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EFSA SCIENTIFIC COLLOQUIUM
SUMMARY REPORT

CUMULATIVE RISK ASSESSMENT OF PESTICIDES TO HUMAN HEALTH: THE WAY FORWARD

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CUMULATIVE RISK ASSESSMENT OF PESTICIDES TO HUMAN HEALTH:

THE WAY FORWARD

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About EFSA

The European Food Safety Authority (EFSA) was established and funded by the European Community as an independent agency in 2002 following a series of food scares that caused the European public to voice concerns about food safety and the ability of regulatory authorities to fully protect consumers.
In close collaboration with national authorities and in open consultation with its stakeholders, EFSA provides objective scientific advice on all matters with a direct or indirect impact on food and feed safety, including animal health and welfare and plant protection. EFSA is also consulted on nutrition in relation to Community legislation.
EFSA's work falls into two areas: risk assessment and risk communication. In particular, EFSA's risk assessments provide risk managers (EU institutions with political accountability, i.e. the European Commission, European Parliament and Council) with a sound scientific basis for defining policy-driven legislative or regulatory measures required to ensure a high level of consumer protection with regard to food and feed safety.
EFSA communicates to the public in an open and transparent way on all matters within its remit.
Collection and analysis of scientific data, identification of emerging risks and scientific support to the Commission, particularly in case of a food crisis, are also part of EFSA's mandate, as laid down in the founding Regulation (EC) No 178/2002 of 28 January 2002.

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PREFACE

I am very pleased to provide you with this booklet on Cumulative Risk Assessment of Pesticides in the Scientific Colloquium Report Series. This booklet contains the summary report as well as all relevant background documentation of EFSA's Science Colloquium entitled: Cumulative Risk Assessment of Pesticides to Human Health: the Way Forward.

This seventh Colloquium organised by EFSA took place in Parma, Italy, on 28 and 29 November 2006 and was attended by some 100 participants from nearly all Member States, Bulgaria, Romania, Turkey, USA, and Australia.

EFSA organised this Colloquium to allow for an open scientific debate on methods available and data needed for conducting a cumulative risk assessment for pesticides with a common mode of action as well as to explore the scientific basis for combining some pesticides, not sharing a common mode of action, in a hazard assessment. Participants discussed the choice of data and methodology for combined exposure assessment; and possibilities for joining efforts internationally to further develop harmonised approaches.

The meeting proved very successful indeed with useful considerations for the Panel on plant protection products and their residues (PPR-Panel) as well as for cumulative risk assessment outside the pesticides remit. Participants agreed that it was important to get started with cumulative risk assessment in a step-wise approach. The first priority will be substances that share a common mode of action (dose addition) for which data are already available in the US. Good models do exist and could be used. Methodologies are not yet defined and may vary regarding compound and type of exposure (acute, chronic). Guidelines will be needed for probabilistic modelling and cumulative exposure and cooperation between Member States, other bodies and EFSA will be necessary to establish these.

I am thankful for the contributions of all participants and for the open and lively discussions. Special appreciation is expressed to the Co-Chairs of the Colloquium, the Chairs and Rapporteurs of the various discussion groups and, in particular, to Ian Dewhurst and Rolaf van Leeuwen who drafted the summary report of the meeting.

Herman B.W.M. Koëter
Deputy Executive Director
and Director of Science

I. INTRODUCTION

EFSA Science Colloquia aim to achieve a better understanding of the fundamental scientific issues related to risk assessment for food and feed and are therefore organised in a way to provide ample opportunity for an interactive exchange of expert views. To that end the Science Colloquia are sufficiently informal to allow for substantial debates if needed. However, at the same time, they are adequately structured and managed to enable participants to reach conclusions and make recommendations, as appropriate. This Colloquium on *Cumulative Risk Assessment of Pesticides to Human Health: The Way Forward* was the seventh in this series.

Regulation (EC) No. 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin emphasises the importance to develop a methodology to take into account cumulative and possible synergistic effects of pesticides to human health. There is no generally agreed framework/approach yet for combined risk assessment of pesticides at the European or International level. However, there are activities ongoing at European and International level concerning approaches to cumulative risk assessment of pesticides which have a common mode of action. In the light of these developments EFSA considered it timely to organise a scientific colloquium to evaluate existing methodologies, and, if appropriate, identify new approaches. The outcome of this colloquium will provide a contribution to EFSA PPR Panel discussions.

The objectives of the colloquium were to:
(i) have an open scientific debate on the advantages and disadvantages of the scientific approaches and methods available and data needed for conducting a cumulative risk assessment for pesticides with a common mode of action (dose-addition);
(ii) explore the scientific basis for combining some pesticides, which do not share a common mode of actions (response-addition, possible synergistic or antagonistic effects), in a hazard assessment;
(iii) discuss the choice of data and methodology for combined exposure assessment; and (iv) discuss possible joint efforts between EU Member States, EFSA, and possibly non-EU Member States and international organisations to further develop harmonised approaches to performing combined risk assessments of pesticides.

The meeting took place in the Star Hotel du Parc, Parma on 28 and 29 November 2006 and was attended by just over 100 participants from nearly all Member States, Bulgaria, Romania, Switzerland, Turkey, USA, and Australia. Details of the programme and a list of participants can be found at Annexes 1 and 2 respectively.

The Colloquium started with some general presentations, which outlined the issues, described the underlying science and presented information on cumulative risk assessments for pesticides that had already been conducted. Slides from these presentations are presented in Annex 3. Key points from these presentations included:

- Cumulative risk assessment is a term that can create confusion: in the framework of the current discussion, it refers to the assessment of the risk from exposure to more than one pesticide;
- Pesticide residues are a high level concern for EU consumers, and consumers should be better informed about the risk arising from pesticides;
- Multiple residues of pesticides have commonly been found in EU monitoring schemes using composite samples;
- A number of methodological options exist with respect to consumption, residue and effect data; a pragmatic strategy needs to be developed and agreed to within the EU;
- Basic science indicates that compounds with similar mechanisms of toxicity will act with dose addition;
- Many effects exhibit a sigmoidal dose-response, and there is a need to take aspects of the dose-response curve(s) into account when considering combined toxicity;
- Determining which compounds should be in a common mechanism group is not straightforward as the necessary data are often not available from routine regulatory studies;
- If additional data / research are required, which organisations should sponsor this?;
- When, how frequently, and by whom should cumulative risk assessments be performed, and how should new compounds and new uses be incorporated?;
- Cumulative risk assessments could be very resource intensive, therefore some screening / prioritisation stage should be considered.

Participants then divided into 4 discussion groups (DG) to discuss and debate various aspects of cumulative risk assessments of pesticides. Discussion groups 3 and 4 held a brief combined session to agree on common points. The discussion groups reported back to the plenary session and a general discussion took place. The themes and topics addressed by the discussion groups were:

DG1: Cumulative hazard assessment

- What are the criteria for grouping compounds into a common mechanism group?
- Can any advice be given on which groups of pesticides should be prioritized, e.g. Organophosporus compounds (Ops), pyrethroids, on the basis of the toxicological endpoint or other considerations?
- What method(s) should be used to estimate cumulative hazard, e.g. TEF/PEF (toxicity/potency equivalency factors), or combined MOE (margin of exposure). What are the relative advantages and disadvantages of these methods?
- What point of departure (e.g. No Observed Adverse Effect Level (NOAEL), benchmark dose) should be used in estimating hazard for the purposed of a cumulative risk assessment?
- What are the minimum data requirements for including a compound in such an assessment? If these are not met, what defaults should be used, e.g. are there circumstances where it could be assumed that a compound should be considered in a particular common mechanism group, in the absence of information to the contrary?

DG2: Non-dose-addition effects

- What combined effects are of concern, e.g. effect addition, synergy?
- What toxicological effects are of concern from combined exposures? Can these be prioritized?
- How should compound groups be identified for such consideration?
- What default assumptions should be used in such an assessment?
- What study design would be necessary to enable such assessments to be undertaken, i.e. that enables the nature and magnitude of the combined effect to be determined? How can the various forms of combined effect be distinguished most easily and pragmatically?
- What method(s) should be used to estimate combined hazard, e.g. TEF/PEF (toxicity/potency equivalency factors), combined MOE (margin of exposure). What are the relative advantages and disadvantages of these methods?
- What point of departure (e.g. NOAEL, benchmark dose) should be used in estimating hazard for the purposed of a combined risk assessment?
- What are the minimum data requirements for including a compound in such an assessment? If these are not met, what defaults should be used e.g. are there circumstances where it could be assumed that a compound should be considered in a particular combined risk group, in the absence of information to the contrary?

DG3: Choice of data for combined exposure

Scenarios

- Consider if there is a need to distinguish between actual exposure assessments and assessment of the safety of MRLs.
- Do acute and chronic exposures need to be considered for each type of assessment?
- Is it appropriate to consider all food types together?

Consumption data

- What are the sources of information, how are the data collected?
- Are data available for the general population and relevant subgroups?
- Use of the individual records from surveys or use of distributions modeled from surveys?
- Include seasonal/regional patterns?
- How to deal with "outliers"?
- Timelines and frequency of consumption surveys?
- Quality of the data, e.g. how many individuals per commodity?
- How to deal with uncertainty and variability?
- How can an interdependence of consumption levels be taken into account?

Residue data

- What are the sources of information, how are the data collected?
- Should the input be residue data from monitoring studies, from supervised field trials or a combination (e.g. in the case of MRL setting, should one use field trial data for the commodity in question and monitoring data for the "background", i.e. all other commodities)?
- Include seasonal/regional patterns?
- How to deal with "outliers"?
- How to deal with processed commodities (e.g. juices)?
- Quality of the data, e.g. valid analytical methodology, assessing the residue of concern, etc.?
- How to deal with uncertainty and variability?
- How can an interdependence of residue levels be taken into account?

DG4: Methodology for combined exposure

- What methodology should be chosen in order to assess consumer exposure to residues of pesticides – could either deterministic or probabilistic methods be used?
- What are the criteria for a model to estimate combined exposure?
- What are the requirements for the model?
- How to deal with uncertainty and variability?
- Interpretation of the results, when should safety concerns be raised?
- Which models are now available and what are the lessons learnt in their development?
- Is one of the models appropriate or should a new model be developed?

Prof. Alan Boobis (*Imperial College London, UK*) and Dr. Ursula Banasiak (*Federal Institute for Risk Assessment, Germany*) were co-chairmen. Dr. Rolaf van Leeuwen (*National Institute for Public Health & Environment, Netherlands*) and Dr. Ian Dewhurst (*Pesticides Safety Directorate, UK*) acted as overall rapporteurs. Prof. David Coggon (*University of Southampton, UK*), Prof. Corrado Galli (*University of Milan, Italy*), Dr. Bernadette Ossendorp (*National Institute for Public Health & Environment, Netherlands*) and Mr. David Miller (*US Environmental Protection Agency, USA*) offered to be discussion group chairs; while Prof. Angello Moretto (*University of Milan, Italy*), Dr. John Christian Larsen (*Danish Institute for Food and Veterinary Research*), Dr. Britta Michalski (*Federal Institute for Risk Assessment, Germany*) and Dr. Caroline Harris (*Exponent International, UK*) were the corresponding discussion group rapporteurs.

II. SUMMARY OF THE DISCUSSIONS

Discussion Group 1: Cumulative hazard assessment

Before moving to the main discussion topics, the discussion group clarified some aspects of terminology. Whereas understanding the mechanism of action requires the knowledge of the specific biochemical events leading to toxicity, the characterisation of certain key events that are most crucial in causing the toxicity is sufficient to identify mode of action. It was considered that grouping of compounds can be made on the basis of a common mode of action; in the context of the colloquium and of this report common mechanism of action is used in a broader sense to encompass a common mode of action.

The group's discussions concentrated on 5 main headings:

Criteria for grouping compounds into a common mechanism group

A number of existing frameworks and guidelines are already available that set out criteria to **identify and define a common mechanism group of compounds (e.g. EPA , ILSI , IPCS).** In most instances Structure-Activity Relationship might be used to establish a preliminary grouping of compounds and initiate an evaluation of common mechanisms of toxicity.

For more in-depth assessments, toxicity data need to be considered. Identification of the mode of action can be relatively easy when there is a well established critical single target (e.g: neural acetylcholinesterase for organophosphorous compounds and carbamates). However, the presence of multiple targets (e.g. pyrethroids and endocrine disruptors) and feed-back mechanisms (e.g. endocrine disruptors) might complicate the identification of a common mechanism group. There are currently different approaches and options regarding strength of evidence for commonality of mode of action. For example, the US EPA preference is for grouping only when the scientific basis is sound enough. This approach can be compromised by the lack of information on mode/mechanism of toxic action of many pesticides, as well as by the limited basis (within the EU) for requiring mechanistic studies. Data would have to be obtained from the open literature or, as in the case of EPA, from specially commissioned studies. Alternatively, a simpler and possibly more conservative approach is to assume a common mode of action when compounds have the same end-effect and when there is no evidence indicating a different mode of action. With this approach, more uncertainty will be introduced regarding the assumption of dose addition. Also, there are likely to be, more compounds in a common mechanism group or more common mechanism groups identified.

The discussion group proposed that a higher priority be given to groups of compounds for which there is sound scientific evidence of a common mechanism/ mode of action and less uncertainty regarding the assumption of no interactions other than additivity on the common mechanism of toxicity.

Groups of pesticides to be prioritised

Initially, the group discussed the fundamental basis for prioritisation and concluded that prioritisation should be based on public health and scientific considerations and not driven by "interest groups".

A number of tools that could assist prioritisation were identified and discussed. Epidemiological evidence was considered unlikely to provide useful information in most instances. Biomonitoring data for the general population might indicate the most frequently found compounds (or their metabolites), and also provide information on possible geographical or social differences (e.g.: agricultural areas vs urban areas). Analyses performed as part of the NHANES project in the USA (http://www.cdc.gov/exposurereport) have produced data on pesticides, but there was uncertainty about the viability of performing such work across the EU. As mentioned previously, compounds for which there is a clear understanding of the mode of action or of a common target with a possibly common mode of action, were considered to merit a high priority. Groups that include compounds with "low" reference doses in the context of their usage patterns or of results from monitoring programmes should be more closely scrutinised than those for which predicted exposures are only a small percentage of reference doses.

A lack of high quality data on toxicology or dietary exposure should not be a reason for dismissing a group of compounds. Rather, the lack of data might be a stimulus for further investigation. The assessment should start where data are available, but the missing information should always be kept in mind.

The use of existing assessments (e.g.: those produced by EPA) must be considered. In particular, it was noted that toxicological evaluations can be adapted from other bodies' assessments, whereas dietary assessment should be done for the specific (European) scenario. However, if cumulative assessment elsewhere showed no problems, this indicated a low priority in Europe unless use patterns were clearly different. As a consequence it was stressed that global cooperation needs to be improved and promoted.

Use patterns and residue monitoring data should be considered in setting priorities:

- Routine findings in monitoring data of compounds from a common mechanism group, including non-approved uses;
- Compounds found on the most highly consumed food items or associated with food items that play a significant part in the diet of certain sub-groups (e.g.: children);
- Market analysis showing what are the most widely used pesticides and on what crop(s);
- Food items that require / receive multiple treatments;
- An analysis of likely future trends in uses (e.g.: new products coming to the market; old products likely to lose their market share);
- Sources of exposure other than pesticides in food, such as biocides; veterinary drugs; drinking water; occupational exposures and naturally occurring compounds should be taken into account, at least qualitatively.

Groups of compounds that most likely need to be prioritised on the basis of hazard and, partly, exposure considerations were:

- Organophosphorus (OP) compounds: there were many compounds within the group but to date only one had completed its re-evaluation and been placed on the list of authorised substances under the EC pesticides legislation (Annex 1 of 91/414/EC);
- Carbamates (cholinesterase inhibiting): only acute exposure might need to be considered, and there might be scope for combining the assessment with that for the OPs;
- Conazoles: there are many compounds within the group; prioritisation in the USA was awaiting data from ongoing research that might clarify the basis for grouping such compounds;
- Pyrethroids: the possibility of sub-grouping was considered and note was taken of ongoing research in the USA;
- Dicarboximides (vinclozolin, procymidone, chlozolinate and iprodione):
- Microtubule / Spindle inhibitors;
- Phthalimides (captan and folpet);
- Dithiocarbamates.

For the latter groups, and possibly others, a cumulative assessment is normally performed by default as the analytical method determines a common residue e.g. as CS_2 for dithiocarbamates.

Methods of estimating cumulative hazard and their advantages and disadvantages

The Hazard Index approach, where the sum of the individual ratios of exposure: reference dose should be less than 1, already includes safety factors. It is suitable for rapid screening as the reference doses are generated during the individual evaluations but might not work well with existing probabilistic software packages. Reference dose values are influenced by the choice of dosing levels / spacing possibly leading to communication problems. Additional work is required to produce an adjusted hazard index if the original reference dose is not based on the end-point for the common mechanism group.

