

**ACTION PLAN ON THE RISK ASSESSMENT OF MIXTURES
OF PESTICIDES AND SIMILAR SUBSTANCES**

Food Standards Agency
March 2005

PREAMBLE

The Action Plan to take forward the recommendations of the Report of the COT (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment) Working Group on Risk Assessment of Mixtures of Pesticides (WiGRAMP) and Similar Substances consists of:

- the text, which provides an overview on work already underway and sets out barriers to progress on implementation of the Working Group's recommendations; and
- an attached table, which shows the action proposed in response to the recommendations; targets for completion of the work, and identifies the Government Department responsible for taking the action forward.

The recommendations of the COT Report are attached at Annex A.

The Action Plan has been prepared by officials from the Food Standards Agency, with input from the Department for the Environment, Food and Rural Affairs's (Defra) Veterinary Medicines and Pesticides Safety Directorates (VMD and PSD), the Health and Safety Executive's (HSE) Biocides and Pesticides Unit and the Department of Health (DH). The Medicines and Healthcare products Regulatory Agency (MHRA) and the Environment Agency (EA) have also been kept informed of developments.

Any references in the Action Plan to 'we' shows that this is the view of the Food Standards Agency.

Please note:

The Action Plan indicates whether the recommendations deal with taking forward work towards either:

- aggregate exposure assessment which is based on exposure from all sources such as food, air and water; or
- common mechanism group risk assessment (sometimes known as cumulative risk assessment) which is necessary when there is exposure to more than one substance with a similar toxicological mode of action and thus substances may act together; or
- a combination of these two processes.

Common mechanism group risk assessment may require consideration of different substances arising from the same or different sources of exposure.

ACTION PLAN ON THE RISK ASSESSMENT OF MIXTURES OF PESTICIDES AND SIMILAR SUBSTANCES

INTRODUCTION

1. The COT Report was published on 15 October 2002. The COT concluded that the probability of any human health hazard from exposure to mixtures of these substances, each present at a low level, is likely to be small and that their effects are unlikely to be other than additive.
2. Current regulatory systems evaluate individual substances. The COT has recommended that aggregate and common mechanism group risk assessments are carried out on all agricultural and non-agricultural pesticides and veterinary medicines which belong to the high priority common mechanism groups (to be identified through work to implement recommendation 11.2).
3. A draft action plan to implement the COT's recommendations was issued for full public consultation on 31 July 2003. Replies to the consultation have been considered and a summary of these with responses to the comments have been posted on the website of the Food Standards Agency¹. These responses were considered in the development of the finalised Action Plan.

IMPLEMENTATION OF THE RECOMMENDATIONS

4. Regulation of agricultural and non-agricultural pesticides and veterinary medicinal products is governed by EC legislation. The UK cannot unilaterally add requirements to the authorisation process of these substances, as this would be illegal. Also, much of the UK's food supply is imported and hence standards for imported foods must be as rigorous as for home-produced. We therefore see implementation of the COT recommendations as a two-stage process:

Stage 1: carry out the necessary underpinning work highlighted by the COT recommendations; and

Stage 2: argue vigorously in the relevant bodies (e.g. the European Commission and the Codex Alimentarius Commission) for any necessary changes to EC legislation and international standards.

5. Work has already begun to implement some of the actions, principally the underpinning work at Stage 1. Details are given in the table. Highlights to date are:

- The Agency and other Government Departments have begun work to identify and prioritise common mechanism groups. We will then assess combined exposure for the highest priority groups.
- The Agency and PSD have committed to funding research. VMD has added this area of work to its list of considerations for research funding.
- The Agency's initial requirement for new research was published on 8 May 2003 and commissioning work is currently in progress.

