

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

**Food Standards Agency
July 2003**

PREAMBLE

The draft 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 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 draft 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 Control Agency (MCA) and the Environment Agency (EA) have also been kept informed of developments.

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

Comments are sought from Stakeholders on the Action Plan attached.

Please note:

The draft 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 of these substances with a **similar toxicological mode of action and substances may thus 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.
2. 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.
3. 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).

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 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, PSD and VMD have all committed themselves to funding research.
 - The Agency's requirement for new research was published on 8 May 2003.
 - An External Programme Co-ordinator to manage the research programme has been appointed by the Agency.

- A project is already underway which is funded by the Interdepartmental Liaison Group on Risk Assessment (ILGRA) to evaluate the suitability of current exposure methodology for use in combined risk assessment. This is the first step to developing a methodology for estimating the aggregate exposure for various population groups;
- The Pesticide Residues Committee and Veterinary Residues Committee are reviewing surveillance programmes and are considering how to address the COT's recommendation to modify the surveillance programmes.
- 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. Although 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 is reviewing all organophosphate and carbamate cholinesterase-inhibiting agricultural and non-agricultural pesticides in use in the UK. The ACP will now carry out a combined risk assessment for this group of compounds and experience from this exercise will be fed into the work in implementing recommendations 11.2 and 11.3.
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' <http://europa.eu.int/comm/environment/ppps/home.htm>) 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' http://europa.eu.int/comm/press_room/press_packs/health/pp_health_en.htm) that focussing on single pollutants will lead to 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 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.

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.

REPORTING BACK TO THE FOOD STANDARDS AGENCY BOARD

9. The Agency will hold periodic stakeholder meetings to report on progress. 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.

Glossary

ACP	Advisory Committee on Pesticides
BCC	Biocides Consultative Committee (this will deal with what are currently called non-agricultural pesticides)
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
Defra	Department for the 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
IGHRC	Interdepartmental Group on Health Risks of Chemicals
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

Recommendation	Actions	Timetable	Comments
	<p>Implementation of the recommendations is envisaged as a two stage process:</p> <p>Stage 1: carry out the necessary underpinning work highlighted by the COT recommendations; and</p> <p>Stage 2: argue vigorously in the relevant bodies (e.g. the European Commission and the Codex Alimentarius Commission) for changes to EC legislation and international standards.</p>		
STAGE 1 - UNDERPINNING WORK			
<p>11.2 Generate a framework to decide <i>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"> Autumn 2003 Mid 2004 	<ul style="list-style-type: none"> This recommendation is achievable.
<p>11.3 When it is <i>appropriate to carry out risk assessment of combined exposure</i>, certain toxicological approaches should be taken depending on the type of toxic action and/or interaction.</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. 	<ul style="list-style-type: none"> Late 2003 to review progress PSD will start work on this exercise during 2003. Completion date Mid-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.
	<p>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 based on assessment of mixtures might operate</p>		

Recommendation	Actions	Timetable	Comments
<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.

Recommendation	Actions	Timetable	Comments
<p>11.5 To accommodate <i>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"> • A one year research project funded by Interdepartmental Group on Health Risks from Chemicals (IGHRC) has begun that will review currently available methods for exposure assessment and choose one or more for evaluation. • The project will need to be extended 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 exposure assessment as necessary. 	<ul style="list-style-type: none"> • Project to report in autumn 2003. • To be considered autumn 2003 • Mid 2004 	<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.
Surveillance			
<p>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></p>	<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"> • Success is readily achievable.

Recommendation	Actions	Timetable	Comments
<p>11.7 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.</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: <ul style="list-style-type: none"> • setting up 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"> • Call published by FSA on 8 May 2003 • After autumn 2003 	<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.
<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"> • Started in 2002 and to be 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.

Recommendation	Actions	Timetable	Comments
Research			
11.9 <i>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.</i>	<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. 	<ul style="list-style-type: none"> The methods developed will be equally applicable to single pesticides and other substances.
11.10 <i>Develop markers to enable early and reliable detection of systemic responses and health effects arising from such exposures.</i>	<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. 	<ul style="list-style-type: none"> The methods developed will be equally applicable to exposures to single pesticides.
11.11 <i>Characterisation of possible variability in human responses to mixtures of residues.</i>	<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. 	
11.12 <i>Experimental research to characterise nature of and dose-response relationships for combined actions.</i>	<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. 	
Additional work			
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.	<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"> Time-scale to be decided but will be less than 1 year to completion 	

Stage 2			
<p>11.1 Change to approval system such that pesticide and veterinary medicine authorisation considers mixtures from all sources of exposure</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, 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 other Directives, concerns from multiple exposures may occur. They have agreed that the policy for handling this would need to be developed under a wider chemicals framework. In the interim, if a concern is highlighted under the BPD this will be brought to the attention of 	<ul style="list-style-type: none"> • From March 2003 • Autumn 2003 (depending on timing of Commission's proposal) • From June 2004 • From April 2003 as BPD reviews continue • As BPD reviews continue 	<ul style="list-style-type: none"> • Success depends on the adoption of the approach into the EU regulatory and CODEX advisory systems

	<p>the relevant Scientific Committee.</p> <p>Mixtures of active substances in products will be considered at MS level when authorisation of a product is requested.</p> <p>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.</p> <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. 	<ul style="list-style-type: none"> • As applications are received • 2004/5 onwards 	
<p>11.13 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.</p>	<ul style="list-style-type: none"> • The data collected under 11.8 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 (11.8). 	
<p>11.14 Review extent and adequacy of information available to domestic user of pesticides and veterinary medicines of its extent and ease of comprehension</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. 	<p>Extent and content of information that needs to be disseminated will depend on outcome of changes to assessment process.</p>

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.