The Point of Departure Index (PODI) uses the sum of the ratios of exposure to a point of departure for each individual compound. The POD is based on the critical effect for the common mechanism group. The sum should be less than the agreed group safety factor, which need not be the defaults (e.g. 10 x 10) used for setting reference values. The POD can be an NOAEL or an interpolated value e.g. a benchmark dose (see below). The Margin of Exposure (MOE) approach is the reciprocal of the PODI and similar considerations apply.

The stage at which safety (uncertainty) factors are applied differs between the available methods. Irrespective of the method used to cumulate there should always be a clear statement regarding the safety factors applied, even if this is only qualitative. Science policy input to the risk assessment (e.g. permitting or not permitting the use of human data) should also be transparent.

The Toxic Equivalents Factor (TEF) or Relative Potency Factor (RPF) uses the toxic potency of members of the common mechanism group to normalise exposures to an index compound. The summed exposures are then compared with the reference dose for the index compound. It requires a high level of confidence in the common mode of action and relies heavily on having high quality data on the index compound. TEFs have been widely used (e.g. dioxins), work well with existing probabilistic modelling software, and permit the TEF / RPF to be adjusted to fit the database (e.g. for age, sex, study duration, availability of human data).

For all the approaches, *in vitro* data could be of value in identifying the common end-point to be addressed *in vivo*.

Point of departure to be used in estimating hazard in cumulative risk assessment

Both available approaches, NOAEL and benchmark dose have advantages and disadvantages that vary with the data available. Regulatory toxicology studies were designed for purposes of identifying NOAELs and LOAELs (the dose where changes become statistically and / or biologically (in-) significant) for individual compounds. The NOAEL (and LOAEL), however, is dependent on the dose spacing in the study protocol (which might be large or small). The entire dose response is utilized in deriving a benchmark dose (BMD). The BMD provides a better index of potency and a more consistent basis to compare potency among a group of compounds. The BMD approach is a technical exercise that requires time and proficiency to carry out reliably. Good dose response data are needed to provide estimates of BMDs with small confidence intervals. At minimum, it is preferable to have two responding groups on the linear part of the dose-response curve, which may not fit well with results from current regulatory studies. An advantage of the BMD is that it provides a measure of variability and thus a means to quantify the uncertainty with weaker data sets. Nonetheless, more resources (time and data) are needed compared to the adjusted hazard index.

If an existing study, which provides a NOAEL/LOAEL, is unsuitable for deriving a benchmark dose and additional data are required, then animal welfare aspects need to be considered. For new compounds where there is no existing data, studies compatible with benchmark dose derivation should not use more animals than traditional protocols designed to provide NOAELs.

Minimum data requirements for including a compound in a cumulative assessment - if not met, what defaults should be used?

The minimum data requirements are dependent on other decisions such as how refined the risk assessment needs to be and the degree of certainty required for defining the common end-point and mode of action.

Ideally, data should be available to i) define the key events to identify the mode of action; ii) provide adequate information on the dose-response to allow good estimates of benchmark doses; iii) identify the time course of effects, for use in acute and chronic assessments; iv) provide information on representative mixtures.

The absolute minimum data set should be that required to support authorisation of the individual compounds. Where there are uncertainties or missing information these should be described. The uncertainties could be described qualitatively, semi-quantitatively or by using calculated upper and lower confidence limits.

Recommendations

- A short-term goal should be the development of a tiered approach to performing cumulative assessments.
- Wherever possible, use should be made of existing knowledge such as available on the USEPA Cumulative web site (see http://www.epa.gov/pesticides/cumulative)
- Cumulative assessments are an international issue and there is scope for the EU to collaborate with the US EPA and other bodies.
- A long-term goal should be to revise the current toxicity testing paradigm to a risk based and tiered approach that more efficiently obtains targeted data on kinetics/dosimetry, mode of action, and dose response, which will benefit both aggregate and cumulative risk assessments.

Discussion Group 2: Non-dose-addition effects

Before starting their deliberations the group discussed the main characteristics of "non-dose- addition effects" and defined two situations; a) compounds in a mixture do not interact (do not influence the toxicity of the others), b) compounds do interact, producing either synergism, potentiation or antagonism. These interactions can occur both in the toxicodynamic phase (e.g. endocrine disruptors) and in the toxicokinetic phase (e.g. interference with transport, metabolism (activation, detoxification), distribution, and elimination of another compound). The discussion group decided that effect addition is not relevant to consider for mixtures where exposure is below the NOAEL for each individual compound. However, in these situations it may be relevant to consider synergism or potentiation. Antagonistic interaction of compounds, although it may occur in some cases, is not of public health concern and is not a priority for cumulative risk assessment.

Compound groups for consideration

Selection of compounds should be based on the toxicological profile and the mechanism of action. If it is plausible that compounds would interact at effect levels for the relevant toxicological endpoints, then the possibility for synergism at lower doses should be explored.

In situations of intentional use of combinations of pesticides co-exposure is likely to occur and consideration should be given to potential non-dose-additive effects. An example of such a case is the combined use of piperonyl butoxide and pyrethroids where the first compound is used to enhance the toxicity of the latter.

The question was raised whether impurities could be as equally relevant an issue as residues. Currently, information is lacking to answer this question.

Default assumptions to be used and study design

Available studies have not shown interaction leading to toxic effects when exposure is below the NOAEL for each of the compounds operating by simple dissimilar action. However, for pesticides this has never been adequately demonstrated and should therefore be investigated. So far OPs and pyrethroids are predicted not to interact at low levels.

The overall feeling was that interactions between compounds could possibly occur when exposure is at the LOAEL for each of the compounds considered.

There is no standard study design to evaluate the potential interaction of compounds. Partial factorial designs have been used in animal studies, but these studies are very expensive and are not considered the way forward. In any case the dose-response range should be explored for potential interactions possibly by using probabilistic methods.

The isobole method is a useful approach to explore additive, synergistic or antagonistic effects of mixtures of compounds *in vitro*. This method is, however, expensive to perform in vivo because of the series of multiple combinations of test compounds needed for an appropriate effect assessment.

In studies on non-additive effects in particular the potential for kinetic interactions (induction/inhibition) should be addressed. Where *in vivo* data are lacking the usefulness of PB/PK modelling to get insight in the potential for interaction should be explored. In special cases (e.g. intentional combined use of pesticides) such information should be provided by the applicant.

Methods to be used to estimate combined hazards and their advantages and disadvantages

Just as for compounds with a common mechanism of action for compounds with a dissimilar mode of action the hazard index (HI) or the point of departure index (PODI) approach can be applied for the cumulative risk assessment.
The hazard index is the sum of the hazard quotients (HQ= Exp/ADI) of the individual chemicals in a mixture, i.e. the sum of exposure to each chemical expressed as a fraction of its health based guideline (ADI).

$$HI = \Sigma_i Exp_i / ADI_i$$

It should be noted that for ADI one can also read ARfD. The advantage of this approach is its transparent and easily understandable nature. The disadvantage, however, is that the ADI does not form the most appropriate metric for a cumulative risk assessment, because in their derivation usually an uncertainty factor is applied, and this uncertainty factor may not only be science driven but might also incorporate policy driven assumptions.

The point of departure index (PODI) sums the exposures of each compound expressed as a fraction of their respective NOAEL or BMD instead of a comparing them with the ADI or TDI.

$$PODI_i = \Sigma_i Exp_i / (NOAEL_i \text{ or } BMD_i)$$

Arguments for the choice of the NOAEL or BMD as point of departure (POD) are identical to those presented above for the compounds with a common mechanism.

The margin of exposure (MOE) approach is the reciprocal of the PODI approach, and sums the exposures to the compounds in terms of their relative potencies expressed as risk units. Currently there are no established criteria for the magnitude of an acceptable MOE for mixtures of chemicals. EPA has suggested to derive a cumulative risk index (CRI) by combining the MOEs for chemicals with different uncertainty factors or simply the ADI and TDI.

$$CRI = 1/\Sigma_i Exp_i/ADI_i$$

It was discussed that in case interaction is foreseen an additional factor could be introduced to adjust for the potential effect of the combined exposure. A literature search on the range of synergies reported so far could provide a basis for the determination of such an additional adjustment factor. It should be noted that such a factor does not affect the ADI or the TDI.

The TEF concept is based on a common mechanism of action for the compounds involved, thus dose additivity applies, and therefore the TEF approach is not applicable for the evaluation of a mixture of compounds with a dissimilar mode of action.

Point of departure to be used in estimating hazard in cumulative risk assessment

The point of departure index (PODI) could be based on the NOAEL as well as on the BMD, but the BMD may not be always applicable because standard toxicity studies are not well suited to derive a BMD (see also the arguments presented above for compounds with a common mechanism). The Hazard Index (HI) using the ADI is of lower priority, but may be a practical tool for screening purposes.

The PODI approach could be used in the risk characterization. In situations were there is limited information on interaction and residue levels are very low it should be explored whether the threshold for toxicological concern (TTC) approach could be used.

Minimum data requirements for including a compound in a cumulative assessment - if not met, what defaults should be used

Before considering compounds for a cumulative risk assessment there must be information indicating that there is a possibility of co-exposure to the respective compounds. If exposure to each of the compounds does not occur within a reasonable time frame, there is generally no reason to assume interaction. Next to co-exposure there should also be a plausible hypothesis for effect interaction of two or more compounds.

The minimum data set should comprise the data required for authorisation of each of the individual compounds, or additional information already available on the effects of combined exposure. In specific cases there could be a need for data to be produced (or predictions) on the potential interaction.

The discussion group came to the conclusion that interaction of compounds with simple dissimilar actions are not of concern at levels below the ADI for all these compounds. Occurrence of complex dissimilar actions is considered to be rare when residue levels are below the regulatory limit (MRL). In general, cumulative risk assessment of pesticides should be carried out in situations were co-exposure is likely to occur. This is particularly the case for the intentional use of combinations of pesticides.

In the cumulative risk assessment distinction should be made between acute and chronic effects. Particularly timing of exposure is an important item due to the influence of kinetic interactions.

In general it was concluded that in case of concern for interactions of pesticide residues it is the risk manager who has to decide what follow-up action is needed.

Recommendations

- Potential non-dose-addition effects should also be considered for chemicals with a common mechanism of action.
- When examples of synergy are obtained read-across could be helpful in the generation of a working hypothesis.
- For the assessment of interactions the applicability of probabilistic methods in the hazard assessment should be explored.
- If concern persists as regards to co-exposure and plausibility of interactions, more data should be requested.
- Toxicity testing of pesticides should focus more on generating data to explore the potential for interactions and the derivation of BMDs.
- Research to explore low-dose (doses below the NOAEL) non-dose-addition effects of combined exposure to pesticides should be supported.
- More "real" exposure data should be used in the risk assessment. This is particularly helpful for probabilistic modelling.
- In case interactions are foreseen, an additional adjustment factor may be used in the risk assessment process.
- A literature search should be carried out to identify the range of synergies that could form a basis for the derivation of such an additional adjustment factor.

Discussion Group 3: Choice of data for combined exposure

As starting point for their deliberations, the discussion group had an initial reflection on the situations for which a combined risk assessment should be carried out and decided to limit the current discussion to: i) plant protection products not including biocides or veterinary drugs, ii) food, and thus excluding drinking water, and iii) oral intake, not considering other routes of exposure.

The group thoroughly discussed the different situation for which a cumulative risk assessment should be considered. Some participants were of the opinion that the focus should be on the risk of chronic cumulative exposure, whereas others put the focus on acute exposure. The group came to the conclusion that in principle four different scenarios could be considered for a cumulative risk assessment: MRL setting and actual exposure assessments for both acute and chronic exposure. These scenarios might require different data sets. For acute assessments one should focus on the edible portion of food commodities on the market, whereas for chronic assessments the focus should be more on raw agricultural commodities.

Consumption data

For both acute and chronic consumption estimates, a selection of data from food surveys should be used that is representative for the whole year and every day of the week. Consideration should be given to the number of days during which the consumption data are collected and the number of respondents. This information is essential to provide a reliable estimate of the number of consumers in the overall population. Special attention should be given to consumption situations of relevant subgroups (e.g. consumers only, high consumers, different age groups).

It is essential, for acute risks, to have information on what food items are consumed at what time of the day by a single consumer, on a single day, to provide an appropriate estimate of the time dependency and the possibility for interactions of different compounds. This implies that detailed information on the food items concerned is needed and thus that raw consumption data (in contrast to aggregated data) must be available.

For acute estimates of consumption, data from single days (dietary records, 24h recalls) should be used rather than data from food frequency questionnaires or dietary history methods. For chronic consumption estimates all kind of survey methodologies can be used, but sometimes it is necessary to apply statistical methods to fit the data for purpose, e.g. recommendation of EFCOSUM to extrapolate from short-term intakes to long-term intakes via the Nusser method.

The same food consumption survey could provide data for all the different scenarios, but depending on the question addressed or the methodology chosen (e.g. deterministic or probabilistic) different values could be extracted from the database. Therefore the raw data from these databases should be accessible.

There are several sources for consumption data available:
i) National food consumption surveys with nutrient intake data on the individual level. However, the European Food Consumption Survey Method (EFCOSUM), aiming at comparable methodology for consumption data collection, concluded that there is still a regrettable lack of internationally comparable data. In addition to that, the discussion group noted that the level of aggregation of existing consumption data will not always fulfil the needs for a cumulative assessment, and it questioned whether the information on the portion size was precise enough, and if the duration and number of recalls were adequate;
ii) EFSA Concise Database, this database is under construction and contains aggregated consumption information for 16 classes of food items from a limited number of European countries;
iii) SAFE FOODS, this 6th framework project comprises data from 6 national consumption surveys, which are ready to be used in a probabilistic cumulative assessment.

In general there is a lack of consumption data for most of the EU member states, and the existing food surveys apply different methodologies, are not up-to-date, and cover different subgroups. EFSA has started to set up a Food Consumption Data Base and will provide guidance to member states to collect consumption data in a comparable manner.

Residue data

Monitoring of residues should focus on the edible portion of food commodities on the market. By measuring actual residues in food commodities on the market we can get much better estimates of actual exposure than by using residue data from field trials. In principle the whole range of residue data should be considered. Residue data can be adjusted by processing factors if appropriate.

Residues should also be measured according to the residue definition for risk assessment and not only according to the definition for enforcement of legislation. Alternatively, conversion factors can be applied to convert the monitored amount into the amount relevant for the risk assessment. Monitoring/enforcement data could be biased (e.g. targeted sampling) and usually no numerical information is reported by the Member States to European Commission for residue levels below the MRL.

Not all Member States are measuring the same substances or the same commodities and the applied analytical methods and their respective LOQs may be different. For all compounds in the group considered, the LOQ should be in the same range and fit for the purpose of a meaningful cumulative risk assessment. It should be decided how to handle "non detects". The U.S has a policy on this entitled "Assigning values to non-detected/ non-qualified pesticide residues in human health food exposure assessment", it is available at: http://www.epa.gov/pesticides/trac/science/trac3b012.pdf. This document provides good guidance for handling "non detects" and could be followed in order to harmonize the applied analytical methods.

For Northern and Southern Europe residue data are available from supervised field trials carried out under critical or realistic good agricultural practice.

There was no overall agreement on the use of models to estimate residue data based on application conditions and properties of the substances concerned. In addition, it was also questioned whether market shares (that change over time) to estimate the percentage of crops treated should be considered in the context of MRL setting.

The group discussed the need for additional information and concluded that the EU monitoring programmes should be checked with respect to the appropriateness of the residue data for combined exposure assessment. If needed, the monitoring programmes should be amended. Also the methodologies for deriving "actual use" data (e.g. farmer's records) of pesticides should be explored.
Finally it was concluded that it is desirable that residue monitoring programmes (e.g. the EU coordinated monitoring program) should provide residue data for individual food units (e.g. a single apple or pear, or one head of lettuce) rather than data from composite samples.

Combined exposure assessment

For a cumulative assessment within the framework of MRL setting, it should be checked whether the existing information provided for the marketing authorisation of the various compounds offers an acceptable basis for an exposure assessment. For new registrations, the impact of the new information on existing assessments needs to be assessed to adopt for the range of pesticides on the market.

For the situation of MRL setting, the necessary residue information could be formed by a combination of monitoring data and data from supervised field trials. For new applications (e.g. intentional use combination) residue data from

supervised trials for the respective commodity or compound combination should be provided by the applicant.

An assessment of acute combined exposure could cover one food commodity with residues of multiple pesticides. In this case a deterministic approach using a large portion could be applied as currently done in the MRL setting and in enforcement procedures, or a probabilistic approach could be used as refinement. For an assessment of different compounds in different food items, only a probabilistic approach is appropriate.

For a deterministic assessment of chronic cumulative exposure, particularly for compounds with a common mechanism of action, the mean "cumulative" level per food commodity needs to be considered. However, methods to cumulate the respective levels and to average over a longer period of time need to be further developed.