¹ <http://www.food.gov.uk/multimedia/pdfs/wigrampresponses.pdf>

- Linda Shuker (replaced by Len Levy in 2005), of the Institute of Environment and Health, has been appointed by the Agency as Programme Co-ordinator to manage the research programme.
- The Interdepartmental Liaison Group on Risk Assessment (ILGRA), a subgroup of the Interdepartmental Group on Health Risks from Chemicals (IGHRC), conducted a review of multiple source exposure models and made recommendations regarding an initial aggregate exposure screening methodology, and identified a model which was considered the most appropriate for the UK requirements. This is the first step to developing a methodology for estimating the aggregate exposure for various population groups;
- The Pesticide Residues Committee has reviewed its monitoring programme to take into account the COT's recommendation for modifications. It has organised some larger surveys, within resource constraints, but collection of fully representative data would not be entirely consistent with the programme's compliance monitoring role.
- The initial view of the Veterinary Residues Committee were sought in October 2002 and the Committee will discuss the issue again when time permits.
- The Environment Agency (EA) has developed bioassays to assess complex mixtures of effluents.

INTERNATIONAL ACTION

6. We are monitoring and evaluating the progress of the US Environmental Protection Agency (EPA) in its efforts to carry out combined risk assessments. It has recently published its first example, (organophosphates) for public comment. The results so far do not appear to indicate concerns or trigger any need for immediate regulatory action. PSD facilitated a meeting with the US EPA (held in November 2002) to discuss with them the methodology used in this work and to establish whether it can be used to carry out combined risk assessments in the UK. Although some details may need to be adjusted to reflect the UK situation, it was agreed that the general approach had many aspects which could be used. The ACP has reviewed all organophosphate and carbamate cholinesterase-inhibiting agricultural and non-agricultural pesticides in use in the UK. The ACP has agreed a method for assessing the toxicology and will now carry out a combined risk assessment for this group of compounds. In the first instance, this will concentrate on dietary exposures to pesticides as there are insufficient data available at present to allow study of other sources of exposure. Experience from this exercise will be fed into the work in implementing recommendations 11.2 and 11.3 of the action plan.

7. The outputs from this action plan will put the UK in a strong position, collaborating with other Member States, to take forward the COT recommendations at a European level. Indeed, the European Commission has already acknowledged (in the Communication 'Towards a Thematic Strategy on the Sustainable use of Pesticides'² that 'An important shortcoming of Directive 91/414/EEC is that it is primarily based on the assessment of individual compounds...' and has recommended 'further research and development into potential synergistic and antagonistic effects of plant protection products, in particular in frequently used combinations of active substances'. In addition, the European Commission has stated (in the Communication 'A European Environment and Health Strategy'³ that focussing on single pollutants will lead to

² <http://europa.eu.int/comm/environment/ppps/home.htm>

³ http://europa.eu.int/comm/press_room/presspacks/health/pp_health_en.htm

underestimation of health impacts because people are exposed to a combination of pollutants and that assessments will be rendered more efficient by taking into account cocktail effects, combined exposure and cumulative effects. Codex too has begun to consider the way forward in this area. The UK will take all opportunities to argue that combination effects must be taken into account where appropriate in the future. Work on Recommendations 11.2 and 11.3 will be presented to the Commission, EC regulatory bodies and Codex to provide a mechanism as to how this can be achieved. International contacts have the COT Report and have been invited to contribute to the consultation process. Scientists in Denmark and the Netherlands have recently published relevant work⁴.

8. Officials have concluded that it would be helpful to have an assessment of the impact of the recommendations within the EU, taking into account exposure to agricultural and non-agricultural pesticides and veterinary medicines that will arise from products imported from third countries. This work is included in the research programme. Work is in progress to commission a project to address this.

REPORTING BACK TO THE FOOD STANDARDS AGENCY BOARD

9. The Agency will hold periodic stakeholder meetings to report on progress. The Board will receive a finalised Action Plan and the Agency will report to the Board on progress on all recommendations and on feedback from the initial stakeholder meetings.

CONCLUSIONS

10. The COT considered that the probability of any health hazard from exposures to mixtures of these substances (combined exposure), each present at a low level, is likely to be small and that their effects are unlikely to be anything other than additive. Nonetheless, it identified areas of uncertainty in the risk assessment process and made recommendations for further action. The action plan describes how these recommendations are being taken forward.

⁴ References to documents from The Netherlands and Denmark: Cumulative exposure to acetylcholinesterase inhibiting compounds in the Dutch population (young children) P.E. Boon, J.D. Van Klavern, RIKILT, Combined Actions Of Pesticides In Food, Trine Klein Reffstuf, Institute of Food Safety and Nutrition and Combined Actions Interactions of Chemicals In Mixtures, The toxicological effects of exposure to mixtures of industrial and environmental chemicals, (ISBN 8791399084), Danish State Information Centre.

