panel had agreed with the proposals made by the authors of the review that further mechanistic research would be the best way forward.

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39. The ACP also agreed that further mechanistic research was necessary. In addition, they considered that further epidemiology could be useful where exposure to specific pesticides could be ascertained with reasonable confidence (e.g. cohort studies of pesticide production workers or long-term prospective studies of pesticides users). The review indicated a correlation between recalled pesticide exposure and Parkinson's Disease, but did not point to a particular toxic mechanism or a hazard from a specific compound or group of compounds. PSD is currently evaluating proposals for further research.

A copy of the full report can be found at

http://www2.defra.gov.uk/research/project_data/More.asp?I=PS2601&SCOPE=0&M=PSA&V=NR%3A080

Biomonitoring studies of pesticide applicators: evidence for genotoxicity

40. The MTP and ACP requested advice from COM during summer 2004. A review was initiated at the COM meeting in October 2004. The COM reported to the ACP in November 2005.

41. One aspect of this review is that since no genotoxic carcinogen is approved, there should be no evidence for genotoxicity in UK pesticide applicators. It is noteworthy that there are no published studies in UK pesticide workers. All the evidence comes from EU, USA, and a number of other countries particularly from South America. The Ontario College report specifically mentions this aspect of potential chronic ill health associated with pesticides.

The COM statement can be found on the COM internet site. <http://www.advisorybodies.doh.gov.uk/pdfs/pesapp.pdf> The COM had reservations regarding the quality of the available studies and their interpretation. No specific pesticides active ingredient could be identified for regulatory action. COM is currently considering further work on approaches to conduct and evaluation of biomonitoring studies.

Chronic Fatigue Syndrome/ME

42. Chronic fatigue syndrome (CFS) is a controversial disorder with different case definitions, aetiological models and proposed treatments. The Independent Working Group established by DH to promote better understanding of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) published a report in 2002 which helps to clarify the issues of diagnosis, treatment and care. The working group noted reports suggesting an association between exposure to environmental toxins, such as organophosphorous compounds, and development of disease in isolated cases. The working group concluded that the balance of evidence indicates this is not a common or widespread trigger

43. Some research has been undertaken as part of the response to the COT report on Organophosphates http://archive.food.gov.uk/dept_health/archive/cot/op.htm. The COT report focussed on OPs used as pesticides, human medicines or veterinary medicines, particularly sheep dips, and evidence for neurotoxicity. The COT report was published in November 1999. This report identified a range of symptoms including CFS claimed by sheep dippers who had used OP pesticide mixtures. The COT identified a number of gaps in knowledge at that time, in particular the possibility that OPs cause ill health in a small subgroup of exposed sheep dippers. This is a particularly difficult question to address and some of the studies have not yet been completed. Nonetheless, it is true to say none of the research completed to date has provided convincing evidence for this hypothesis. The area will need to be considered in detail when all of the research is complete. In response to the COT recommendations, a cross-Government group was established to manage a programme of new research work to address the knowledge gaps. The work of this group took forward the cross-Government co-ordination of information and research on OPs established in 1997ⁱ and is ongoing. A range of projects designed to investigate the possible health effects of exposure to low doses of organophosphates funded by Government funded is summarised on

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the VMD website at <http://www.vmd.gov.uk>. (There is information on nine projects on the website). The research programme has not yet been completed and will be the subject of discussion by the Interdepartmental working group on OPs

44. Symptoms consistent with CFS have been reported by people who consider their health has been affected by exposure to pesticides. The Veterinary Medicines Directorate (VMD) collects self-assessed reports of ill health in humans associated with veterinary medicines under their Suspected Adverse Reaction Surveillance Scheme. The reporters have mainly been sheep farmers.

45. An update report to the Veterinary Products Committee (VPC) dated January 2005 . Further evaluation will be undertaken when all of the research projects have been completed.

47. It is likely that the exposure scenarios pertaining to sheep dippers have limited relevance for bystanders following agricultural application of pesticides. Since the ACP review of OP approvals review completed in 2000 many OP pesticide products have been withdrawn.

Multiple Chemical Sensitivity

48. The COT considered the evidence for an association between exposure to chemicals and MCS in 1999 and 2000. Members noted there were no consistent patterns of symptoms or exposure data to define the condition, and concluded that on the basis of knowledge current at the time, there was insufficient evidence to make comments on potential mechanisms or to recommend further research in this area.