Recommendations

- Residues should also be monitored in the edible portion of food commodities on the market and not only in raw agricultural commodities.
- In dietary surveys, data should be collected on separate, non-consecutive days rather than on consecutive days.
- A decision should be made how to handle non-detects (lower-, middle-or upper bound).
- Raw consumption data of all the different food consumption surveys should be made available rather than aggregated data.
- Food codes to be used by member states for consumption surveys and residue monitoring programmes should be harmonized
- EFSA should conduct a Europe-wide food survey that is representative for the entire European Union (all the 27 Member States). This does not necessarily mean food surveys in all the individual member states, but rather in representative regions with a comparable diet (e.g. diet clusters).
- EU pesticide residue monitoring programmes should be checked whether they are appropriate for cumulative risk assessment and amended, if needed.

Discussion Group 4: Methodology for combined exposure

In order to determine the appropriate methodology, the discussion group needed to agree the scenarios to be addressed and the stage at which cumulative exposure assessments should be performed. The methods should be able to cover MRL setting and actual exposure assessments for both acute and chronic timescales. The approach used by the US EPA could be used as a starting point but would need to be adapted to EU philosophies (e.g. to exclude the contribution of drinking water; review the use of the variability factor; and whether to correct for the percentage of the crop that was treated).

Cumulative exposure assessments should be performed as part of a baseline assessment for a group of chemicals and when considering authorisations for pesticide uses. Cumulative exposure assessments should not be used to resolve either MRL exceedances in traded lots or the acceptability of traded lots.

What methodology should be chosen in order to assess consumer exposure to residues of pesticides – could either deterministic or probabilistic methods be used?

The data requirements and modelling needs were different between acute and chronic assessments. It was envisaged in the future that acute, chronic and an assessment between these two areas would be possible. However, the priority for development was considered to be the acute assessment.

Deterministic models could be used for acute cumulative assessments if only a single item of food was being considered (e.g. a bunch of grapes with multiple OP residues); the applicability to composite samples was unclear (especially if the composites were formed from mixed or pooled lots (where samples not sharing the same treatment history were combined) and there were concerns that they might tend to over-estimate the risk if there were many compounds in the group.

Probabilistic modelling could be used for cumulative acute exposure modelling provided data were not from pooled or mixed lots. If data were from pooled or mixed lots (as they could well be in samples taken for routine surveillance) it is possible to extrapolate to individual items using software such as MCRA or MaxLIP. However, individual item data are the preferred option. Sampling from mixed lots is less problematic for chronic assessments.

There were concerns that the output might not be clear to risk managers for example when there was a low probability of exceeding an acute reference dose (ARfD).

What are the criteria for a model to estimate combined exposure?

Complex models tended to produce complex results; therefore the models should be the simplest that provide the necessary output. The US had considerable experience of modelling cumulative exposures and the EU should make use of this. Guidelines on the use of probabilistic modelling were being considered by EFSA; these addressed the running of the models and generating the output, but they do not currently cover interpretation of results/output or risk management. The guidelines for probabilistic modelling were considered to be a higher priority than guidelines on cumulative assessments. It was noted that a draft guideline had been provided to the European Commission as part of the Monte Carlo (Framework 6) project.

The initial aim should be to develop a model to perform a cumulative assessment based on existing uses. Including new uses was unlikely to become an issue until existing uses had been modelled.

What are the requirements for the model?

The most critical aspect of any model is that it should be transparent. All stakeholders, particularly external ones, could gain confidence in a model if they had information on the underlying data and processes, and received some training in the general principles of modelling techniques. Confidence would be further increased if the model could replicate results and was subjected to external peer review, validation and verification. There were benefits in having a model that could produce information on appropriate data to collect to improve the results.

There are a number of food consumption databases in the EU and the model should be compatible with as many of these as possible. There might be issues associated with getting EU specific data into existing models. This might be helped by some pooling of existing databases before populating the model with the data, provided this did not compromise the ability to address regional differences. Some models permitted a correction for the proportion of a particular crop that was treated; currently there was no agreed EU position on whether to use this information in the context of MRL setting since this market share changes over time. The use of proportion of crop treated in cumulative exposure assessments need to be discussed within the EU.

The model must have sufficient power for its intended purpose. The underlying data must be extensive enough to permit the necessary number of iterations to be performed. The power required was linked to a need for the risk managers to

define what was an acceptable level of exposure in terms of the tail of the distribution e.g. 97.5, 99 or 99.99 percentile.
A flexible, modular approach would permit exposure estimates to be performed in a stepwise manner e.g. starting with dietary exposures to pesticides then adding other routes such as water, household uses (biocides) and veterinary uses.

How to deal with uncertainty and variability?

Uncertainty and variability would both apply to the output of the model. If the model indicated that there was an exceedance of a reference dose by some population sub-groups, sensitivity analysis could be used to indicate the degree to which certain inputs or default assumptions contributed to that exceedance.

The models would ideally be capable of separating uncertainty (the unknown; e.g. confidence limits around a margin of exposure (MoE)) and variability (variation of the known), MoEs varying with the chosen percentile of the distribution) but it is recognized that quantitatively separating uncertainty and variability is very difficult. Uncertainty was associated with data on all parameters and there was no agreed approach to deal with this. Uncertainty analysis could be used to provide information on where there are crucial data gaps. By using modelling in an iterative way, it might be possible to address uncertainty.

Outliers should be considered. Rather than just including or excluding these, an assessment of their impact on the output should be made.

Interpretation of the results; when should safety concerns be raised?

Probabilistic models produce a distribution of predicted exposures, often with a long tail. There was no agreement on how much of the tail to include in an assessment. The choice of the appropriate percentile of the distribution to use was ultimately the responsibility of risk managers.

It is possible that the percentile could vary between similar assessments, depending on the supporting data. Factors to consider would include the number of simulations performed; relevance of the data (e.g. extensive monitoring data rather than supervised field trials); the types of foods (staples or niche products) and chemicals (low hazard or high hazard) contributing to high-end exposures. Expressing results as a MoE rather than stated as being above or below a reference dose could permit a more flexible approach to risk characterisation.

Which models are now available and what are the lessons learnt in their development?

The discussion group discussed six existing models: MCRA; CREMe; DEEM / Calendex; CARES; Lifeline and SHEDS. The latter four had been the subject of a comparative exercise in the USA and had produced similar results. The US EPA Science Advisory Panel (SAP) members noted that although the various models used in some cases different approaches and input data, the models predicted similar exposures at the high end of the distribution (e.g., 99th percentile). The SAP recommended that EPA OPP continue to use all three models as one method of incorporating model uncertainty into an assessment and recommended that EPA continue the process of understanding the strengths and weaknesses of each model. They suggested that it might be useful to possibly include simple statistical and mechanistic models in the comparisons as well.

Is one of the models appropriate or should a new model be developed?

Given the reproducibility of results from four of the models and the costs involved there seems little to be gained from developing completely new software. However, there was no reason why Member States should not modify the models to incorporate specific consumption / residue data.

Models need to be developed that could be used in the prospective assessment of new uses i.e. would produce valid results based only on field trials data where all samples would have been treated.

Recommendations

- The process of performing cumulative assessments should begin as soon as possible. This should be a stepwise approach starting with acute dietary exposures of currently authorised uses.
- Groups of high priority chemicals should be identified.
- Guidelines should be finalised for probabilistic modelling and developed for cumulative exposure assessments.
- Best use should be made of existing models rather than developing completely new ones.
- More training should be made available on the general principles of exposure modelling. This would improve understanding and acceptance of modelling.
- Although they are not always compatible with modelling, best use should be made of the existing data.
- Sensitivity analysis could then be used to identify data gaps, evaluate default assumptions, and prioritise future data collection.
- Use existing monitoring data but be aware of its limitations and biases (e.g. targeted and not random sampling).
- The suitability of supervised trials data for use in cumulative assessments including new compounds should be investigated.
- Use data generated elsewhere when appropriate (e.g. toxicity considerations).
- Experience gained from initial assessments will be valuable in developing future approaches to cumulative assessments.

III. FINAL DISCUSSION

The final discussion showed that there was general consensus on the importance and need of a cumulative risk assessment of pesticides, although opinions on the most appropriate method to tackle the issue, in particular how to deal with exposure scenarios, sometimes differed. The general feeling was that the cumulative risk assessment for compounds with a common mechanism of action is more important than that for compounds with a dissimilar action.

The meeting discussed the possibilities for carrying out a cumulative risk assessment and concluded that the currently available data do not facilitate a meaningful risk assessment on an EU-wide scale, but that such an assessment is certainly possible based on the information of some of the member states. Therefore it was concluded that improvement of the available data needed for a cumulative risk assessment is an important issue for the near future.

IV. OVERALL RECOMMENDATIONS

- Scientific cooperation in the area of cumulative risk assessment of pesticides is an important issue and it should be advocated that approaches are developed for a better harmonisation in risk assessment procedures. Collaboration between EFSA, WHO and FAO could be instrumental for this.
- Cooperation between EFSA and the EU member states for cumulative risk assessment of pesticides is needed.
- In addition to the dietary route, also other sources of exposures to pesticides should be included in the longer term.
- Residue monitoring schemes and food consumption surveys might need to be modified to provide more appropriate data that could be used in a cumulative risk assessment.
- Because cumulative risk assessment is a general issue and broader than exposure to pesticides alone, it is recommended that EFSA take this issue further than only pesticides.
- The timeframe of exposure to interacting compounds is an important issue; however, it should be realized that interaction of compounds in the body is not necessarily the result of simultaneous exposure, because the kinetic behaviour of various compound differ. PB/PK modelling might be an appropriate methodology to clarify this issue.
- A framework for cumulative risk management should be developed.
- It was welcomed that the PPR Panel will prepare an opinion on specific actions needed for the near future based on the outcome of this colloquium.

ANNEXES

V. ANNEXES

Annex 1: Programme of the Colloquium
Annex 2: Participants at the Colloquium
Annex 3: Presentations made at the Colloquium
Annex 4: Slides of Discussion Groups

Annex 1: Programme of the EFSA Colloquium

EFSA Scientific Colloquium on Cumulative Risk Assessment of Pesticides to Human Health: The way forward
28-29 November 2006, Parma, Italy

PROGRAMME

Chair: Alan Boobis
Co-chair: Ursula Banasiak
Rapporteurs: Ian Dewhurst, Rolaf van Leeuwen

Tuesday 28 November 2006

08.30-9.00	Briefing meeting with overall chair and rapporteurs, discussion group chairs and rapporteurs	
09.00-13.00	**Session 1: INTRODUCTORY PLENARY SESSION**	
09.00-09.20	Welcome and Introduction to EFSA	Herman Koëter
09.20-09.40	Combined risk assessment of pesticides and MRL setting - European Commission perspective - EFSA perspective	Bas Drukker Daniela Brocca
09.40-09.50	Discussion	
09.50-10.10	Scientific issues related to combined risk assessment of pesticides	Timothy Marrs
10.10-10.20	Discussion	
10.20-10.40	US experience of combined hazard assessment of pesticides	Vicki Dellarco
10.40-10.50	Discussion	
10.50-11.20	COFFEE/TEA BREAK	

11.20-11.40	European experience of combined hazard assessment	Marcel van Raaij
11.40-11.50	Discussion	
11.50-12.10	Combined exposure assessment of pesticides	Philippe Verger
12.10-12.20	Discussion	
12.20-12.30	Introduction to discussion groups	Juliane Kleiner
12.30-13.30	LUNCH	

13.30-16.00 Session 2:
DISCUSSION GROUPS (DG)

DG 1

Cumulative hazard assessment	Chair:	David Coggon
	Rapporteur:	Angelo Moretto

DG 2

Non-dose-addition effects	Chair:	Corrado Glli
	Rapporteur:	John Christian Larsen

DG 3

Choice of data for combined exposure	Chair:	Bernadette Ossendorp
	Rapporteur:	Britta Michalski

DG 4

Methodology for combined exposure	Chair:	David Miller
	Rapporteur:	Caroline Harris

16.00-16.30 COFFE/TEA BREAK

16.30-18.30 Session 3:
REPORT BACK OF DISCUSSION GROUPS OUTCOME

16.30-16.45 Report back from DG 1 Angelo Moretto

16.45-17.00	Discussion	
17.00-17.15	Report back from DG 2	John Christian Larsen
17.15-17.30	Discussion	
17.30-17.45	Report back from DG 3	Britta Michalski
17.45-18.00	Discussion	
18.00-18.15	Report back from DG 4	Caroline Harris
18.15-18.30	Discussion	
20.00	DINNER	

Wednesday 29 November 2006

09.00-11.00	**Session 4: CONTINUATION OF DISCUSSION GROUPS**	
09.00-10.00	Discussion on possible implications of the recommendations	
10.00-11.00	Discussion groups to prepare their conclusions and recommendations	
11.00-11.30	COFFEE/TEA BREAK	
11.30-13.30	**Session 5: FINAL PLENARY SESSION - DISCUSSION AND CONCLUSION**	
11.30-12.30	Report back to Plenary	Angelo Moretto John Christian Larsen Britta Michalski Caroline Harris
12.50-13.30	Discussion, conclusion and recommendation from the colloquium	
13.30-14.30	LUNCH	
14.30	Colloquium adjourns	

Annex 2: Participants at the Colloquium

Name	Affiliation	Country	Discussion Group (DG)
Mr. Abdelkarim Abdellaue	Norwegian Food Safety Authority	NO	2
Prof.Dr. Arpad Ambrus	Hungarian Food Safety Office	HU	4
Mrs. Fulya Arican Öznur	Ministry of Agriculture and Rural Affairs	TU	4
Ms. Gillian Asbury	Food Standards Agency	UK	3
Dr. Ursula Banasiak	Federal Institute for Risk Assessment (BfR)	DE	4
Dr. Susan Barlow	Independent consultant in toxicology	UK	
Dr. Thomasina Barron	Department of Agriculture & Food	IE	1
Dr. Diane Benford	Food Standards Agency	UK	2
Dr. Albert Bergmann	Austrian Agency for Health and Food Safety	AT	1
Mrs. Urska Blaznik	National Institute for Public Health	SLO	3
Dr. Claudia Bolognesi	National Institute for Research on Cancer	IT	1
Prof. Alan Boobis	Imperial College London	UK	2
Dr. Polly Boon	Institute of Food Safety (RIKILT)	NL	2
Dr. Marta Borges	National Food and Economy Safety Authority (ASAE)	PT	1
Dr. Saskia Bosman-Hoefakker	Board for the Authorisation of Pesticides (CTB)	NL	1
Dr. Gianfranco Brambilla	National Health Institute (ISS)	IT	4
Dr. Monika Bross	BASF	DE	3
Mr. Arne Büchert	Danish Institute for Food and Veterinary Research (DFVF)	DK	3

Name	Affiliation	Country	Discussion Group (DG)
Dr. Giovannella Ciucani	SIPCAM	IT	2
Prof. David Coggon	MRC - University of Southampton	UK	1
Prof. Lucio Guido Costa	University of Parma	IT	2
Mr. Jean Pierre Cugier	French National Institute for Agricultural Research (INRA)	FR	4
Dr. Roberto Da Gasso	Expedia Mediterranean Regulatory Consulting Company (MRCC)	IT	1
Dr. Peter Day	European Crop Protection Association (ECPA)	BE	4
Dr. Vicki Dellarco	US Environmental Protection Agency	USA	1
Dr. Ian Dewhurst	Pesticides Safety Directorate (PSD)	UK	1
Dr. Bas Drukker	European Commission	BE	4
Mr. Bruno Dujardin	Federal Public Service of Health, Food Chain Safety and Environment	BE	3
Dr. Ivana Fegert	BASF	DE	1
Dr. María Luisa Fernández-Cruz	Spanish National Institute for Agrarian and Food Research and Technology (INIA)	ES	3
Ms. Jorid Frydenlund	Norwegian Food Safety Authority	NO	1
Prof. Corrado Galli	University of Milan	IT	2
Prof. Dr. Ursula Gundert-Remy	Federal Institute for Risk Assessment (BfR)	DE	2
Dr. Jadwiga Gzyl	Institute for Ecology of Industrial Areas	PL	4
Mr. Paul Hamey	Pesticides Safety Directorate (PSD)	UK	4
Mr Denis Hamilton	Department of Primary Industries and Fisheries	AU	3
Prof.Tony Hardy	Central Science Laboratory	UK	2

Name	Affiliation	Country	Discussion Group (DG)
Dr. Caroline Harris	Exponent International Ltd	UK	4
Dr. Ragna Bogen Hetland	Norwegian Institute of Public Health	NO	1
Dr. Renske Hittenhausen-Gelderblom	Food and Consumer Product Safety Authority (VWA)	NL	3
Dr. Karsten Hohgardt	Federal Office of Consumer Protection and Food Safety (BVL)	DE	4
Dr. Hannele Huuskonen	National Product Control Agency for Welfare and Health	FI	1
Mrs. Anna Irzl	Austrian Agency for Health and Food Safety	AT	4
Mrs. Bodil Hamborg Jensen	Danish Institute for Food and Veterinary Research (DFVF)	DK	4
Niklas Johansson	Karolinska Institute	SE	2
Dr. Michael Kaethner	Bayer CropScience	DE	4
Dr. Iain Kelly	Bayer CropScience	USA	4
Mrs. Ingrid Kernmayer	Austrian Agency for Health and Food Safety	AT	3
Dr. Dubravka Kipči	Croatian National Institute of Public Health	HR	1
Dr. Werner Kobel	European Crop Protection Association (ECPA)	CH	2
Ms. Kalliopi Kokkinaki	Hellenic Ministry of Rural Development and Food Directorate of Plant Produce Protection	GR	4
Dr. Arnold Kuchen	Swiss Federal Office of Public Health	CH	3
Dr. Frank Laporte	Bayer CropScience	FR	3
Mr. John Christian Larsen	Danish Institute for Food and Veterinary Research (DFVF)	DK	2