Glossary

ACP	Advisory Committee on Pesticides
BCC	Biocides Consultative Committee (this deals with non-agricultural pesticides)
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
Defra	Department for Environment, Food and Rural Affairs
DH	Department of Health
EA	Environment Agency
EPA	US Environmental Protection Agency
FSA	Food Standards Agency
HSE	Health and Safety Executive
IEH	Institute for Environment and Health
IGHRC	Interdepartmental Group on Health Risks of Chemicals (formerly ILGRA)
MCA	Medicines Control Agency
PRC	Pesticide Residues Committee
PSD	Pesticides Safety Directorate
VMD	Veterinary Medicines Directorate
VPC	Veterinary Products Committee
VRC	Veterinary Residues Committee

TABLE

COT Recommendation	Actions	Timetable	Comments	Progress to date (August 2007)
	Implementation of the recommendations is envisaged as a two stage process: Stage 1: carry out the necessary underpinning work highlighted by the COT recommendations; and Stage 2: argue vigorously in the relevant bodies (e.g. the European Commission and the Codex Alimentarius Commission) for any necessary changes to EC legislation and international standards.			
STAGE 1				
Regulatory				
<p>11.2 <i>Generate a framework to decide when to carry out combined risk assessments of exposures to more than one pesticide and/or veterinary medicine.</i></p>	<p>FSA, VMD, PSD and HSE will:</p> <ul style="list-style-type: none"> • Identify groups of compounds with common mechanism of action and hence will need to be considered for combined risk assessment. • Prioritise list of groups and publish this after agreement by VPC, ACP and BCC. 	<ul style="list-style-type: none"> • To be determined after the first stage of the IEH work, which is expected by November 2004. 	<ul style="list-style-type: none"> • The first action has been achieved for organophosphates and carbamates. Work has yet to begin prioritising other groups, e.g. pyrethroids, benzimidazoles and conazoles, or on production of a framework. Work has been commissioned with IEH to progress data collection on the remaining groups of compounds. The timescale for completion of the identification and prioritisation of these groups will depend upon the output of this work. 	<p>The IGHRC has recently produced a report "Chemical mixtures: a framework for assessing risks". This is too broad in scope for our specific needs but provides some useful pointers. The US EPA has extensive guidance on cumulative and aggregate risk assessment and also EFSA are currently considering the issue. We are now aiming to distil relevant information from these sources to generate a functional framework adequate for our immediate needs and that could be built upon as knowledge of the UK situation improves.</p> <p>The IEH pilot study on establishing common mechanism groups for pesticides and similar substances is now on the FSA website at: http://www.food.gov.uk/multimedia/word/docs/iehreport.</p> <p>The FSA has published a critique of the US EPA approach to grouping organophosphates and N-methylcarbamates: http://www.food.gov.uk/safereating/pesticides/pestmixbranch/cmgaassessment.</p>