49. The COT considered a review of potential association between allergy (in particular nut allergy) and MCS in 2000. Members considered that when such cases were investigated it often led to a diagnosis of a specific allergy. Members were concerned that the term "multiple" was being applied to patients simply because a specific cause had not been established.

50. COT concluded that there was no reason to change its view on MCS, namely that no diagnostic definition was available.

51. There is more published literature available and COT may wish to review this information.

Cancer

53. All pesticides are tested in two species for carcinogenicity. No genotoxic carcinogen is approved for use as a pesticide. All tumours seen in animals are rigorously evaluated. [DN: why the question mark] Post market monitoring consists of regular evaluation of the literature. There are two cancers which have been cited extensively regarding a potential association with pesticides.

Prostate cancer

54. Prostate cancer is the most common cancer in men in the UK, with over 24,700 new cases a year (2000 data). Prostate cancer is the second largest cause of death from cancer in the UK. There were 9,900 deaths reported in 2002 accounting for around 13% of cancer deaths in men. Around 70% of these deaths are in men aged over 70 years. The mortality rate for prostate cancer peaked in the early 1990s and has now fallen to 25 per 100,000 population at risk. The lifetime risk for being diagnosed with prostate cancer is 1 in 14. The cancer develops from cells within the prostate gland. The majority of prostate cancers are slow growing and many men are unaware that they have this cancer. However, a small number of prostate cancers grow more quickly and may spread to other parts of the body. Cancer Research UK reported a 57% increase in prostate cancer incidence in Great Britain between 1991 and 2000.

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55. The COC undertook a review of the literature on prostate cancer during 2003/4. overall the COC concluded that the increase in incidence of prostate cancer reported over the past 2-3 decades is largely accounted for by improved identification of cases due to increased numbers of individuals undergoing surgery for benign prostatic conditions and the use of Prostate Specific Antigen Screening. One conclusion reached by COC regarding pesticides did receive some media attention.

56. “The Committee concluded that there was some limited evidence to suggest an association between farmers/farm workers, exposure to pesticides and increased risk of prostate cancer. The possibility of such an association being causal could not be discounted and the published literature should continue to be monitored for further studies. Members commented on the need for improved measures of exposure to pesticides and in particular herbicides. It was considered that the potential association between herbicide use by farmers and farm workers should be kept under review.”

57. The MTP and ACP were aware of the ongoing review of COC and discussed the COC conclusions in January 2005. ACP has recommended a further meta-analysis of studies on pesticide manufacturers to evaluate whether any links to specific pesticides can be drawn. Defra is to fund this research.

58. The COC epidemiologist and ACP chairman have advised (in preparation for attendance of Select Committee on Food, Environment and Rural Affairs on 21 February 2005) that any risks to bystanders would be exceedingly small and not measurable by current epidemiological techniques.

Breast Cancer

59. The COC has recently finalised its evaluation of whether a number of organochlorine (OCI) insecticides may cause breast cancer. The Committee evaluated the hypothesis that organochlorine insecticides might increase the risk of breast cancer by virtue of their claimed oestrogenic effects. Thus, if a particular chemical had no oestrogenic activity *in vivo*, then there was no rationale as to why it could be considered as a risk factor for breast cancer. The Committee has published both a detailed technical statement and a non-technical summary.

60. The conclusions are tabulated below. Essentially after consideration of substantial amounts of evidence COC found no evidence for an association regarding DDT and metabolites, lindane and for beta HCH. It was recommended that dieldrin is kept under review.

Conclusions on the individual chemicals considered in the 2003/4 review (None now approved in the UK for use as pesticides)

OCI	Does the chemical have oestrogen-like effects in animals?	Are the levels detected in human tissue significant?	What is the relationship between human exposure to a particular OCI and breast cancer?	Are people who are exposed to environmental levels of a particular OCI at increased risk of developing breast cancer?
<i>DDT</i>	Yes, although its effects are very weak.	Levels of DDT are known to be declining.	There is no evidence for a link.	No.
<i>Dieldrin</i>	No.	Levels of dieldrin are known to be declining.	Overall there is insufficient information to draw any conclusions.	No definite conclusions drawn. To be kept under review..