Name	Affiliation	Country	Discussion Group (DG)
Mr. Oliver Lindtner	Federal Institute for Risk Assessment (BfR)	DE	3
Prof. Timothy Clive Marrs	Edentox Associates	UK	1
Mr. Luis Martin Plaza	European Commission	BE	2
Dr. Christophe Matthys	Ghent University	BE	3
Dr. Ernesto Mazzoli	Ecobest srl	IT	1
Ms. Céline Ménard	French Food Safety Agency (AFSSA)	FR	3
Dr. Otto Meyer	Danish Institute for Food and Veterinary Research (DFVF)	DK	1
Dr. Britta Michalski	Federal Institute for Risk Assessment (BfR)	DE	3
Dr. David Miller	U.S Environmental Protection Agency	USA	4
Dr. Angelo Moretto	International Centre for Pesticides and Health Risk Prevention (ICPS) and University of Milan	IT	1
Prof. Antonio Mutti	University of Parma	IT	3
Dr. Goetz Neurath	GAB Consulting	DE	2
Dr. Pierre Nord	Swedish Chemicals Inspectorate (KEMI)	SE	1
Dr. Bernadette Ossendorp	National Institute for Public Health and the Environment (RIVM)	NL	3
Dr. Mostafa Ould Elhkim	French Food Safety Agency (AFSSA)	FR	4
Dr. Paul Parsons	Syngenta	UK	2
Mrs. Annette Petersen	Danish Institute for Food and Veterinary Research (DFVF)	DK	3
Dr. Rudolf Pfeil	Federal Institute for Risk Assessment (BfR)	DE	1
Dr. Iona Pratt	Food Safety Authority of Ireland	IE	2

Name	Affiliation	Country	Discussion Group (DG)
Dr. Chaido Rizou	National Agricultural Research Foundation (NAGREF)	GR	3
Mrs. Claudie Roy	French National Institute for Agricultural Research (INRA)	FR	1
Dr. Maristella Rubbiani	National Health Institute (ISS)	IT	1
Dr. Fernando Sicbaldi	Isagro Ricerca	IT	3
Mr. Michael Skidmore	Syngenta	UK	3
Dr. Bernhard Stahl	European Crop Protection Association (ECPA)	FR	2
Mrs. Mihaela Tatiana Stancu	National Sanitary Veterinary and Food Safety Authority	RO	4
Mr. Andras Szoradi	International Life Sciences Institute - ILSI Europe	BE	4
Dr. Regine Thums	Crop Protection	DE	3
Prof. Marco Trevisan	Catholic University of the Sacred Heart (UCSC)	IT	3
Dr. Gero Vaagt	Food and Agriculture Organization (FAO)	IT	4
Prof. Rumiana Vachkova-Petrova	National Centre of Public Health Protection	BG	2
Dr. Jacob van Klaveren	Institute of Food Safety (RIKILT)	NL	4
Dr. F.X.Rolaf Van Leeuwen	National Institute for Public Health and the Environment (RIVM)	NL	1
Dr. Marcel T.M. Van Raaij	National Institute for Public Health and the Environment (RIVM)	NL	2
Dr. Rosalia Vanyur	Hungarian Food Safety Office	HU	1
Dr. Philippe Verger	French National Institute for Agricultural Research (INRA)	FR	4
Dr. Rose Vikse	Norwegian Institute of Public Health	NO	2

Name	Affiliation	Country	Discussion Group (DG)
Ms. Sara Visentin	International Centre for Pesticides and Health Risk Prevention (ICPS)	IT	4
Dr. Christiane Vleminckx	Scientific Institute of Public Health	BE	2
Dr. Peter Zweipfenning	Food and Consumer Product Safety Authority (VWA)	NL	2

EFSA Staff

Dr. Bernhard Berger	Panel on plant protection products and their residues
Mrs Lucia Bilardi	Administrative Support
Dr. Henning Bruno	Pesticide risk assessment peer review
Dr. Daniela Brocca	Pesticide risk assessment peer review
Dr. Stef Bronzwaer	Scientific Expert Services
Mrs.Vanessa Descy	Administrative Support
Dr. Muriel Dunier-Thomann	Panel on plant protection products and their residues
Ms. Giulia Frattini	Administrative Support
Ms. Anja Friel	Pesticide risk assessment peer review
Mrs. Claudia Heppner	Panel on contaminants in the food chain
Dr. Juliane Kleiner	Scientific Committee
Dr. Herman Koëter	Deputy Executive Director and Director of Science
Dr. Jose Oriol Magrans	Pesticide risk assessment peer review
Mr. Luc Mohimont	Pesticide risk assessment peer review
Mrs. Hermine Reich	Pesticide risk assessment peer review
Ms. Katty Verhelst	Administrative Support

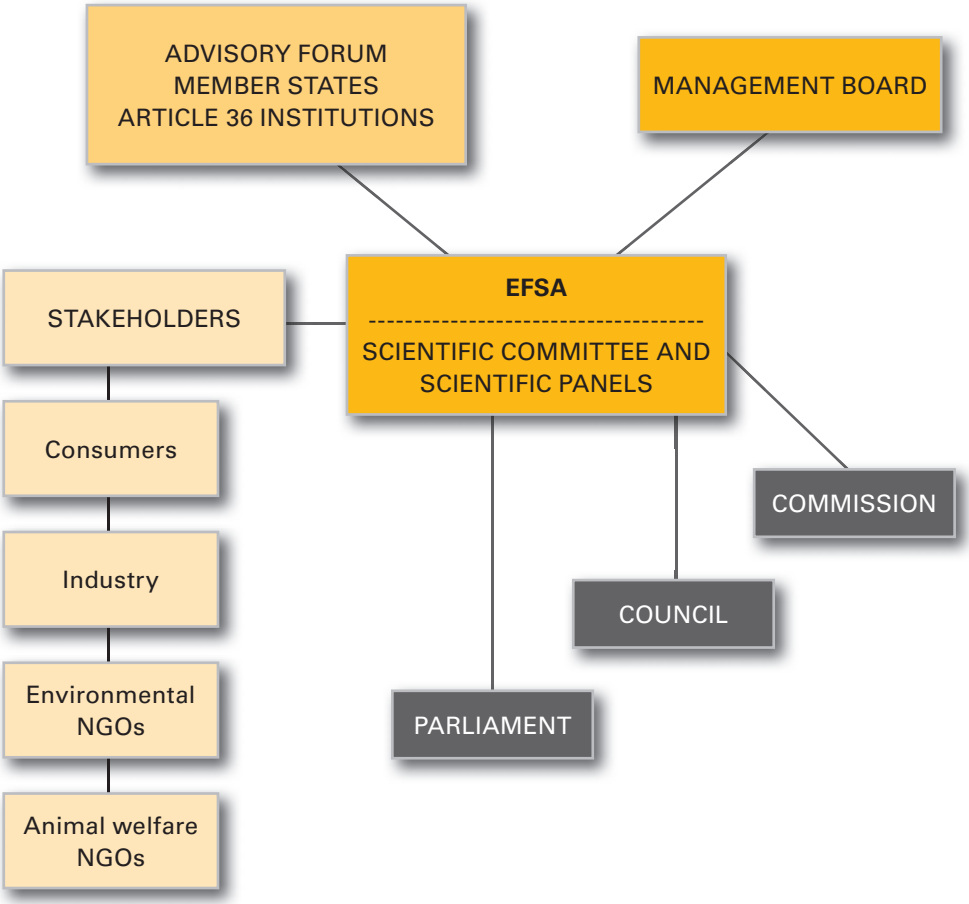
Annex 3: Presentations made at the Colloquium

THE EUROPEAN FOOD SAFETY AUTHORITY: WORKING TOGETHER

HERMAN B.W.M. KOËTER
Deputy Executive Director
and
Director of Science

EFSA's mission

The European Food Safety Authority (EFSA) is the keystone of European Union (EU) risk assessment regarding food and feed safety. In close collaboration with national authorities and in open consultation with its stakeholders, EFSA provides independent scientific advice and clear communication on existing and emerging risks.



EFSA's Mission and Tasks [Reg 178/2002]

- ... provide **scientific advice** and **scientific and technical support** ... [Art. 22. 2];
- ... shall provide **scientific opinions** ... [Art. 22.6];
- ... **collect and analyse data** to allow the characterization and monitoring of risks ... [Art. 22.4];
- promote and co-ordinate the **development of uniform risk assessment methodologies** [Art. 23(b)];
- ... commission **scientific studies** ... [Art. 23(d)];
- ... undertake action to **identify emerging risks**... [Art. 23(f)].

Scientific activities (work themes)

- Providing scientific opinions, guidance and advice in response to questions;
- Assessing the risk of regulated substances and development of proposals for risk-related factors;
- Monitoring of specific animal health risk factors and diseases;
- Development, promotion and application of new and harmonized scientific approaches and methodologies for hazard and risk assessment of food and feed.

Scientific Panels

- Structure defined in the founding Regulation and copied from the Commission;
- Together covering the whole food chain;
- Expert members appointed by Management Board following a call to express interest;
- Maximum of 21 members per panel selected on the basis of scientific excellence, area of expertise, gender and geographical balance.

The 9 Scientific Panels

- Food additives, flavourings, processing aids, materials in contact with food (AFC)
- Additives and products in animal feed (FEEDAP)
- Plant Protection Products (PPR)
- Plant Health Panel (PLH)
- Genetically modified organisms (GMO)
- Dietetic products, nutrition and allergies (NDA)
- Biological hazards (BIOHAZ)
- Contaminants in the food chain (CONTAM)
- Animal Health and Welfare (AHAW)

Scientific Committee

- Comprises the Chairs of all 8 Panels and an additional 6 independent members;
- Provides guidance to all Panels;
- Manages projects involving several Panels;
- Advises EFSA on emerging issues and priorities for scientific work.

A Science Colloquium is:

- an interactive event rather than only a passive listening to lectures;
- a platform for scientists to have in-depth discussions on scientific approaches and methods available and tools and data needed for conducting a risk assessment;
- an event to explore opportunities and limitations for defining a common understanding of the issue at hand and;
- an opportunity to define further research needs.

The Colloquium is not:

- an attempt to agree on the details of a preferred strategy or approach, if any;
- an attempt to finalise a blue print for the work ahead of us;
- a "what is right and what is wrong" discussion.

Science Colloquia

- Setting threshold levels for Dioxins and PCBs (2004);
- Qualified Presumption of Safety of microorganisms (2004);
- Collection of European Food Consumption Data (2005);
- Principles of risk assessment of animal health and welfare (2005);
- Consumption based dietary guidelines (2006);
- Risk/benefit analysis (June 2006).

"Do not follow where the path may lead.
Go where there is no path …
and leave a trail."

(Anonymous)

REGULATION (EC) N. 396/2005

ON MAXIMUM LEVELS OF PESTICIDES (MRLS) IN OR ON FOOD AND FEED OF PLANT AND ANIMAL ORIGIN REQUIRES CUMULATIVE RISK ASSESSMENT

Health & Consumer Protection Directorate General
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Regulation (EC) N. 396/2005 adopted by European Parliament and the Council but not yet implemented

- will **apply** 6 months after adoption by Commission of annex I, II, III and IV.
- **application date** foreseen: not likely before begin 2008

Until then: existing MRL Directives and national legislation of the EU Member States will apply.

Contents of this presentation:
- Why we are changing the legal framework;
- What are the differences in the new Regulation;
- Cumulative risk assesment in the Regulation.

Why change legal framework?

Complexity of present legislation

- 4 parent Council Directives (86/362/EEC, 86/363/EEC, 76/895/EEC, 90/642/EEC);
- each with different provisions for the same problems;
- complicated lists of MRLs, both at national and at Community level; no complete picture; insufficient information exchange;
- Result: problems for the internal market and for the importers and enforcement;
- Avoid duplicating work (mss to copy and paste EU MRLs in national legislation);
- Role of EFSA defined (required by reg 178/2002);
- Under 91/414/EEC a simplified approach needed for all 470 unsupported active substances.

Improvements and simplifications

- Regulation: directly applicable;
- Clear and transparent: list of all EU MRLs, if not explicitly mentioned: Default residue level <0.01 mg/kg;
- Responsibilities divided between Commission, EFSA and Member States;
- Clear procedure for application;
- Accessible database with information;
- Shelf life taken into account;
- Complete harmonization: no more trade problems.

Emphasis on information and transparency

- Improve information to consumers about risks arising from pesticides;
- Member States *should* apply the "*name and shame*" principle (publishing the names of business operators whose products exceed the MRLs);
- Member States *should* publish the results of national monitoring annually on the Internet (providing all individual data);
- MRLs should be set at the lowest achievable level consistent with good agricultural practice (GAP) with a view to protecting vulnerable groups such as children and the unborn.
- **Cumulative and synergistic effects considered, when methodology in place.**

Work on the implementation of the Regulation in progress

- Commission works with Member States and EFSA on the 4 Annexes that are the condition for the application of the Regulation.
- Annex 5, 6 and 7 will be developed later.

Annexes in Bold: Conditions for Applicability of the Regulation

Annex I	List of commodities (done)
Annex II	EU MRLs (to copy from current leg)
Annex III	Temporary MRLs (principal part of the work: COM collected nMRLs, EFSA: exposure assessment)
Annex IV	List of active substances for which no MRLs are required
Annex V	Substances for which a different default MRL applies
Annex VI	Processing factors
Annex VII	Fumigants

- Cumulative and synergistic methodology are not a condition for the application of the Regulation. Nevertheless Commission takes this very seriously.
  - Asked EFSA after adoption of the Regulation to develop methodology;
  - Pleased with this colloquium, kick-off of this new development;
  - Ideally we would have liked to see the methodology in place before the application date of the Regulation;
  - Can be used in the framework of the review of the existing MRLs one year after the application of the Regulation.

Current MRLs need to be checked with new methodology

- So far only few countries (USA, NL, UK) have used Cumulative and synergistic methodology for exposure assessment.
- Where this was done: no spectacular different conclusions on the acceptability of MRLs.
- No reason to sit back and do nothing. We have a responsibility to the EU consumers to verify that their food is safe using all possible exposure routes.
- Also because it was never done at EU level we expose ourselves to criticism, and we have heard some criticism from some consumer organisations lately.
- The development of such methodology is an important challenge for those working in risk analysis: politically, scientifically and administratively.

Cumulative and synergistic effects

Mentioned 3 times in In Regulation 396:

- Recital (6): *It is also important to carry out further work to develop a methodology to take into account* ***cumulative and synergistic effects****. In view of human exposure to combinations of active substances and their cumulative and possible aggregate and synergistic affects on human health, MRLs should be set after consultation of the European Food Safety Authority established by Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority, and laying down procedures in matters of food safety (Hereinafter the Authority).*

In Regulation 396, chapter II:

Article 14
Decisions on applications concerning MRLs

1. Upon receipt of the opinion of the Authority and taking into account that opinion, a Regulation on the setting, modification or deletion of an MRL or a Decision rejecting the application shall be prepared by the Commission without delay and at the latest within three months, and submitted for adoption in accordance with the procedure referred to in Article 45(2).

2. With regard to the acts referred to in paragraph 1, account shall be taken of:

(a) the scientific and technical knowledge available;

(b) the possible presence of pesticide residues arising from other sources than current plant protection uses of active substances, and their known cumulative and synergistic effects, when the methods to assess such effects are available;

In Regulation 396, Chapter VII:

Article 36
Support measures relating to harmonised pesticide MRLs

1. Support measures relating to harmonised pesticide MRLs shall be established at Community level, including:

(a) a consolidated database for Community legislation on MRLs of pesticide residues and for making such information publicly available;

(b) Community proficiency tests as referred to in Article 28(3);

(c) studies and other measures necessary for the preparation and development of legislation and of technical guidelines on pesticide residues, aimed, in particular, at developing and using methods of assessing aggregate, cumulative and synergistic effects;

How to deal with Cumulative and synergistic effects?

- Recital 6: methodology to be developed.
- Article 14: effects to be taken into account when methodology is developed.
- Article 36(c) studies etc for preparation of guidelines, for development of methodology.
- Most logical is that EFSA develops such guidelines. Commission has asked EFSA to do this. EFSA has put this under self tasking. Colloquium is result.
- Three aspects to be addressed:
  - 1) Risk assessment: How can additivity or synergy be demonstrated? Experimentally or theoretically? How to add up the effects of pesticides with similar mode of action? Toxic equivalents.
  - 2) Risk management: if pesticides with similar mode of action are additive, what are the consequences for manufacturers of single substances. Do we need additional data requirements e.g. info about the additivity regarding substances of competitors? When exposure not acceptable which uses to delete? The most toxic?
  - 3) Risk communication: how do we inform the general public?
- First issue to address is of course risk assessment;
- Hopefully the other issues addressed as well;
- I wish everybody a good and fruitful colloquium!