				<p>The Wigramp interdepartmental Science Group has agreed to include both organophosphates and <i>N</i>-methylcarbamates in a single common mechanism group.</p> <p>The Science Group is currently working on establishing a benzimidazoles common mechanism group.</p> <p>The FSA has also commissioned research to identify common mechanism groups of pyrethrins and pyrethroids: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10020/.</p>
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COT Recommendation	Actions	Timetable	Comments	Progress to date
<p>11.3 <i>When it is appropriate to carry out risk assessment of combined exposure, certain toxicological approaches should be taken depending on the type of toxic action and/or interaction.</i></p>	<ul style="list-style-type: none"> • Develop guidelines for carrying out risk assessments based on the information on common mechanism of action groups from 11.2 and exposure data. • An exercise will be undertaken to carry out a combined risk assessment for cholinesterase inhibiting pesticides whose continuing use is supported by the recent ACP reviews of the individual compounds. The exercise will require extension to include pesticides that give rise to residues in imported produce. The outcome of this work will be a document which can be presented to the Commission and other regulatory bodies to show how a regulatory system might operate. 	<ul style="list-style-type: none"> • To be reviewed in light of progress on 11.2 • PSD started work on this exercise during 2003. The initial assessment is due to be completed in October 2004 and work should be finalised by the end of 2004. 	<ul style="list-style-type: none"> • This recommendation is achievable. The guidelines will be used to demonstrate to the Commission how the approach may be used on an EU-wide basis. • Approaches for considering cumulative toxicity in carrying out risk assessments for OPs and carbamates were agreed in Autumn 2003. Work is in progress to carry out the combined risk assessment within the timescale set. 	<p>The Med Tox panel of the ACP has a working paper (unpublished) on cumulative risk assessment. The initial assessment was completed by October 2004. This involves probabilistic modelling using Dutch consumption data and could be updated using FSA data once these have been transformed. As data become available it could be extended to include non-food sources of exposure. The use of both toxicological equivalence factors and an ADI/ARfD approach was explored, both based on the same endpoint.</p> <p>The guidelines are not yet at a stage where they could be presented to the Commission.</p> <p>The FSA is currently formulating UK consumption data for input to the Dutch (MCRA) model.</p> <p>The PRC reports currently include deterministic combined risk assessments of residue mixtures in single commodities. See PRC report with section on multiple residues (pages 30/31): http://www.pesticides.gov.uk/uploadedfiles/Web_Assets/PRC/PRC_2004_Q3_Report.pdf.</p>

COT Recommendation	Actions	Timetable	Comments	Progress to date
<p>11.4 <i>Approval of pesticides and veterinary medicines should include more formal analysis and possibly experimental investigation of the potential for combined toxic action or interaction due to addition of other substances to the formulations employed.</i></p>	<ul style="list-style-type: none"> PSD and HSE will develop guidelines to show how to consider risk from the product not just the active substance. Veterinary medicine assessment is already based on the formulation of the product. Preliminary data on tank mixing (i.e. when two products are mixed together prior to application) in British agriculture has been considered by the ACP. PSD is taking this forward. There are already restrictions on tank mixing of anticholinesterase compounds. 	<ul style="list-style-type: none"> Late 2005 End 2003 	<ul style="list-style-type: none"> The guidelines will be used to demonstrate to the Commission how the approach may be used on an EU-wide basis. No need for veterinary medicines guidelines as assessment is already based on the formulation of the product. No action is considered necessary for co-administration of veterinary medicines because, it is not good veterinary practice to administer products with identical activities. Veterinarians consider aspects of concurrent administration with other treatments. Tank mixes are relevant to people exposed at the time of application, but not to residues in food as they do not differ from those arising from sequential applications. 	<p>PSD has developed guidelines approved by ACP, on the assessment of mammalian toxicity to mixtures of compounds in a pesticide product: http://www.pesticides.gov.uk/uploadedfiles/Web_Assets/PSD/CombinedToxicity20050408.pdf.</p> <p>The Commission has seen this. PSD uses these guidelines for assessing mixtures of compounds in the formulation of a product.</p> <p>VMD currently take product formulation into account when assessing user safety and calculating withdrawal periods.</p> <p>PSD has an R&D project looking at the potential effects of tank mixing on dermal penetration.</p>

COT Recommendation	Actions	Timetable	Comments	Progress to date
<p>11.5 <i>To accommodate analysis of all sources of exposure and concurrent exposure to more than one pesticide will require changes in the methods used for risk assessment, including in some cases, the use of probabilistic exposure assessment.</i></p>	<ul style="list-style-type: none"> The Interdepartmental Liaison Group on Risk Assessment (ILGRA), a subgroup of the Interdepartmental Group on Health Risks from Chemicals (IGHRC), conducted a review of multiple source exposure models and made recommendations regarding an initial aggregate exposure screening methodology, and identified a model which was considered the most appropriate for the UK requirements (CaITOX). The project will need to be extended after evaluation of data available so that sources of exposure such as residential, public hygiene, wood treatment and veterinary medicines such as flea treatments are addressed in case studies. Exposure estimates based on current methodology will be made for organophosphates to be used in conjunction with the combined risk assessment noted under 11.3. PSD will take the lead and the Agency will contribute its expertise on 	<ul style="list-style-type: none"> Project reported in autumn 2003. Interdepartmental workshop to discuss data and models for exposure estimation held on 28 January 2004. Completion depends upon the availability of data on all sources of exposure. Data are available for exposure from food but not from other sources. Data from non-food sources will be collected as part of the project to address recommendation 11.7. This project will be completed in November 2006. 	<ul style="list-style-type: none"> Success depends on the necessary methodology and data on exposure from non-food sources being available. The latter is being progressed under 11.7. Methods reviewed were not considered suitable by FSA. The project will not be supported for extension by FSA to further work on mixtures until the extent and quality of data available for UK exposure assessment has been evaluated by Departments. The timetable to be reviewed following the meeting on 28 January 2004. See 11.3. 	<p>IGHRC has published an evaluation report on current exposure models: http://www.silsoe.cranfield.ac.uk/ieh/pdf/mark_niewenhuijsen_finalreport.pdf.</p> <p>The models recommended use US data, some of which are built into the software. The project will not be extended to include UK case studies using a range of sources of exposure until the extent and quality of UK data is evaluated.</p>