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-HCH	Yes, although its effects are very weak.	Levels of β -HCH are known to be declining.	Overall there is no evidence for a link.	No.
Lindane	No.	No.	Overall there is insufficient information to draw any conclusions.	No.

61. Although COC has reached quite definite conclusions for all but one OCI, there has been continued interest in the media and by stake holder groups who do not appear to accept these conclusions. COC has recently agreed to expand its consideration of breast cancer to all environmental chemicals during its horizon scanning discussion in November 2005.

Ongoing pesticides research into possible effects on human health being funded by UK Government.

62. The following is a brief survey of information from HSE, FSA, Defra and PSD.

63. There has been insufficient time to fully evaluate this. From the available information it is not possible to provide an estimate of overall funding.

64. Information from HSE

No estimate of research funding available

1 The reporting of pesticide related illness in General Practice

The aim is to identify cases of pesticide related illness (including those arising from bystander exposure) diagnosed over one year in a representative sample of General Practices. The number of alleged cases presenting to, but not confirmed by, the GP will also be recorded.

This project is still in progress and is due to report in September 2006. Contractors for HSE are the former MRC Institute of Environment and Health at Leicester and the MRC General Practice Research Network. The results will be published as an HSE Contract Research Report. (NB RCEP officials have visited this project.)

2 The HSE Pesticide Users Survey

This is a long term project initiated by HSE based on the requirement for pesticide sprayers new to the work to obtain certificates of competence via the National Proficiency Test Council. Those seeking certification are asked if they are prepared to join this research project: approximately 65000 have been included to date and recruitment continues. The survey, has two main elements.

The first element is a prospective cohort mortality and cancer incidence study of all survey members. Information on pesticide exposure and the use of control measures will be collected intermittently from those in the survey. As most recruits are young and follow up is relatively short at this stage it will be some time before useful results can be obtained on the causes of death and cases of cancer in cohort members. This element of the survey is funded by HSE.

The second element is the availability of the cohort to bona fide researchers who wish to undertake morbidity studies in the survey population or who may wish to conduct nested case

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control studies of particular diseases. HSE has had discussions with several researchers about surveys of respiratory and skin disease in pesticide workers, about their reproductive capacity and about risks of specific cancers. HSE would expect researchers to obtain funding from elsewhere for these projects.

HSE has recently transferred the management of the Survey to its Health & Safety Laboratories, because they are better placed to take advantage of the capacity of the Survey for further development.

3 The "Green Card Scheme"

This HSE funded project ran for 28 months from June 1991 to September 1993 so the outputs are rather dated. More up to date information in incidence will become available from the current GP based reporting scheme mentioned above.

Clinicians in the West Midlands and Trent regions were asked to report cases of suspected pesticide related illness to the West Midlands Poisons Unit, the incentive being the availability of advice on management of cases. Using the same criteria as were then used by the HSE Pesticide Incidents Appraisal Panel cases were categorised as to the likelihood of pesticide causation. About 70 cases per year were judged to be "Confirmed" or "Likely". For 64% and 31% respectively cases were classed as mild or moderate in severity.

Research reports are available in HSE and the headline statistics mentioned above were published in HSE's annual statistical volume at the time.

Additionally, there have been, and still are, cross-government research projects on OPs, primarily related to the long term effects of exposure to veterinary medicines. If these indicated effects as a result of chronic exposure to active substances used in non-agricultural pesticides then the implications for non-agricultural use would be considered by HSE.

HSE Biocides and Pesticides Unit has commissioned, and continues to commission, research related to pesticides exposure. However the focus is primarily on exposure levels.

64. Defra (PSD)

PA1722 development and study of methods for assessing worker and environmental exposure to pesticides (2000-2002), cost £164, 639.

PA1724 Minimising operator and bystander exposure to pesticides during glass house application and re-entry tasks (2000-2001), £94,565

PS2604 Biological monitoring of pesticide exposures (2004-2005) £74,339.

65 Veterinary Medicines Directorate

Background

66. The Government (Defra/DH/HSE) has funded a number of research projects into the effects in humans of exposure to organophosphates (OPs), in particular OP based sheep dips. In addition projects have also been funded into the research of alternatives to OP's. This research forms a key part of the Government's Four Point Plan on OPs, announced in December 1999.