Documents on line

Regulation:
http://europa.eu.int/eur-lex/lex/RECH_naturel.do

Status of Active substances + MRLs sorted by pesticide/crop/commodity+guidance on import tolerances etc
http://europa.eu.int/comm/food/plant/protection/pesticides/index_en.htm

EU MRLs and Highest National MRLs (draft TMRLs submitted to EFSA) on line

http://ec.europa.eu/comm/food/plant/protection/resources/publications_en.htm

COMBINED RISK ASSESSMENT OF PESTICIDES AND MRL SETTING: EFSA PERSPECTIVE

Brocca Daniela
European Food Safety Authority
Pesticide Risk Assessment Peer Review (PRAPeR) - MRLs

Contents of the presentation:

- Why CRA is needed at EU level:
  - 1. EU consumers' concern;
  - 2. Actual pesticide residue situation in EU (monitoring);
  - 3. Legal framework;
  - 4. EU capability to deal with CRA.
- EFSA's needs and actions;
- Conclusions.

1 – EU consumers' concern

- As consumers, Europeans are alert;
- Already in 1998, a EU survey revealed that the issue most important to consumers was Food Safety ;
- In February 2006, results of the most recent EU survey on Risk Issues(*) were published…

(*) Special Eurobarometer 238/Wawe 64.1 –TNS Opinion & Social European Commission – February 2006

Q: "What are all the things that come to your mind when thinking about possible problems or risks associated with food?"

Food poisoning	16%
Chemicals/pesticides/toxic substances	14%
Obesity	13%
Illness/health problems	9%
GMOs	8%
Food additives	7%
…	…

Q: "For each of the following issues, please tell me if you are very worried, fairly worried, not very worried or not at all worried by it?"

Pesticide residues in fruits, vegetables or cereals	63(*)
New virus like avian influenza	62
Residues in meats like antibiotics or hormones	62
Unhygienic conditions in food handling	62
Bacteria contamination	61
Pollutants (e.g. Hg or dioxins)	59
.....	...

(*) Replies transformed from "worry scale" to numerical values – average index for EU

2 – Actual pesticide residue situation in EU

2004 EU annual report on Monitoring of Pesticide Residues(*)

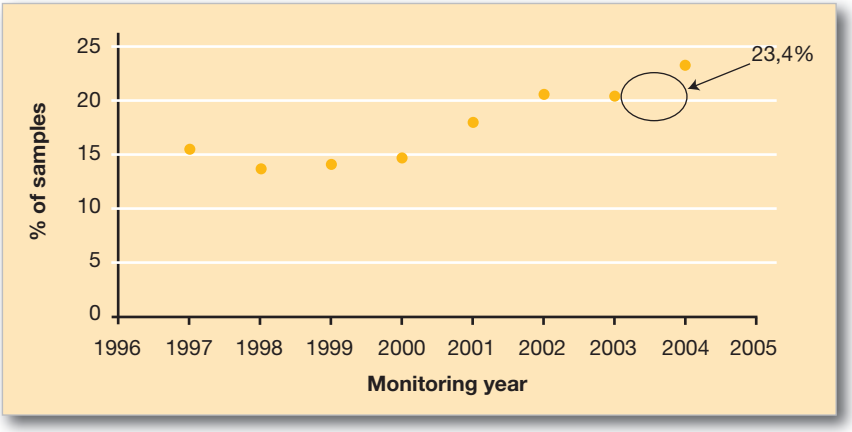
- Raw/processed commodities of plant origin considered;
- Ca. 55.000 samples analyzed;
- Average of 169 pesticides analyzed at national level (range 41 – 595).

EU Monitoring 2004 Samples with multiple residues

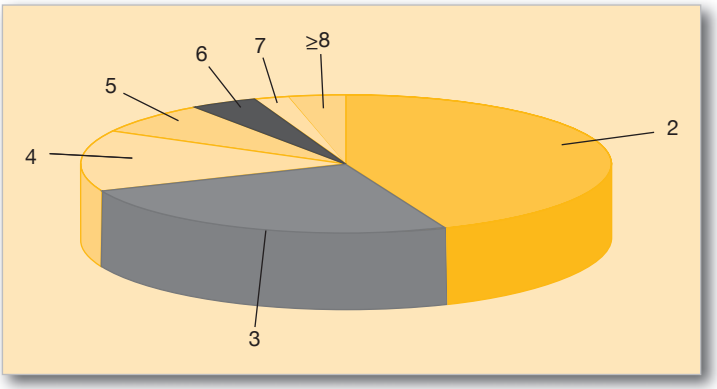
(*) "Monitoring of Pesticides Residues in products of Plant Origin in the European Union, Norway, Iceland and Lichtenstein – 2004"; Commission of the European Communities, SEC(2006) 1416

EU Monitoring 2004 Samples with multiple residues

Percentage of samples with multiple residues in fruits, vegetables and cereals



Distribution of samples with multiple residues according to the number of different residues in one sample



	Pesticide 1	Pesticide 2	Pesticide 3	Pesticide 4	Pesticide 5	Pesticide 6
Red currants	Cyprodinil	Fludioxonil	Maneb-group	Tolylfluanid	Tebuconazole	Trifloxystrobin
Clementine	Chlorpyriphos	Malathion	Methidathion	Imazalil	Phenylphenol	Thiabendazole

Organophosphate

3 - Legal framework

- The new EC Regulation 396/2005 on MRLs emphasizes the importance:

  "***to carry out further work to develop a methodology to take into account cumulative and synergistic effects of pesticides***".

- COM underlies the urgency and the need to set up such a methodology to address cumulative and synergistic effects (letter from COM to EFSA - July 2006).

4 – EU capability to deal with CRA

- Currently, no agreed international/European CRA methodology is available.
- Currently, in EU pesticide approval/MRL setting context, CRA of pesticide residues is not performed.

EFSA's needs…

- An agreed terminology/definition for CRA;
- An indication of what sources of pesticide residues are to be considered in CRA at EU level;
- A strategy to screen what pesticide combinations should be object of CRA;
- An operational methodology to carry out CRA.

…and EFSA's actions

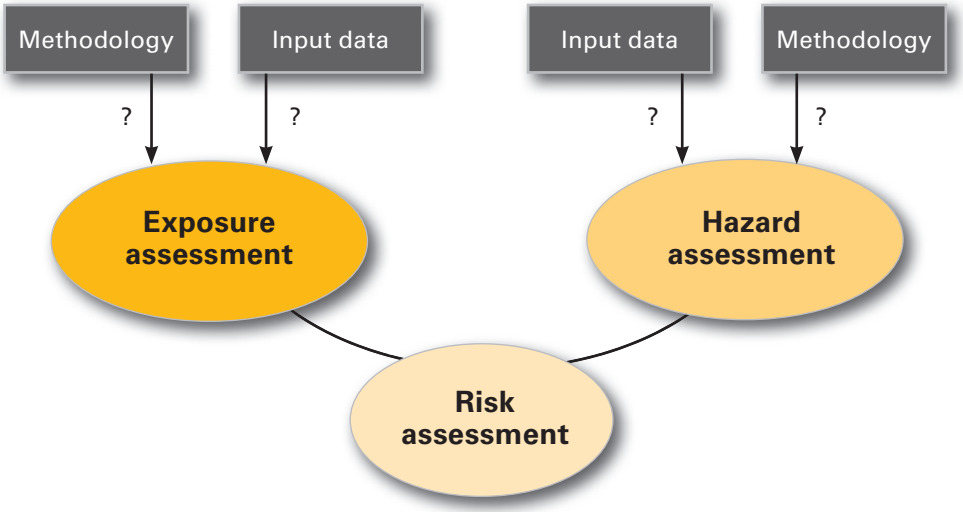
- PPR Panel(*) agreed with COM on the urgency and necessity of taking into account cumulative and synergistic effects of pesticides

- PPR Panel self tasked a question to evaluate the suitability of existing methodologies and, if appropriate, to identify new approaches

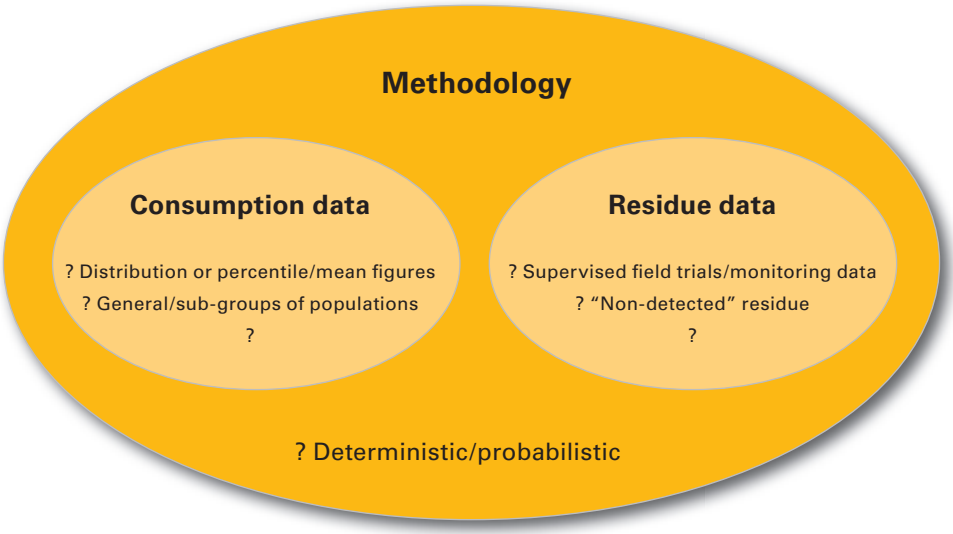
- EFSA scientific colloquium on CRA: the outcome of the colloquium will make a significant contribution to the PPR Panel's opinion

(*) EFSA's Panel on Plant Protection Products and their Residues

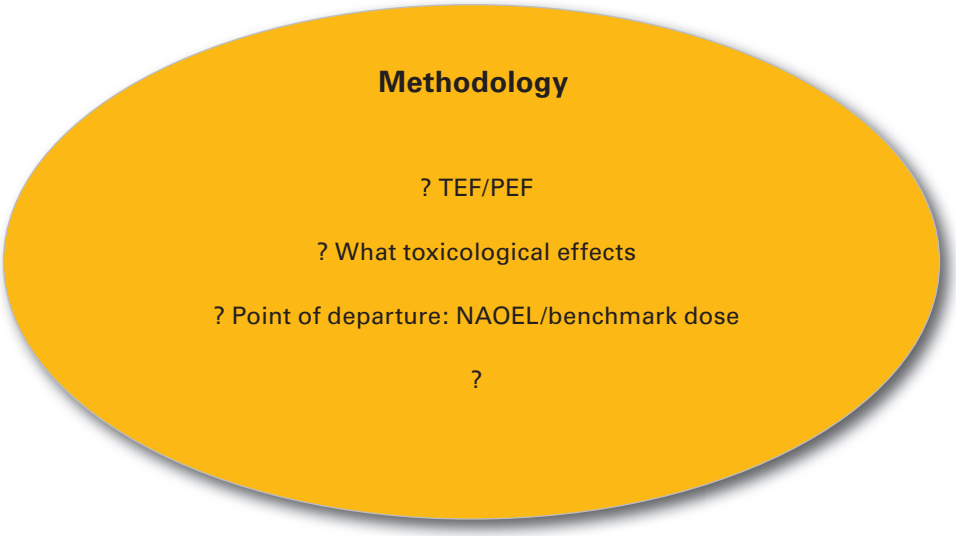
Considerations



Exposure Assessment



Hazard Assessment



Conclusions

- At present, no CRA is performed at EU level in the framework of pesticide approval/MRL setting;
- EU needs to develop capability/methodology to deal with CRA;
- In particular, EFSA needs operational tools;
- Outcomes of this colloquium will be further elaborated to build up the missing capability/methodology (PPR Panel opinion);
- As a result, EFSA welcomes an open debate within the scientific community and wishes a fruitful discussion during these two days scientific forum.

CUMULATIVE RISK ASSESSMENT

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Cumulative risk assessment:

1. Waffle about definitions
2. Basic science of mixtures
3. Common mechanism groups
4. How to cumulate

Terminology

- Cumulative risk assessment
  (more than one pesticide at a time);
- Aggregate risk assessment
  (all routes/pathways of exposure);
- Probabilistic "risk" (exposure) assessment
  (use of distributions rather than point estimates of exposure).

- Term introduced by the Food Quality Protection Act in the United States of America;
- Does not refer to pharmacological cumulation;
- Refers to consideration of exposure to more than one pesticide at a time;
- "Cumulative" not a very satisfactory term;
- Invites confusion with pharmacological accumulation.

Cumulative risk assessment: is it necessary ?

- It is based upon simple and well-recognised toxicological principles that:
  - pesticides with a similar mechanism of toxicological action will act similarly;
  - pesticides with a different mechanism of toxicological action will act independently.

Toxicology of mixtures:

Some basic considerations

TERMINOLOGY			
TYPE OF COMBINED EFFECT	**SUBTYPES**	**SYNONYMS**	**OBSERVED EFFECTS**
Non-Interactive	Simple Similar Action	Additivity	Dose Addiction
	Simple Dissimilar Action	Indipendent Action	Response Addiction
Interactive	Potentiation	Synergy	Greater than dose additive effect
	Antagonism		Less than dose additive effects

Simple similar action

- Dose/concentration additivity;
- It is likely to occur when the chemicals in the mixture act:
  - **in the same way,**
  - **by the same mechanism(s) (possibly at the same macromolecule),**
  - **differ only in their potencies.**
- effect is obtained by summing the doses of the individual compounds, having adjusted for differences in their potencies.
- If R(x) is the dose-response function of A and B, the response for a mixture with dose x_A of A and x_B of B is: $R(x_A + x_B)$

Simple dissimilar action

- results in response addition;
- the modes of action and possibly the nature and sites of action differ among the chemicals in the mixture;
- the constituents do not modulate the effect of other constituents of the mixture.

Response addition

- applies if each individual of the population has a certain tolerance to each chemical of the mixture;
- exhibits a response only if the concentration exceeds the tolerance dose;
- Where those who respond to constituent A, would not be able also to respond to constituent B eg death **and**
- susceptibility to A and to B are not correlated;
- the proportion of responders in the mixture is equal to:

$$R(x_A) + R(x_B) - R(x_A)R(x_B),$$

- There could be complete positive correlation in susceptibility of individuals to components of the mixture, in which case the proportion of individuals responding would always be determined by the more toxic component of the mixture.
- There could be complete negative correlation (seems unlikely), where the individuals most susceptible to one component in a mixture are least susceptible to another. In this case the percentage responding to the mixture will be equal to the sum of the percentages responding to each of the components $([R(x_A) + R(x_B)]$.
- **These relationships have been most widely studied in respect of death as a study outcome and with binary mixtures.**
- **When other outcomes are considered, it would be possible to have individuals, which would respond to both constituents (in different ways).**

Default assumptions

- Pesticides of the same toxicological group will show simple similar action (dose addition);
- Pesticides with different toxicological actions will show simple dissimilar action;
- No interaction will occur (no potentiation or antagonism).

Evidence base

- Moderately good for simple similar action;
- Difficult to design studies on simple dissimilar action.

A group that has tried to do it is Jonker et al in Holland. They gave mixtures of chemicals at their (individual) LOAELs, NOAELs and fractions of their NOAELs.

See: Jonker et al. (1990). Food. Chem. Toxicol. 9, 623-631. Jonker et al. (1993a). Food Chem. Toxicol. 31, 45-52. Jonker, D., Woutersen, P.J., van Bladeren, H. et al. (1993b). Food Chem. Toxicol. 31, 125-136. Jonker et al (1996). Food Chem. Toxicol. 34, 1075-1082.

Implications of the toxicology of mixtures 1

- With compounds with the same toxic action dose additivity is going to occur:
  - There is a good theoretical basis for saying this;
  - There is a reasonable evidential basis for saying this.
- Therefore not to do cumulative risk assessment is to ignore science soundly based in theory and on evidence.

Implications of the toxicology of mixtures 2

- With compounds with a different mode of toxic action effect addition is going to occur:
  - There is a good theoretical basis for saying this;
  - There is a some evidential basis for saying this.

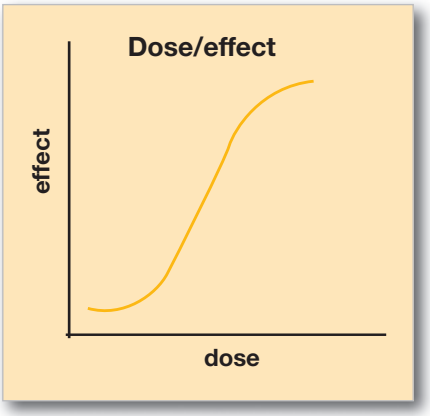
Interactions

Anything other than dose addition or response addition is defined as an interaction.