	exposure assessment as necessary.			
COT Recommendation	Actions	Timetable	Comments	Progress to date
11.6 <i>Dietary and food consumption surveys in the UK should continue to cover all social, age and ethnic groups within the population.</i>	<ul style="list-style-type: none"> FSA will feed this recommendation into the current review of the Agency's programme of consumption surveys. Review questionnaire sent in August 2002, report due mid 2003. VMD and PSD consulted in review. 	<ul style="list-style-type: none"> September 2003. 	<ul style="list-style-type: none"> Recommendation was fed into FSA Nutrition Review. Food intake data is currently collected for different age groups. The FSA Board considered a paper on the Review of the Agency's Dietary Survey programme in December 2003, and agreed to move toward a rolling programme of nutrition surveys (subject to further feasibility work). The Board will consider more detailed proposals later in 2004. These will address the different age groups covered by the current National Diet and Nutrition Survey, including children 1.5 to 4.5 years. The collection of new food intake data for infants and pregnant women will be considered separately. 	The FSA's dietary survey programme is moving towards a rolling programme. Fieldwork for a pilot study was completed in July 2007 and fieldwork for the rolling programme is planned to start in April 2008. It is possible that additional urine and blood samples could be taken for pesticide analysis.

COT Recommendation	Actions	Timetable	Comments	Progress to date
<p>11.7 <i>Aggregate exposure assessment will require robust data on all pathways of exposure and sources of variation in such exposure, development of probabilistic exposure assessment, contingent on changes in residue surveillance.</i></p>	<ul style="list-style-type: none"> Data on food and non-food sources of exposure from UK produced and imported products will be collected by setting up a literature-based project to collect all publicly available data. Literature project included in research programme advertisement. Once common mechanism groups identified through 11.2, the project will be extended to collect data from other sources. This will enable us to identify where more data must be generated. HSE will lead on non-food sources of exposure; FSA/VMD/PSD will collaborate to collate other data. A future objective is to identify a mechanism whereby collected data can be kept up to date and in a central repository. 	<ul style="list-style-type: none"> Project started in June 2004. To be completed in November 2006 with interim reports in September 2004 and September 2005. 	<ul style="list-style-type: none"> Robust data on all pathways of exposure to pesticides and veterinary medicines and on sources of variation in exposure will be obtained. Priority is data on non-food sources. HSE to take this forward. Sources of biocide exposure available on outcome of literature project above. Biocidal Products Directive aims to address this across EU. It may be difficult to identify source of exposure if substance also used as a pesticide/ industrial 	<p>There is currently one research project addressing this: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10005/.</p> <p>This uses a CSL dietary exposure assessment model and includes FSA ingredients consumption data. Modelling of the non-food pathways is still in progress.</p> <p>FSA is in discussions with HSE on taking forward the collection of non-food source data and setting up a central depository. The above research project will inform on sources of exposure.</p>