67. Abstracts were presented at a meeting held at Dstl, Porton Down, Wiltshire on 17 December 2002, involving representatives of interested Government Departments (including Departments sponsoring the research) and those conducting the research.

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The meeting was arranged to:

- consider the draft findings of a recently concluded study, prior to their peer review and publication;
- enable Government Departments to review the progress of current projects in the OP research programme,
- facilitate an exchange of ideas and experiences and foster collaboration between researchers; and
- identify any areas where further research was needed.

Abstracts Of Government Sponsored Research Into Effects Of Organophosphate Exposure

- VM0279 Dose Effect Profiles for OP Sheep Dip on Brain Electrical Activity and Cognitive Performance in non-human primates.
- VM0299 Review of OPIN register of suspected OP-related health complaints (Survey of health complaints among sheep dippers: the "SHAPE" study).
- VM02115 Disabling neuropsychiatric disease in farmers exposed to organophosphates. Study of the Health of Agricultural Workers (SHAW).
- VM02116 Investigation of Possible Autoimmune Responses Induced by Organophosphate Exposure.
- VM02117 Characterisation of non-acetylcholinesterase actions of organophosphates by identification of novel protein targets.
- VM02126 A case-control study of neuropsychological and psychiatric functioning in sheep farmers exposed to OP pesticides.
- VM02301 Prediction of susceptibility to long-term genotoxic effects of organophosphate pesticide exposure.
- VM02106 Development of database on research on organophosphate compounds related to public health (Survey of research projects on organophosphates (SRPOP)).
- VM02112 An analytical study of human OP sheep dip reports received by the VMD 1985-2000.

Abstracts Of Government Sponsored Research Into The Alternatives to Organophosphates

- OD0544 Immunological approaches to the control of sheep scab.
- OD0545 Studies on the Biological Control of the sheep scab mite *Psoroptes ovis*.
- OD0546 Endocrinology and in vitro culture of sheep scab.
- OD0536 Biochemical and physiological studies to identify potential targets for the control of *Psoroptes ovis*.
- OD0537 Biochemical and immunological studies in sheep infected with the mite, *Psoroptes ovis*.

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- OD0538 Studies on the biological control of sheep scab mite, *Psoroptes ovis*, using entomopathogenic fungi.
- OD0539 Potential targets for biologically based novel methods of control of the sheep scab mite by study of its basic biology and endocrinology.

FSA

68. Follow up research to the COT report on mixtures of pesticides. The projects are due to run up to 2010

T10 MIXTURES RESEARCH PROGRAMME – SUMMARY OF PROJECTS

PROJECT NO.	CONTRACTOR	PROJECT TITLE
T10002	Health and Safety Laboratory, Sheffield	Biomarkers of effect from exposure to mixtures of organophosphate pesticides
T10003	Health and Safety Laboratory, Sheffield	Cost-effective biomarkers of exposure to mixtures pesticides – method development
T10004	Imperial College, London	Use of protein profiles to characterise the concentration effects curves for mixtures of estrogenic compounds
T10005	Institute of Occupational Medicine	Estimation of human uptake of pesticides and veterinary medicines from all potential exposure pathways
T10008	Health and Safety Laboratory, Sheffield	Dose-response and mixture response of pesticides in in vitro and in vivo
T10009	ADAS Consultancy	Development of diagnostic immunoassays for biomarkers of pesticide exposure
T10010	University of Newcastle	Investigation of direct measurement of phosphorylation of the active site of esterases as sensitive biomarkers of organophosphate exposure
T10011	CXR Biosciences	Interindividuality in cytochrome P450 and paraoxonase mediated metabolism of mixtures of pesticides

DH

69. No specific costing available as funds are for overall research programme.

70. In recent publications, Cherry *et al.* reported that subjects with self-reported symptoms of ill-health following exposure to sheep dip containing diazinon were much more likely to be of the PON1 192RR genotype of the enzyme paraoxonase, which hydrolyses a range of organophosphates. Earlier experimental studies suggested that individuals of the PON1 192RR genotype had an impaired ability to detoxify the active oxon metabolite of diazinon (i.e. diazoxon). The aim of this study was to investigate the effects of the common polymorphisms of PON1 on diazoxon hydrolysis, measured under more physiological conditions than those used previously.