The mechanistic basis of the interaction be at the chemical, physico-chemical or biological level. Thus interactions between two chemicals in a mixture/ formulation, or interactions in either the toxicokinetic or toxicodynamic phase may occur.

- synergism, synergy, potentiation, supra-additivity - > dose additive effect;
- antagonism, sub-additivity, inhibition - < dose additive effect;
- **Dose vs response in toxicology is usually non-linear**;
- **Log dose/probit effect usually linear;**
- **Need full dose response for all components and for the mixture to establish then type of combined action that is occurring.**

Sigmoid dose/effect curve



- Many papers in the scientific literature claim potentiation, where there is insufficient information to say what type of combined action is occurring.

Breadth of problem

- Some relevant compounds not regulated as pesticides;
- e.g. veterinary medicines – ectoparasiticides (often OPs or pyrethroids) used on farm animals – veterinary fungicides- may leave residues in animal products;
- Natural compounds – anatoxin AS;
- Human pharmaceuticals – probably best excluded because risk assessment is not based on NIB.

Common mechanism groups

A common mechanism group is a group of pesticides with the same toxicological action by
1) acting in the same way on the same tissue/ organ/macromolecule or
2) by being metabolized to the same toxic metabolite.

COMMON MECHANISM GROUPS I

- Identify common mechanism groups;
- easiest with groups such as anticholinesterase OPs when they are all known to act at a single macromolecule (acetylcholinesterase);
- most difficult where compounds have similar effects but possibly by multiple mechanisms eg endocrine disruptors.

(Fenner-Crisp PA 1997. Regul Toxicol Pharmacol; 26: 70-73).

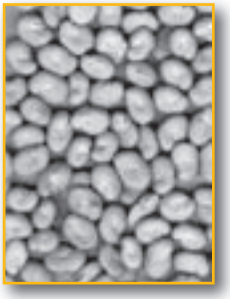
COMMON MECHANISM GROUPS II

- Identify a reference compound with a good data base eg methamidophos for Ops;
- Identify a study which you can use to calculate relative potencies eg rat 90 d study;
- Add the residues together having allowed for potency.

COMMON MECHANISM GROUPS III

- Now when you have intake data on all the pesticides in the group by all pathways of exposure you can do a cumulative and *aggregate risk* assessment.

Aggregate/cumulative risk assessment



BEAN COUNTING

- Identification of common mechanism groups;
- identifying a reference compound (in the TEF approach);
- calculating relative potencies;
- Gathering enormous amounts of data on intakes of pesticides by all pathways/routes.

Adding potency HOW TO CUMULATE

- Hazard index (HI)
  1a. Adjusted hazard index
- Point of departure index (PODI)
- Toxicity equivalence factors (TEFs)
- Combined margin of exposure (MOET)
- Cumulative risk index (CRI)

(Wilkinson CF et al Reg Toxicol Pharmacol 2000; 31: 30-43).

How to cumulate: Hazard Index (HI)

- The hazard index is the sum of the hazard quotients (HQ), where the HQ is exposure/reference dose eg:

$$HI = \frac{Exp_1}{RfD_1} + \frac{Exp_2}{RfD_2} \ldots\ldots\ldots \frac{Exp_n}{RfD_n}$$

Should be <1

HI pros and cons

- HI may be considered inappropriate as it is based on the ADI, which in turn is based upon critical NOAELs and dose spacing and:
- an uncertainty factor (which may be different for the different compounds);
- Relative toxicity thus not well described;
- However can incorporate data from compounds where reference doses are based appropriately on different safety factors eg human studies.

How to cumulate 2: Adjusted Hazard Index (aHI)

- Major problem arises when reference dose is based upon an effect that is not the group effect of the CMG.
- Example is carbaryl, which has a low ADI based on tumors.
- In the aHI, you calculate an "ADI" based on the group property (cholinesterase inhibition with carbaryl).

How to cumulate 3: Point Of Departure Index (PODI)

- Point of departure (POD) is a variable that reflects toxicity quantitatively eg ED_{10} or NOAEL for the chosen study.

$$PODI = \frac{Exp_1}{POD_1} + \frac{Exp_2}{POD_2} \ldots\ldots\ldots \frac{Exp_n}{POD_n}$$

Then to do a risk assessment one needs a group uncertainty factor (often 100).

PODI x UF should be < 1

How to cumulate 4: Toxicity Equivalence Factors (TEFs)

Need an index compound to which the toxicity of each component can be normalized. The TEFs for compounds 1 Index), 2....n are the ratios

$$\frac{POD_I}{POD_1}, \frac{POD_I}{POD_2}, \frac{POD_I}{POD_n} \text{ \&tc (TEF for index = 1).}$$

Then total normalized exposure for index compound and compounds 2 to n are:

$$Exp_i \times 1 + exp_2 \times TEF_2 ....expn \times TEF_n$$

Compare ∑ to RfD for index compound?

TEFs pros and cons

- Developed by the EPA to estimate toxicity of mixtures of structurally related dibenzo-ρ-dioxins &tc
- Has been suggested that:
  - It places too much stress on the toxicological data base of the index chemical;
  - The TEF should not be based on ADIs but some other metric.

How to cumulate 5: Margin Of Exposure (MOE)

$$MOE = \frac{POD}{Exp} (?= \frac{ED10}{Exp})$$

$$MOET = \frac{1}{1/MOE_1 + 1/MOE_2 ... 1/MOE_N}$$

Need to develop a group uncertainty factor (?100). MOE_T should > UF

MOE_Ts: pros and cons

- MOE: - already widely accepted that an MOE > 100 is acceptable **and**
- the point of departure (POD) used to generate the MOE is (roughly) proportional to the toxicity of each component.

How to cumulate 6: Cumulative Risk Index (CRI)

$$RI = \frac{POD}{Exp \times UF} = \frac{Rfd}{Exp}$$

$$CRI = \frac{1}{1/RI_1 + 1/RI_2 + 1/RI_3 \ldots\ldots 1/RI_N} = \frac{1}{HI}$$

Disadvantage: RfD depends on uncertainty factor/dose spacing and may not be directly proportional to toxicity.

Conclusions 1

- The case for cumulative risk assessment is scientifically unchallengeable.

Conclusions 2

- Major scientific problems;
- Identification of common mechanism groups is not always easy;
- The best method to relate toxicity between members of common mechanism groups needs careful thought.

The end

- Risk Managers
- Better paid
- Wear suits

CUMULATIVE RISK UNDER THE 1996 FOOD QUALITY PROTECTION ACT (FQPA): HAZARD & DOSE RESPONSE COMPONENT

Dr. Vicki Dellarco
U.S. Environmental Protection Agency
Office of Pesticide Programs

What had to be done to implement cumulative risk assessment!

- Interpret FQPA
- Develop guidance, methods, software
- Compile, analyze, & manage data
- Document the process & ensure transparency, public comment & peer review

Visit: http://www.epa.gov/pesticides/cumulative

Our legislative language defined cumulative risk under FQPA!

"... reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."

". . . available information concerning the cumulative effects of such residues and other substances that have a common mechanism of toxicity ..."

Common mechanism was our organizing principle!

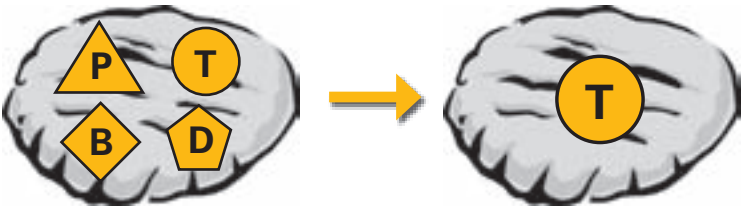
- Permitted
  - Identification of pesticides of interest
  - Quantification of risk by relating each pesticide's toxic potency to other members in the group

    - Concept of Dose Addition & the Relative Potency Factor (RPF) Approach

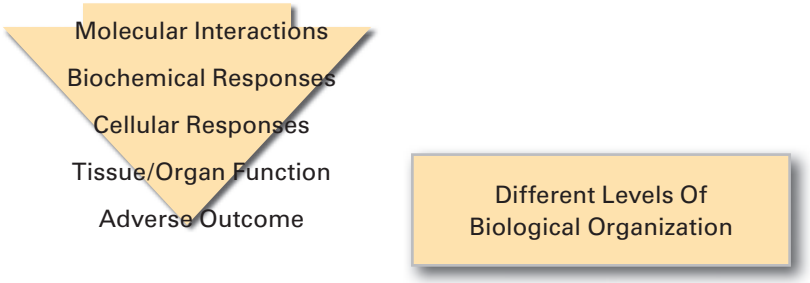
$$RPF = \frac{\text{Index Chemical Potency (BMD)}}{\text{Chemical X Potency (BMD)}}$$

Relative Potency Factor Approach

RPFs for each chemical convert their specific residues (B,D,P,T) on a food sample to a common residue (T)



What constitutes a common mechanism of toxicity?

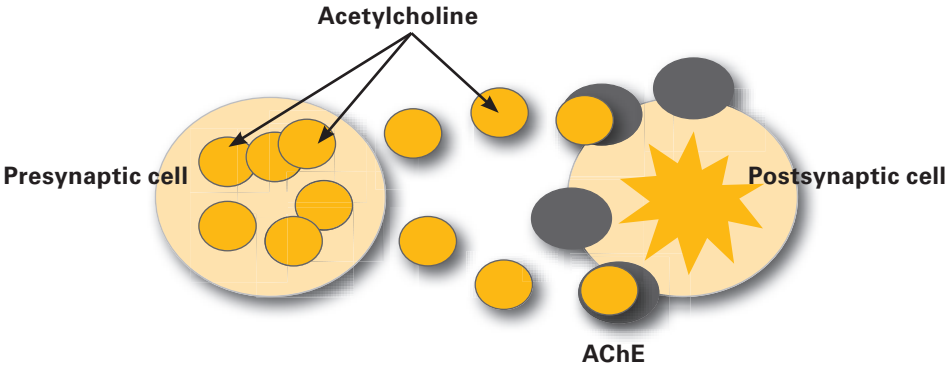


What constitutes a common mechanism of toxicity?

- **Definitions**
  - Mechanism of Toxicity — "...major steps leading to an adverse health effect following interaction of a pesticide with biological targets. All steps leading to an effect do not need to be specifically understood..."
  - Common Mechanism of Toxicity — "...two or more pesticide chemicals that cause a common toxic effect...by the same, or essentially the same, sequence of major [or key] biochemical events..."

**1999 Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity -http://www.epa.gov/pesticides/trac/science/#common*

- Three general principles to guide common mechanism determinations:
  1. Cause the same critical effect
  2. Act on the same molecular target at the same target tissue
  3. Act by the same biochemical mechanism of action
- Consider other mechanisms & effects
- Organophosphates (OPs)
  - Inhibition of cholinesterase via phosphorylation
- N-methyl carbamates
  - Inhibition of cholinesterasel via carbamylation
- Distinguished carbamates & OPs because of significant differences in pharmacokinetics & pharmacodynamics

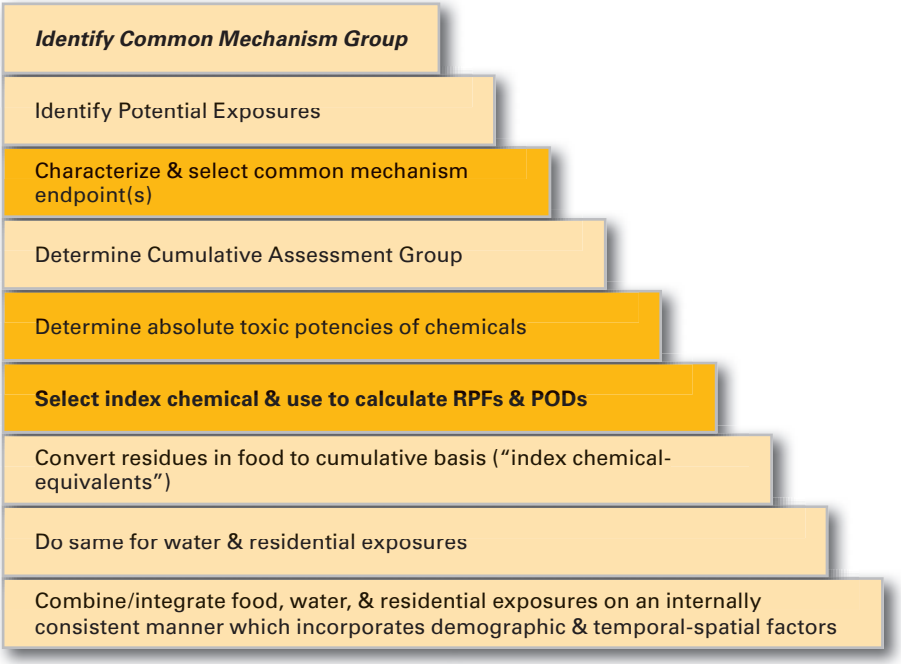


What constitutes a common mechanism of toxicity?

- Triazines
  - LH suppression leading to developmental & reproductive effects
- Chloroacetanilides
  - Nasal tumors via common metabolite producing cytotoxicity & regenerative proliferation

Visit:http://www.epa.gov/pesticides/cumulative

STEPS in Cumulative Risk Assessment (abbreviated version)



Hazard & Dose Response Assessment

- Further analysis of common mechanism
  - Common mechanism endpoint(s)
  - Temporal (Time Course) Considerations
  - PK & PD Interactions
  - Inter & Intra Species Extrapolations

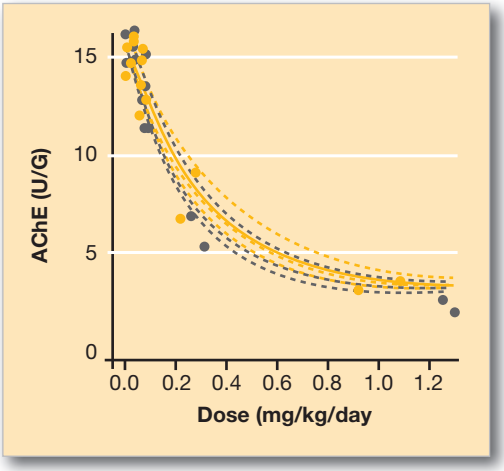
Absolute Toxic Potencies, Relative Potencies & Points of Departure

- What endpoints events are involved in (or associated with common mechanism?
- Are there species, strain, sex, or life stage differences?
- How robust are the dose response data?
- Are there route specific data?

- Uniform & Accurate Measure of Relative Potencies
  - common toxic endpoint
  - same species, sex
  - same level of response
  - studies of comparable methodology
  - route specific data
  - model-derived estimates (BMDs)

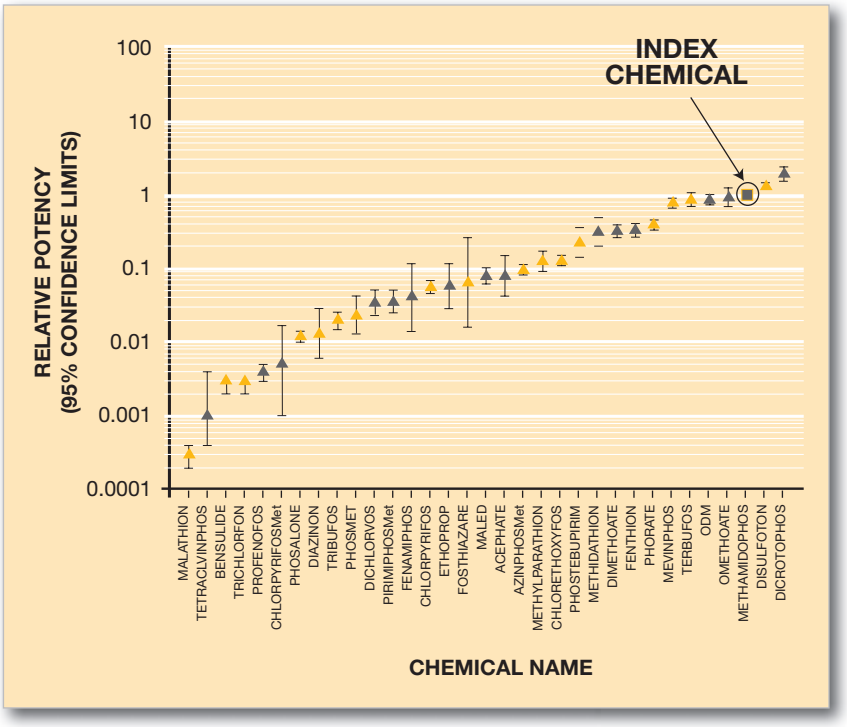
Dose-Response Assessment for Organophosphates

- Rat ChE activity data collected from studies at 21 days or longer (i.e., steady state)
- Multiple studies used to provide robust estimate of potency & incorporate variability across studies
- Exponential dose-response model
- Analyzed power to detect various degrees of rat brain ChE inhibition (BMD_{10})



Final Organophosphate Cumulative Risk Assessment (2006)

Relative Potency Factors for female Brain ChE activity

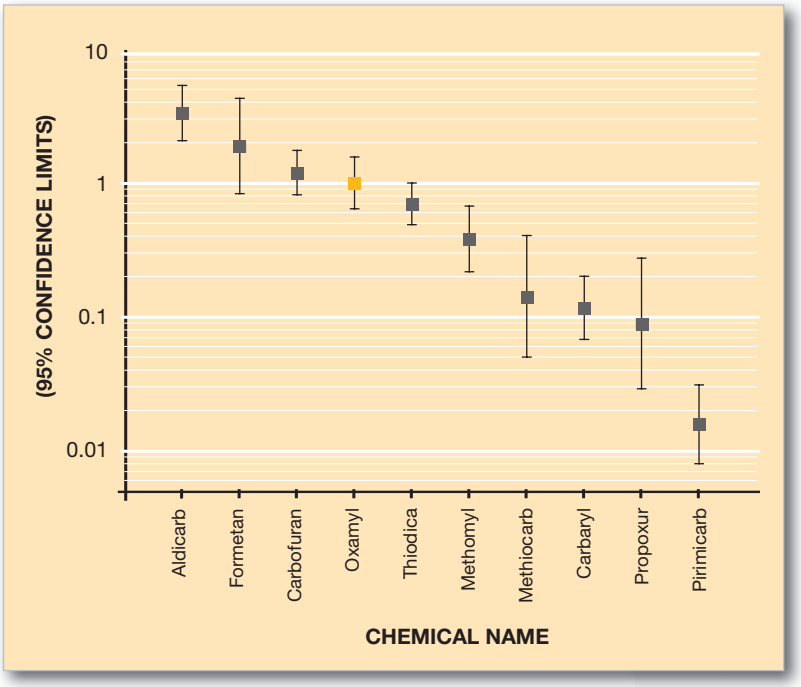


Dose Response Assessment for N-Methyl Carbamates

- Relative potencies for CHE inhibition are estimated along with recovery half lives from acute (single dose) rat dose-time response data at or near peak.
- Dose & Time Course Model Used
  - Dose-response portion of model is similar to that used for AChE inhibition by organophosphates.
  - Time course model reflects an exponential decay of inhibition.
  - When available time course recovery data were used.