			chemical.	
COT Recommendation	Actions	Timetable	Comments	Progress to date
<p>11.8 Residue surveillance programmes should be modified in the light of the need for representative data for probabilistic exposure assessment. The nature of processing and preparation on the bioavailability and chemical nature of residues should be further investigated</p>	<ul style="list-style-type: none"> Both the PRC and VRC have begun a review of the surveillance programmes. PRC has undertaken a public consultation. The programme for 2003 has been revised as a result and further refinements are likely to be made in the future. A case study for a high priority chemical has been included in the research programme. 	<ul style="list-style-type: none"> PRC review started in 2002 and completed in 2003. High priority groups must be identified first. 	<ul style="list-style-type: none"> Success depends on there being a cost effective way of collecting data on multiple residues of veterinary residues. Both the PRC and VRC have acknowledged the need for collection of statistically representative data. Resources will need to be prioritised. The PRC may organise some larger surveys to provide more representative data, but must work within resource constraints and take into account the compliance monitoring aims of the programme. 	<p>The FSA and PSD have agreed to collaborate on producing a paper for the PRC on representative sampling. A similar paper will need to be presented to the VRC. The scope for representative sampling is heavily constrained by current resources for the surveillance programmes.</p> <p>Details of current residue surveillance programmes can be found at: http://www.pesticides.gov.uk/prc.asp?id=955 http://www.vet-residues-committee.gov.uk/.</p> <p>Processing, preparation, bioavailability and the chemical nature of residues is being investigated in two research projects commissioned by the FSA:</p> <p>http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10018/.</p> <p>http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10019/.</p>

COT Recommendation	Actions	Timetable	Comments	Progress to date
<u>Research</u>				<p>The FSA has commissioned 17 research projects to meet the COT recommendations.</p> <p>Details of the research programme dealing with mixtures can be found at: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/.</p>
<p>11.9 Develop methods to provide cost effective biomarkers or other robust indicators of population exposure and body burdens of mixtures of pesticides and relevant veterinary residues.</p>	<ul style="list-style-type: none"> Research to develop methods to show whether people have been exposed to mixtures (biomarkers of exposure) included in programme advertisement. See Chapter 6 of Report. 	<ul style="list-style-type: none"> 5 year programme. FSA call went out on 8 May 2003, resulting in a project which started in March 2004 (to include OPs, carbamates, benzimidazoles, pyrethroids and dithiocarbamates. A further call was 	<ul style="list-style-type: none"> The methods developed will be equally applicable to single pesticides and other substances. 	<p>Information on research into developing biomarkers of exposure to mixtures of substances can be found at: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10003/.</p> <p>A complementary project on OPs and carbamates started in October 2004: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10</p>

		issued in January 2004. Commissioning of complementary project on OPs and carbamates is in progress.		009/ . Two further projects have been commissioned: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10013/ . http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10021/ .
COT Recommendation	Actions	Timetable	Comments	Progress to date
11.10 Develop markers to enable early and reliable detection of systemic responses and health effects arising from such exposures.	<ul style="list-style-type: none"> Research to develop methods to show whether harm has arisen from exposure to mixtures (biomarkers of effect) included in programme advertisement. See paragraphs 6.12-6.14 of COT Report. 	<ul style="list-style-type: none"> 5 year programme. FSA call went out on 8 May 2003, resulting in a project on Ops, which started in March 2004. A further call was issued in January 2004. Commissioning of a complementary project on OPs work is in progress. 	<ul style="list-style-type: none"> The methods developed will be equally applicable to exposures to single pesticides. 	<p>Information on research into developing biomarkers of toxicological effects following exposure to mixtures of substances can be found at: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10002/.</p> <p>A complementary project on OPs started in April 2005: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10010/.</p> <p>One further project has been commissioned: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10014/.</p>

<p>11.11 <i>Characterisation of possible variability in human responses to mixtures of residues.</i></p>	<ul style="list-style-type: none"> • Research to look at differences in responses by groups such as children, the elderly and those with particular genetic susceptibility included in programme advertisement. 	<ul style="list-style-type: none"> • 5 year programme. FSA call went out on 8 May 2003. No suitable proposals were received. A further call was issued in January 2004. Commissioning is in progress for a project on variability in metabolism of pesticides singly and in combination. 		<p>Information on research to investigate the influence of genetic variability in enzyme activity on the toxicity of mixtures of pesticides can be found at: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10011/.</p> <p>One further project has been commissioned: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10015/.</p>
COT Recommendation	Actions	Timetable	Comments	Progress to date
<p>11.12 <i>Experimental research to characterise nature of and dose-response relationships for combined actions.</i></p>	<ul style="list-style-type: none"> • Research to investigate additivity or independent or synergistic effects included in programme advertisement. 	<ul style="list-style-type: none"> • 5 year programme. FSA call went out on 8 May 2003. A project on mixtures of oestrogenic chemicals started in June 2004. A further call was issued in January 2004. Commissioning of a project on anticholinergic carbamates and 		<p>Information on research into the potential interaction of mixtures can be found at: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10008/.</p> <p>Information on research into establishing a concentration-effects curve for mixtures of oestrogenic compounds can be found at: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10004/.</p>