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71. The DH Toxicology Unit at Imperial College London has undertaken work on the genotyping and phenotyping of OP metabolism in humans. The research based on PON1 metabolism used a new advance enzyme assay and produced

72. The work has demonstrated that overall intragenotype variance was significantly higher than intergenotype variance. There was evidence that individuals with a combination of Q and M alleles generally had a lower ability to detoxify diazinon. The data was in contrast to the data from Cherry et al. This has been drawn to the attention of the OP working group investigating sheep dippers who are considering how to take the evaluation forward.

73. This is an important piece of work and has been accepted for publication in Pharmacogenetics.

The Ontario College review

74. A copy of the statement and supplementary statement agreed by the ACP on this report is given below. THE RCEP specifically raised this report with DH. In reaching its conclusions ACP took advice from the two epidemiologists on COC. There was a split in the ACP with the member appointed as an expert in organic farming opting to publish a minority view.

Advisory Committee on Pesticides Statement on the Pesticides Literature Review published by the Ontario College of Family Physicians

'In April 2004, the Ontario College of Family Physicians published a systematic review of the epidemiological literature on possible chronic health effects of pesticides. The review, which focused on papers published during 1992-2003, concluded that "it can be clearly stated that at least some pesticides are carcinogens" and recommended that pesticide use should be reduced.

The Advisory Committee on Pesticides (ACP) considered the report at its meeting in May 2004 when the epidemiologist on the Committee (the Chairman) presented his assessment of the review. He proposed that, in case his views were unrepresentative of wider scientific thinking, opinions should be sought also from a number of other independent epidemiologists. Accordingly, comments were requested from five epidemiological experts who were current or recent members of other Government advisory committees (the Committee on Toxicity, Committee on Carcinogenicity and Advisory Group on Non-Ionising Radiation). To avoid prejudicing their evaluations, they were not shown the Chairman's assessment of the review.

The ACP reconsidered the Ontario report at its September 2004 meeting, along with the feedback from the invited experts. This statement summarises the conclusions of ACP's discussions to date.

For some years, the ACP Medical and Toxicology Panel has annually scrutinised the abstracts of published papers on pesticides and human health to check for findings that might have implications for pesticide regulation in the UK. The material covered by the Ontario review overlaps substantially with that which has already been examined by the Panel, but with some differences (the review covers a somewhat longer time period and includes a few papers written in languages other than English, but is restricted to 16 specified health outcomes).

Some of the conclusions of the report accord with those reached by the Medical and Toxicology Panel. Thus, the Panel has previously noted an apparent consistency of epidemiological reports linking Parkinson's disease with pesticide exposure, and this led to the commissioning of a detailed review of the topic. (See Sept 2001 ACP minutes.) Similarly, we have recently asked the Committee on Mutagenicity to review the literature on biomarkers of genotoxicity in pesticide-exposed workers, in which the frequent report of positive findings seems at odds with the absence of in vivo genotoxicity for almost all

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pesticides when tested individually for regulatory purposes. Other conclusions differ markedly from those of the Panel. For example, the report concludes that “large well-designed cohort studies consistently show statistically significant positive associations” between solid tumours and pesticide exposure, an assertion with which we strongly disagree.

These discrepancies arise from serious flaws in the methods employed in the review. Most important are:

- its failure to take account of all or even most of the relevant epidemiological evidence, and the biases inherent in the way in which material was picked out for inclusion;

- inadequate attention to exposure characteristics and relevant toxicology when interpreting reported associations; and

- its superficial synthesis of evidence, which inadequately explores the impact of the strengths and weaknesses of individual studies.

Overall, the ACP has concluded that the report does not raise any new concerns about pesticide safety that were not already being addressed, and does not indicate any need for additional regulatory action in the UK.

At its meeting on 13 January 2005, the ACP agreed the following supplement to its earlier statement on the pesticides literature review published by the Ontario College of Family Physicians.

Supplementary statement

The above comments on the Ontario review and its implications for risk assessment and regulation of pesticides in the UK in no way detract from the unanimous view of the ACP that unnecessary exposure to pesticides should always be avoided. Pesticides should be used only when the use is justified by potential benefits in pest control and better alternative methods of pest control are unavailable. Moreover, when pesticides are used, they should always be applied in accordance with the instructions on the label, and in a way that minimises people's exposure as far as is reasonably practical.'