Revised N-Methyl Carbamate Cumulative Risk Assessment (2005)

Relative Potency Factors

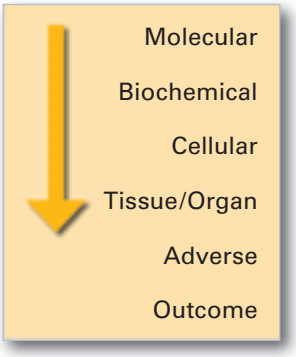


Time Frame (Time Course) Considerations

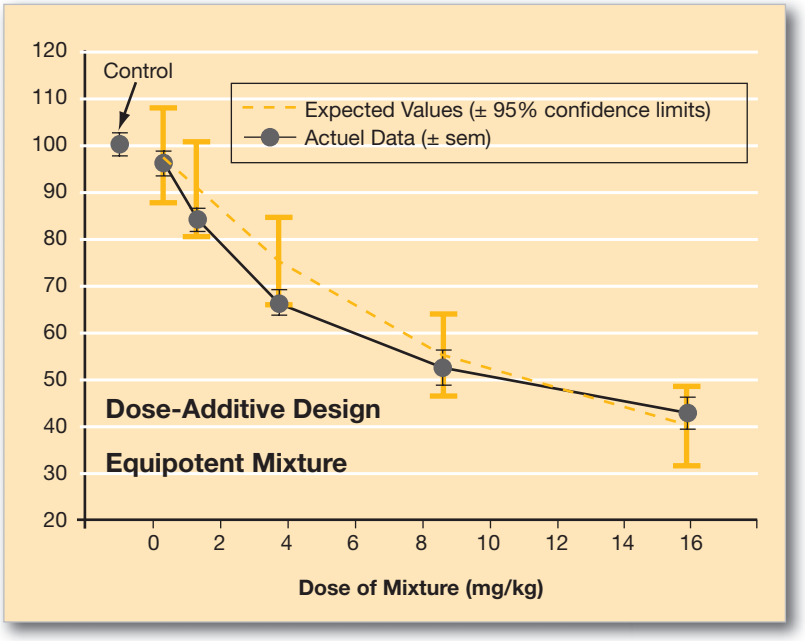
- Toxicity values should be matched appropriately with exposure durations of same time-frame of interest.
  - Need to understand:
    - What is the time to maximum response?
    - How long does the effect persist? What is the recovery time?

PK & PD Interactions

- Departures from additivity may be less likely to occur for common mechanism chemicals than for mixtures involving multiple modes of action.
  - Are well designed mixtures studies available to support assumption of dose additivity at low doses?
  - Do results depend on dose/endpoint?



Carbamate Mixture Study: - Brain Cholinesterase

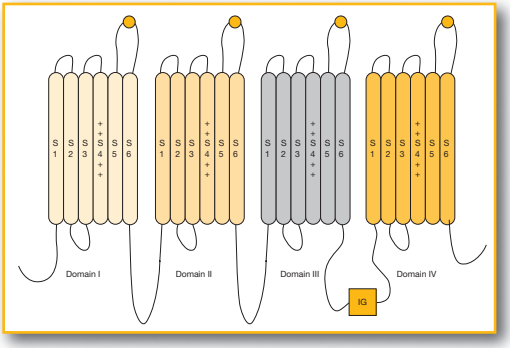


Inter- & Intra- Species Extrapolations

- Interspecies Extrapolation (1-10X UF)
  - Human Studies
    - Sufficiently robust for evaluating inter-species extrapolation & for use in dose-response modeling?
- Intraspecies Extrapolation (1-10X UF)
  - Data available on the variation in sensitivity among humans?
- ▶ FQPA 10X Safety Factor
  - Children's Susceptibility to the Common Mechanism

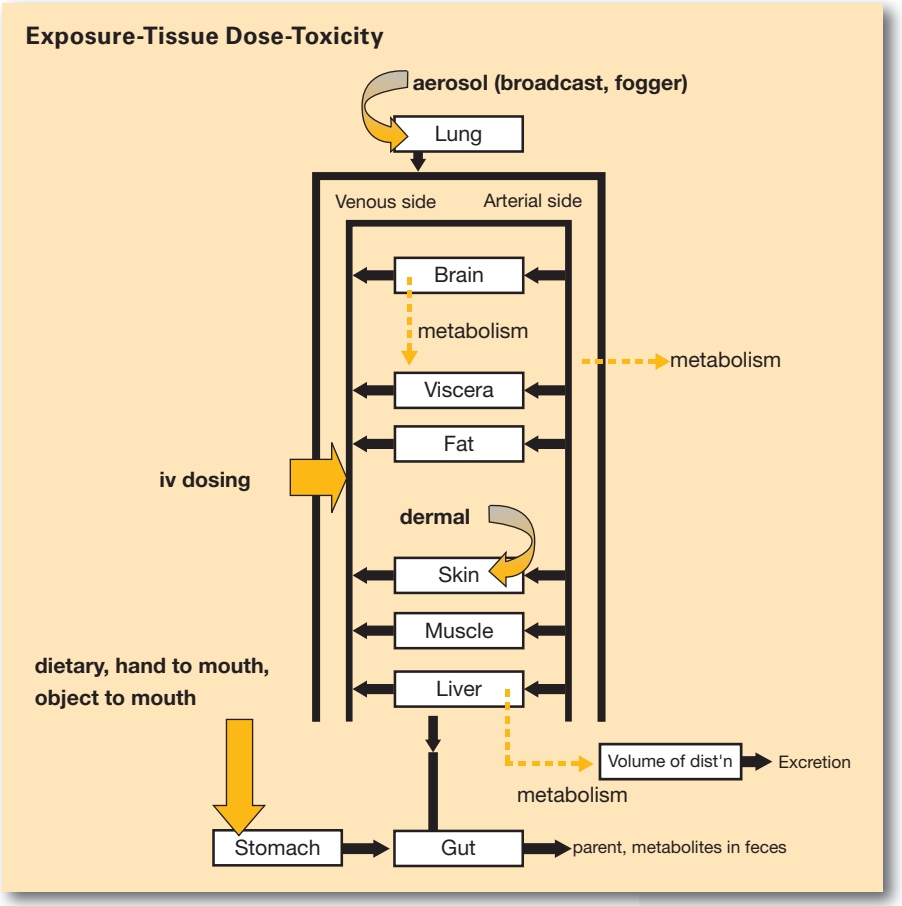
What's the next challenge?

- Pyrethroids
  - How to group pyrethroids by a common mechanism of toxicity?
    - more than one group?
  - At what level of neuronal organization to calculate relative potencies?
    - Molecular - ion channels (multiplicity of targets & in vitro data only)
    - Cellular function - firing rates (in vitro)
    - Behavioral – different endpoints
  - What are the effects of mixtures?
    - Test mixtures (in vitro, in vivo)



Promote Research

- Pyrethroids
  - Tissue Dosimetry & PK modeling
    - Dose metric
      concentration of active form at site of action
    - Linking dose metric to animal effect & human hazard



Final Word: Cumulative Risk Assessment

- Purpose
  - Will be a guide to the risk manager for further refinement & risk mitigation activities
- Goal
  - Use Representative Data and Strive for Realistic & Accurate Assessments
- Approach
  - Careful Stepwise Approach to Implementing Cumulative Risk Assessment

EUROPEAN EXPERIENCES IN COMBINED HAZARD ASSESSMENT: SCIENCE AND POLICY ISSUES.

MARCEL T.M. VAN RAAIJ
National Institute of Public Health and Environment (RIVM)
Centre of Substances and Integrated Risk Assessment (SIR)

Contents of this presentation

- Combined hazard assessment in Europe?
- How to cumulate?
  - Toxicological basis
- Some examples from organophosphorus pesticides
- Problems with exposure data and calculations
- Consequences for risk management
- Current view from Dutch policy and inspection

Cumulative Exposure

- **Cumulation**: total exposure to various substances with a common mechanism of action through a certain route of exposure (e.g. dietary intake);

- **Aggregation**: total exposure to one (or more) substance(s) through several routes of exposure (e.g. food, work place, consumer products)

Combined hazard assessment in EU

- Is there any EU action on combined hazard assessment?
- ~~Pesticides?~~ Not yet
  - Except some occasions e.g. omethoate & dimethoate
- Food additives → Group ADI's
- Contaminants → Dioxins & dioxin-like PCBs
- Some approaches based on "expert judgement"
  - Molecular structure
  - Kinetics
  - Assumptions & "Read Across"
    - E.g. group ADI's
    - Ad-hoc procedures.....
- Some approaches based on relative toxicity information
  - Toxicological Equivalence Factors (TEFs)
  - Relative potentcy Factors (RPF)
  - Based on mechanistic information on the working mechanism
    - E.g. dioxins

Pesticides approaches in EU

- No current EU approach
- Incidental reports on cumulative risk of pesticides in EU
- RIKILT institute for food safety (2003): combined intakes of OPs and carbamates in Netherlands
- Jensen et al. (2003) combined intakes of OPs and carbamates in Denmark
- Various international experimental research papers
- Various overview reports on the issue of combined risk assessment for pesticides (UK, DK, NL.....)

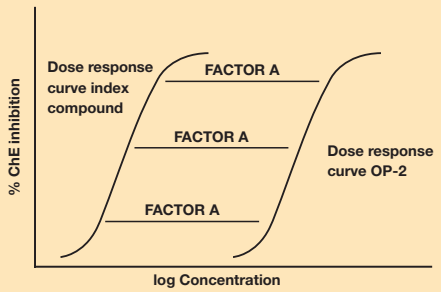
How to sum various substances?

- HAZARD INDEX
  - Based on exposure and a toxicological (limit) value
  - Toxicological limit value is often a health based limit value (e.g. ADI)
  - Relatively simple and fast
  - First screening
- RELATIVE POTENCY FACTORS
  - Directly based on toxicological properties
  - Based on dose-addition
  - Index compound
  - More difficult to establish

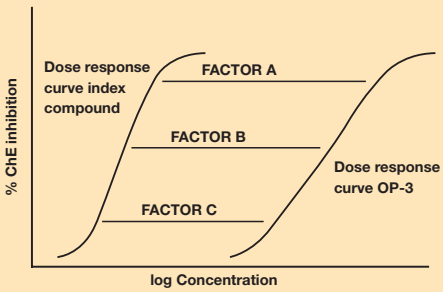
Relative Potency Factors

- RPF approach – principally – is only applicable when the concept of dose addition is valid.
- Dose-addition ?
  - Simple similar action, no interaction
- Effect-addition ?
  - Simple dissimilar action, independent joint action, non interaction

Dose Addition = OK



Dose Addition ≠ OK



▶ Example:

Concentrations of Chlorpyriphos-oxon en Azinophos-Meoxon on ChE inhibition in brain tissue of the rat – in vitro

Inhibitie %	C=O (nM)	AZM=O (nM)	Factor
10	0.49	4.70	9.6
20	0.92	9.80	10.6
30	1.39	15.99	11.5
40	1.97	23.87	12.1
50	3.70	49.80	13.5
60	7.95	121.22	15.2

Richardson et al. 2001 (Toxicol. Appl. Pharmacol.)

RPFs

- RPF approach – principally – is only applicable when the concept of dose addition is valid.

- Dose-addition?
- Effect-addition?

- For OPs, dose addition generally assumed
- Evidence for dose addition, primarily indirect
- Also data available that reject dose addition !

▶ Example 1

Methamidophos (M)

Acephate (A)

Combination exposure provides LESS ChE inhibition in vivo

Singh, 1986 (Toxicol.)

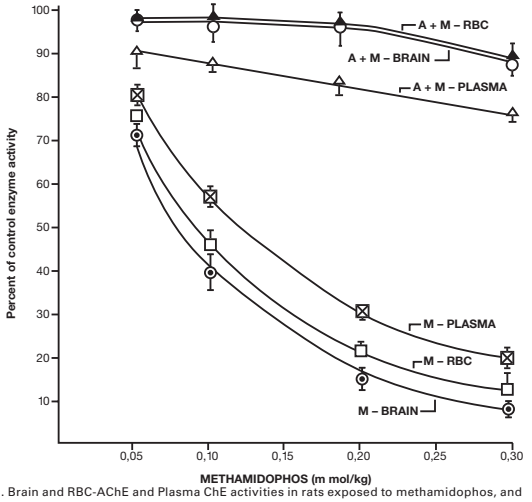


Fig. 1. Brain and RBC-AChE and Plasma ChE activities in rats exposed to methamidophos, and acephate plus methamidophos.M. Brain, M-RBC and M-Plasma are samples obtained from methamidophos exposed rats. A + M-Brain, A + M-RBC and A + M-Plasmaare samples obtained from rats exposed to both acephate plus methamidophos. (Values are mean ± S.D.)

▶ Example 2

Methamidophos (I)

Acephate + M (II)

M + A (30s) (III)

M + A (60s)

Result of combination exposure in vitro is time dependent

Singh, 1986 (Toxicol.)

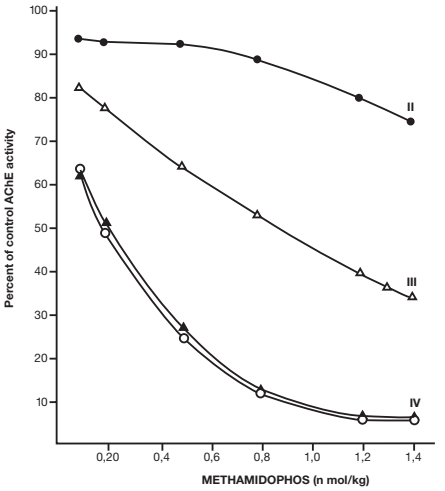
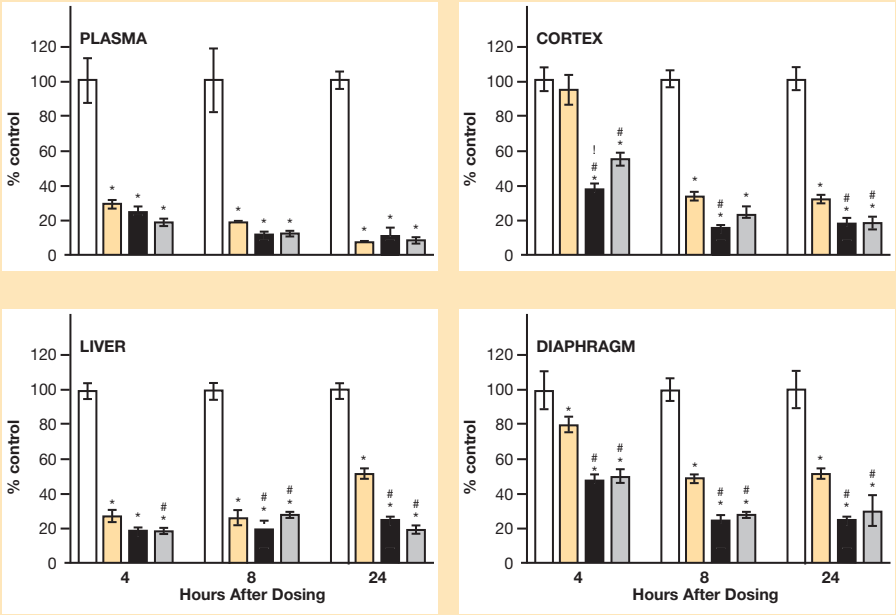


Fig. 3. Residual AChE activity in samples incubated with various doses of methamidophos in presence or absence of acephate. I (–o–) : samples exposed to methamidophos. II : samples exposed to acephate plus methamidophos together. III : samples exposed to acephate 30 s after methamidophos. And IV : samples exposed to acephate 60 s after methamidophos.