		OPs is in progress.		<p>Two further projects have been commissioned: http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10016/.</p> <p>http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10017project/.</p>
Additional Work				
<i>Assessment of the impact of the recommendations within the EU alone taking into account the exposure to products that will be imported from outside the EU.</i>	<ul style="list-style-type: none"> • Research to obtain an estimate of the size of effect of protection from implementation of the COT recommendations within the EU and not world-wide. • Requirement included in FSA research programme advertisement published on 8 May 2003. 	<ul style="list-style-type: none"> • This work has been commissioned as one of the later deliverables of the project described at 11.7. Anticipated completion date is November 2006. 		The project under 11.7 will include this.

COT Recommendation	Actions	Timetable	Comments	Progress to date
<p>STAGE 2</p> <p>11.1 <i>Change to approval system such that pesticide and veterinary medicine authorisation considers mixtures from all sources of exposure</i></p>	<ul style="list-style-type: none"> • All departments will seek international support for these changes, in particular with the European Commission, regulatory authorities in other member States and through the committees of the Codex Alimentarius Commission which develop guidelines. In particular: FSA will take work forward in the Pesticide Codex Committees; and PSD will lobby for changes in the EC during revision of Council Directive 91/414/EEC. • VMD will lobby for changes in the EC to Council Directive 2001/82 once the revisions currently being negotiated have been agreed (it is not possible to introduce new changes at this stage of the negotiations). • The Biocidal Products Directive already requires assessment of exposure for use of all biocidal products containing the same active substance. • Member States and the European Commission have agreed that where a biocidal substance is also regulated by other Directives, concerns from multiple exposures may occur. They have agreed that the policy for handling this would need to be developed 	<ul style="list-style-type: none"> • From March 2003. • Dependent on timing of Commission's proposal but unlikely until late 2005. • From June 2004. • From April 2003 as BPD reviews 23 types of product. Review unlikely to be completed before 2013. 	<ul style="list-style-type: none"> • Success depends on the adoption of the approach into the EU regulatory and CODEX advisory systems • Section 7.1.8 of the draft revised mammalian toxicology testing requirements under Directive 91/414 includes text on considering mixtures. <p>EFSA panel discussion scheduled for 2006.</p>	<p>Both the proposed replacement for Directive 91/414/EEC and the new MRL Regulation (396/2005) include taking into account known cumulative and synergistic effects, when the methods to assess such effects are available.</p> <p>The EFSA PPR Panel is to evaluate the assessment of cumulative and synergistic risks from pesticides to human health in relation to setting MRLs. An opinion is expected before the end of 2007.</p>

COT Recommendation	Actions	Timetable	Comments	
STAGE 2				
11.1 <i>continued</i>	under a wider chemicals framework. In the interim, if a concern is highlighted under the BPD this will be brought to the attention of the relevant Scientific Committee.			
	<ul style="list-style-type: none"> Mixtures of active substances in products will be considered at MS level when authorisation of a product is requested. 	<ul style="list-style-type: none"> As applications are received. 		
	<ul style="list-style-type: none"> Exposures from products containing different active substances having a common mechanism of action will be taken forward by HSE in the EU once appropriate measures for handling this issue have been developed in the UK. 	<ul style="list-style-type: none"> To be taken forward as the reviews begin for those substances for which measures have been identified in the UK. 		
	<ul style="list-style-type: none"> Actions to take forward 11.5, 11.7 and 11.8 are intended to provide the data needed to make aggregate assessments. 			