Pesticide Survey Data

Pesticide Residues in Food and Foodstuffs

75. Monitoring of both home produced and imported food for pesticide residues is carried out by the Government's Pesticide Residues Committee which undertakes a £2.2 million programme of pesticides monitoring in food each year to make sure that they have up to date information about pesticides residues in food. This programme checks whether trading levels (Maximum Residue Levels or MRLs) are being exceeded and whether residues found are in line with those expected from normal use of the pesticide. Results are reassuring but the Committee is not complacent and follows up unsatisfactory residues with suppliers and where necessary by organising additional surveys to more closely monitor the situation. The incidence of residues is not an indicator of safety for consumers. The levels found and how those levels relate to the toxicological reference doses are more important. Risk assessments are carried out for all MRL exceedences, and where there is no reference MRL. Of the 4000 samples taken every year only a very small number, 2-5 samples, contain residues which cause any concern. These are always followed up with suppliers.

Pesticide Residues in Air

76. There is no permanent air monitoring programme in the UK. However, 24/48-hour samples were collected over about one and a half years on two MAFF experimental husbandry farms. The results indicated that mean levels were likely to be many thousands of times lower than the levels at the time of application and support the argument that the use of the spray drift data is conservative. The State of California has a monitoring programme for residues in air of compounds of certain toxicity and volatility, including some pesticides. The monitoring is carried out next to application sites and in urban settings. Data from Germany

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(under conditions more representative of UK conditions) have also been obtained and these, along with the data from California, were presented to the Advisory Committee on Pesticides in January 2003.

Bio-monitoring of Pesticide Residues

77. Data on concentrations of pesticides or their metabolites in humans, especially in blood or urine, can be used in conjunction with appropriate pharmacokinetic information to provide robust information on the total amount to which individuals are exposed. No bio monitoring of pesticide exposure of bystanders has taken place in the UK. Also such data do not appear to be readily available in other countries. However some relevant related data are available, for example the Farm Family Exposure Study done in Minnesota and South Carolina that measured exposures of applicators, their spouses and children to pesticides, which suggest that bystander exposures are very low. An overview of recent published studies was considered by the ACP in Sept 2005. (ACP 26 (315/2005)).

Pesticide Usage Surveys

78. Pesticide usage surveys of all agricultural and horticultural crops are conducted throughout Great Britain on a regular basis, to a programme agreed by the ACP. The data are collected under the powers granted to Ministers under section 16 (11) of the Food and Environment Protection Act 1985. Under this Ministers may require importers, exporters, manufacturers, distributors or users to provide them with such information as Ministers consider necessary for, amongst other things, the purpose of controlling pesticides in the UK.

79. The usage surveys in England and Wales are carried out on behalf of the Pesticides Safety Directorate by Defra's Central Science Laboratory. Parallel surveys are also carried out in Scotland by the Scottish Agricultural Science Agency and in Northern Ireland by their Department of Agriculture and Rural Development. The Central Science Laboratory also maintains a computer database of all usage data collected in England, Wales and Scotland; analysing and interpreting the data; preparing and publishing reports on a GB basis and responding to requests for information on pesticide usage.

80. The surveys of arable crops are conducted every other year and on the majority of other crops every four years and are designed to provide information which is representative of the national pattern of crop production and the use of pesticides. This is achieved by using a balanced statistical sample for each survey to ensure that an appropriate cross-section of growers is targeted. The data gathered are principally used to inform the evaluations made by the Pesticides Safety Directorate but are also used by Defra and other Government Departments to inform and support a range of policies in relation to pesticides and the environment. The surveys are funded by the agrochemical companies who pay for them through the annual levy on UK pesticide sales turnover.

Pesticides Formulation Analysis

81. In order to ensure that formulations available on the market in Great Britain comply with the specifications set out in the approval documents, PSD carries out an annual monitoring programme. A number of active ingredients are selected for analyses through the year. Selection is mainly at random but can be specifically targeted if there are some concerns about a particular active ingredient. Approximately 60% of the available products containing the nominated active ingredients are analysed to assess whether the active ingredient is within generally accepted FAO tolerances from the declared content. If necessary, physico-chemical properties are also analysed. Because of the commercial sensitivity of the information derived from this monitoring programme the results are not published. However the vast majority of products that are analysed are within accepted tolerance levels.