COT Recommendation	Actions	Timetable	Comments	
<p>11.13 <i>Set up central and accessible repository of information about all forms of human exposure to pesticides and similar substances – on a web site or paper repository.</i></p>	<ul style="list-style-type: none"> The data collected under 11.7 will be collated and made accessible to public. Any data base needs to be kept up to date and a mechanism to achieve this must be put in place. 	<ul style="list-style-type: none"> To begin when data have been collected for use in aggregate exposure assessments (11.7). 	<ul style="list-style-type: none"> 	
<p>11.14 <i>Review extent and adequacy of information available to the domestic user of pesticides and veterinary medicines for its extent and ease of comprehension.</i></p>	<ul style="list-style-type: none"> Information is already publicly available – sources are product labels, publications on reviews of active substances, annual reports from the ACP. 	<ul style="list-style-type: none"> To begin when outcome of changes to assessment process is complete. 	<ul style="list-style-type: none"> Extent and content of information that needs to be disseminated will depend on outcome of changes to assessment process. 	

RECOMMENDATIONS FROM THE REPORT

Regulatory

11.1 We recommend that the approval of pesticides used on crops, and authorization of similar compounds used in veterinary medicine should consider all sources of exposure.

11.2 We recommend that a scientific and systematic framework should be established to decide when it is appropriate to carry out combined risk assessments of exposures to more than one pesticide and/or veterinary medicine.

11.3 In the event that it is considered appropriate to carry out risk assessment of combined exposure, the default assumptions should be that chemicals with different toxic actions will act independently (simple dissimilar action), and those with the same toxic action will act additively (simple similar action). In the latter circumstances a toxic equivalency approach might be considered. In specific instances the possibility of interaction, particularly potentiation, may have to be considered. In such circumstances adequate dose-response data will be essential in the interpretation of findings in relation to dietary intakes and other human exposures.

11.4 We recommend that the approval of pesticides and authorization of compounds used in veterinary medicine, should include more formal analysis, and possibly experimental investigation, of the potential for combined toxic action or interaction due to the addition of other substances to the formulations employed. This consideration should also include tank mixes of pesticides.

11.5 Analysis of all sources of exposure to pesticides and of concurrent exposure to more than one pesticide will require changes in the methods used for risk assessment, including, in some cases, the use of probabilistic exposure assessment. This will be contingent on changes in residue surveillance.

Surveillance

11.6 Dietary and food consumption surveys in the UK should continue to cover all social, age, and ethnic groups within the population. Consideration should be given as to whether additional groups need to be covered.

11.7 Aggregate exposure assessment will require acquisition of robust data on all pathways of exposure to pesticides and veterinary medicines and on sources of variation in such exposure.

11.8 We recommend that residue surveillance programmes should be modified in the light of the need for representative data for probabilistic exposure assessment. The effect of food processing and preparation on the bioavailability and chemical nature of residues should be further investigated.

Research

11.9 We recommend that methods be developed to provide valid and cost-effective biomarkers or other robust indicators of population exposure and systemic (body) burdens of mixtures of pesticides and relevant veterinary residues.

11.10 We recommend that valid markers be developed to enable the early and reliable detection of systemic responses and health effects arising from such exposures (biomarkers of effect).

11.11 This work should be extended to the characterisation of the possible variability in human responses to mixtures of pesticides and veterinary medicines.

11.12 We recommend that further work be undertaken, in suitable experimental systems, to characterise both the nature of, and dose-response relationships for, combined actions of pesticides, veterinary medicines and similar substances. Such studies should be performed at doses that include those potentially ingested by humans in the diet. Groups of pesticides having common targets of toxicological action should be identified. Such work might include the identification of sites of action at a molecular level, to identify those groups of compounds that would be expected to show simple similar action. Studies of protein and/or RNA expression, using modern array technology, in relevant systems may be appropriate in some cases. These may be followed up by more detailed mechanistic studies of gene expression and/or enzyme or hormonal activity as necessary. Array technology (RNA and proteins) may be appropriate in some cases, or enzyme or hormonal activity in others.

Public information

11.13 A central and accessible repository of information about all forms of human exposure to pesticides and similar substances should be established.

11.14 The extent and adequacy of the information available to the domestic user of pesticides and veterinary medicines requires review of its extent and ease of comprehension.