▶ Example 3



Order of dosing of 2 OPs determines the outcome of the mixture toxicity

Karanth et al., 2001 (Toxicol. Appl. Pharmacol. 177)

Cumulative exposure calculations

- The RPF approach is used to express all OPs into a single compound.
- When cumulative exposure calculations are performed using RPFs and dose addition is not valid then....
- A part of the calculated exposure is "cooked air".

From a pragmatic point of view:
assumption of dose addition is OK (seems worst case approach)

Fundamental scientific basis: more data needed

Chronic and acute exposure

- Chronic exposure: steady state inhibition
- Acute exposure: peak exposure and time to peak on the toxicological target is important (kinetics!)
- RPF chronic ≠ RPF acute
- The difference between chronic RPF and acute RPF is substance dependent
- Just as in every risk assessment: the toxicological data should match the exposure duration
  - RPFs, exposure calculations, toxicological endpoint (limit value)

OPs & carbamates ?

- Do OPs en carbamates have a "common mechanism of toxicity"? Probably not, although effect addition may occur
- Time scaling:
  - Carbamate exposure (evening) may sum up with a previous OP-induced OP ChE inhibition (morning)
  - OP exposure (evening) does not sum up with a previous carbamate induced ChE inhibition (morning)
- Most international organisations: Not to combine OPs and carbamates, but not all.
  - Interest of Dutch Food and Non-Food Authority: investigate the possibilities of combining OPs and carbamates

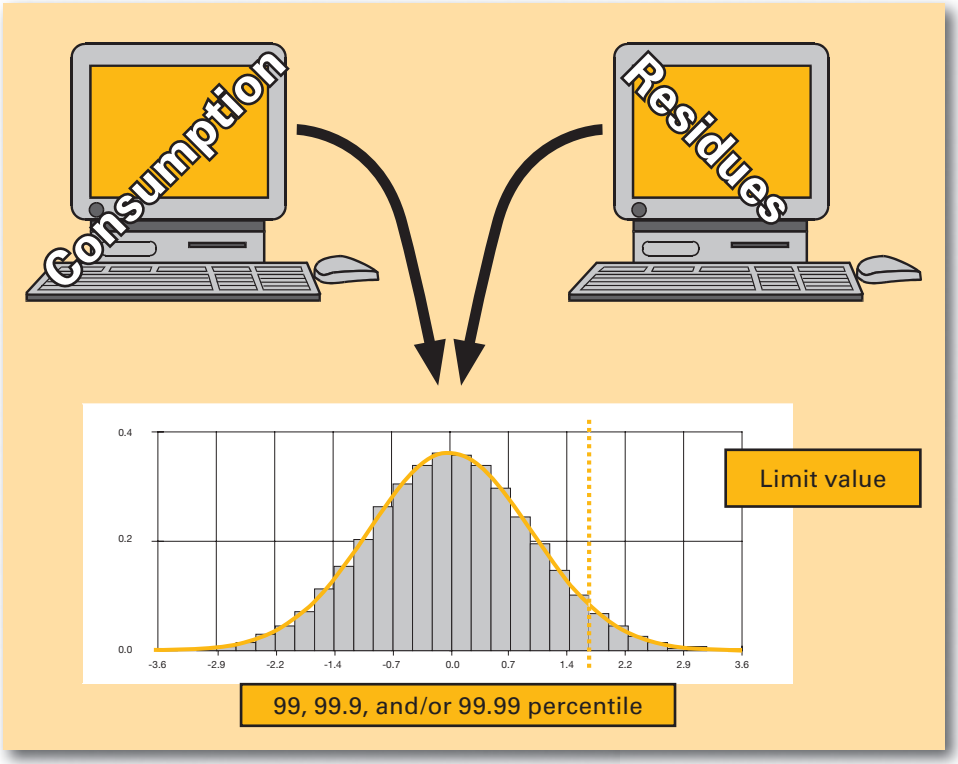
Which pesticides should be combined ?

- There is a need for transparent criteria to decide which substances to cumulate
- US-EPA: Common Mechanism Group (CMG)
  - Mileson et al. (1998)
  - OPs and Carbamates separately
- UK WiGRAMP: similar CMGs as US EPA
  - OPs and carbamates together?
- What will be used in EU?
  - RIVM a.o. will present a report on this issue early 2007.

Residue data?

- In present cumulative exposure calculations, use of monitoring data.
  - Non-random bias
  - What about juices?
  - What about zero's?
  - Taken into account the limitations in the conclusions
- What to do in an admission procedure?
  - What data should we use?
  - Field trials are not adequate for cumulative exposure calculations
  - If we have a new substance: no monitoring data at all !
  - What about regional differences in the EU ?

Monte Carlo Exposure Calculations



- **Monte Carlo Exposure Analysis** (e.g. MCRA – STEM) is an already developed method for probabilistic intake assessment

  but currently.....

  - ▷ It provides a distribution of person-day combinations.
  - ▷ It does not yet provide the "fraction of the population above the limit".
  - ▷ It does not yet provide the "frequency of exceeding the limit".
  - ▷ Further development of this modelling is planned by RIVM and RIKILT to provide methods that provide such output.

http://mcra.rikilt.wur.nl/mcra/rsc/sjablonen/blauw/mcrahomenew.html

Combined hazard assessment: when?

- At what point in an admission procedure is a combined hazard assessment performed?
  - With each new substance?
  - With each extension of the use?
  - Once during a certain period?
- Who is responsible for performing a combined hazard assessment?
  - Industry?
  - Competent Authorities?
  - EFSA?

Policy implications(1)

- Method development in the “risk assessment” area

  But also.....
- Arrange procedures for “risk management” !!!!

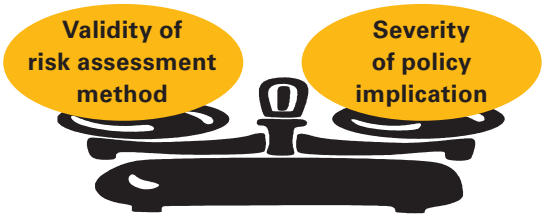
What to do in admission procedure?

- New OP evaluated
- Single OP exposure: no risk
- Cumulative exposure to OPs provides risk

- How to proceed?
  - New OP cannot be allowed?
  - Place a ban on the most toxic OP?
  - Ban the OP with the largest contribution (risk driver) in the cumulative exposure?
  - Control at active substance or product level?
  - Similarities / differences in EU member states?
  - Legal basis?
  - Also take into account other characteristics (operator exposure, environmental issues)?

Policy implications (2)

- Is there a health risk from cumulative OP exposure?..... Possibly
- Should cumulative exposure assessment be an integral part of pesticide policy?
  - **Yes according to consumer organisations, politics, science**
- Take into account our gaps of knowledge and methods.....



CUMULATIVE EXPOSURE ASSESSMENT FOR PESTICIDES WITH LONG TERM TOXIC EFFECTS

PHILIPPE VERGER
French National Institute for Agricultural Research
Methodologies of food risk analysis unit

Objectives

- To estimate the dietary exposure to one or several substances having the same toxicological endpoint;
- To compare the dietary exposure with the health based reference value.

General formula

$$E_i = \frac{1}{n_i \cdot bw_i} \sum_k \sum_t Q_{i,t,k} \cdot C_{i,t,k}$$

Where:

- E_i is the usual intake of individual i (ng/kg body weight/day),
- i is an index for individual: i=(1,...,1434),
- t is an index for time window to assess food consumption and contamination: weeks, days or single occasions of consumption,
- k is an index for food group: k=(1,...,13),
- $Q_{i,t,k}$ is the consumption of food group k on occasion t by individual i (kg),
- $C_{i,t,k}$ is the contamination of food group k encountered on occasion t by individual i (µk/kg),
- n_i is the number of days of food records available for individual i,
- bw_i is the body weight of individual i (kg).

Simplified formula

- For international assessments food are considered to be eaten on a single eating occasion and a single day because of the lack of harmonisation between national food consumption data

$$E = \sum (Q * [C]) / \text{Body weight}$$

Concentration of pesticide residues

- Driving element of the assessment;
- Integration of various data sets to estimate a weighted mean* (deterministic approach) or to build a distribution curve (probabilistic approach);
- In the case of pre-regulation: Supervised Field Trials and proposed MLs.

** WHO consultation, 2000*

Choice of food consumption

- To choose the lowest level including the one for which residue data are available
  - Food
    - Fruits and vegetables
      - Vegetables
        - Leafy vegetables
          - Spinash

Data needed in the case of one chemical

- Concentration of the chemical in food categories in which the chemical occurs;
- Consumption of the corresponding food categories.

Some proposals for discussion in the working groups…

Which data are needed to assess a cumulative exposure?

- ▷ Concentration of each chemical in food categories in which it occurs
- ▷ Consumption of the smallest category including those in which all chemicals occur

  - Example: one chemical occurring in leafy vegetables, the other in spinach only, the considered consumption will be "leafy vegetables".

Pre-regulation dietary exposure assessment

- ▶ Simple approach
- ▶ Conservative estimate
- ▶ Harmonised food consumption data from EU MS based on individuals
- ▶ Residue data from proposed MLs or Supervised Field Trials
- ▶ Comparison with Tolerable Daily Intake

Pre-regulation: in practice

- ▶ Maximum Residue Levels or median of supervised trials (ML >> SFT)
- ▶ Consumption of the smallest category in which at least one of the pesticide is authorised
  - ▷ In practice total vegetable consumption or broad sub-categorisation (Root, leafy…)
- ▶ Estimation of lower (median SRT) and upper (MRLs) bound for dietary exposure

Post-regulation dietary exposure assessment

- Stepwise approach
- Use of the best available data from all sources (occurrence and consumption)
- Deterministic assessment or stochastic modelling
- Consideration of groups at risk

Cumulative exposure

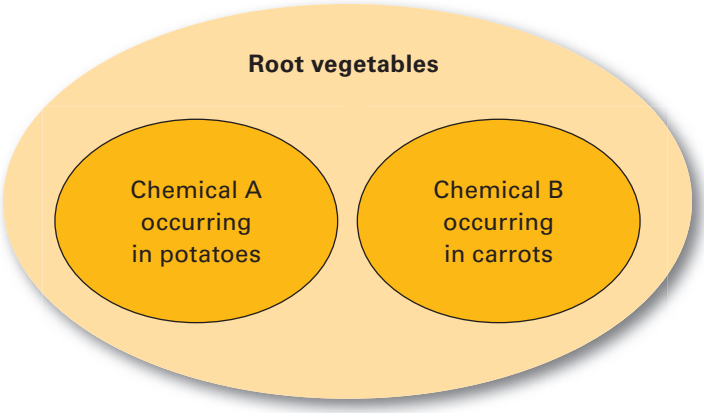
- Assuming additive toxicity i.e. several substances have the same toxic mechanism on the same organ
  - Application of the concept of Toxic Equivalent Factor
  - The concentration of each chemical is multiplied by a coefficient between 0 and 1 if the chemical is less toxic than the chemical of reference and higher than 1 if it is more toxic for the same dose
- Assuming synergistic effects i.e. if 2 chemicals are present in the diet at the same time their toxic effect is more important than the one of each of them at different time.
  - The overall exposure is multiplied by a coefficient between 0 and 1 if the co-occurrence leads to an antagonist effect and higher than 1 if the co-occurrence leads to a synergistic effect

Implication for hazard characterisation

- Existence of additive effects
  - Definition of TEF for each of the substances
- Existence of synergistic (or antagonist) effects
  - Definition of the magnitude of the synergy (50, 120, ...500 % of the initial effect)?
  - Definition of the time window for synergistic effects (same eating occasion, day, week...)?

Implication for exposure assessment

- The considered food consumption should be broad in order to include all the food categories in which at least one chemical occurs: **possible overestimation**



Implication for controls

- In order to avoid unrealistic overestimation in the case of post-regulation risk assessment, data on co-occurrence of residues in the same samples should be collected

Annex 4: Slides of Discussion Groups

INSTRUCTIONS FOR DISCUSSION GROUPS

JULIANE KLEINER
EFSA

Organisational Details

- 4 parallel discussion groups
- 13:30-16:00 DG 1st round
- 16:30-18:30 Touch base with Plenary
- 09:00-11:00 DG 2nd round – Risk Characterisation
- 11:30-13:30 Report back from DGs and Final Plenary session
  - joint efforts with Member States
  - conclusions and recommendations

Working terminology

Cumulative hazard assessment (dose-addition):

two or more chemicals with a common mode of action

Non-dose-addition effects (Combination toxicity):

effect/response addition, synergistic effects, antagonistic effects

DG 1 Cumulative hazard assessment

- Criteria for grouping compounds into a common MOA assessment group
- Possibility for prioritisation of pesticides to work at?
- Approach to be taken to combine potency/toxicity (e.g. TEF)
- What should be the point of departure
  (e.g. NOAEL, BMDL10)
- Minimum data requirement for including a compound in a cumulative hazard assessment

DG 2 Non-dose-addition effects

- What combined effects are of concern
- What tox. effects are of concern from combined exposure
- How to identify compound groups
- What default assumptions should be used
- What study design to be used
- Approach to be taken to combine potency/toxicity (e.g. TEF)
- What should be the point of departure (e.g. NOAEL, BMDL10)
- Minimum data requirement for including a compound in a combined hazard assessment group

DG 3 Choice of data for combined exposure

EA for MRL setting VS EA for actual exposure (chronic and acute exposure)

- Consumption data (e.g. data collection, general population, relevant subgroup, individual records vs modelled distribution, seasonal pattern, outliers, timelines, quality of data, interdependence of consumption lev.)
- Residue data (e.g. data collection, monitoring studies vs supervised field trials, seasonal pattern, outliers, quality of data, interdependence of residue levels)

DG 4 Methodology for combined exposure

- Methodology: deterministic Vs probabilistic
- Criteria for model to estimate combined exposure
- Requirements for models (e.g replicate results
- How to deal with uncertainties and variabilities
- Interpretation of results, When should safety concerns be raised
- Lessons learnt from available models

Discussion groups - 2nd day

- Continuation of discussion by taking into account outcome of other discussion groups
- Consideration on integration of information from combined exposure assessment and hazard assessment
- Possible joint actions with Member States, EFSA , non-EU MS and international organisations and prioritisation of actions
- Conclusion and recommendation from working group

Summary Report of Colloquium

- Draft summary report of colloquium to be prepared by rapporteurs (Dec. 07)
- 1st review by DG chairs and rapporteurs (Jan. 07)
- Review of revised draft by all participants (Feb.07)
- Publication of summary report and power point presentations on EFSA website (March 07) and in EFSA Science Colloquium Report Series (May 07)

DISCUSSION GROUP 1

CUMULATIVE HAZARD ASSESSMENT

Day 1

MECHANISM IS MEANT TO BE MODE OF ACTION

Methods and their advantages and disadvantages to be used to estimate cumulative hazard

HAZARD INDEX (from the reference dose)

- Existing probabilistic software may not work well with this system (need to be tested).
- More practical to do quickly.
- Reference Doses have already safety factors in them.
- Science policy input in safety factors (e.g.: no use of human data).
- May be used for a quicker screening.
- Influenced by dose spacing.
- Adjusted hazard index for the common effects requires more work.
- Problems of communicating the results (2 is not necessarily different from 4)

POINT OF DEPARTURE INDEX

- Describes the toxic potency better than the adjusted hazard index.
- Needs more work than adjusted hazard index.
- If the NOAEL is used, the process is easier than if the benchmark dose is used.
- If not enough data, large confidence intervals (e.g.: triazines vs OPs).

TEF/PEF

- Uncertainties can be "qualitatively" defined (applies to all methods, quantitatively if benchmark dose is used).
- Needs more confidence of the mode of action.
- Works with existing probabilistic software.
- Adjustment can be made for age, sex and availability of human data.

MOE

- it is the reciprocal of the Point Of Departure.
- it has not a pre-defined level of acceptability (safety factors)

Point of departure to be used in estimating hazard in cumulative risk assessment

NOAEL

- Influenced by dose spacing.
- Fits with current testing guidelines.
- Already harmonised.
- Animal welfare needs to be considered in comparison with testing strategy for benchmark dose.
- NOAEL is where changes may became statistically insignificant (e.g. trend, with low dose non significant effects).

BENCHMARK DOSE

- Current studies are NOT designed for benchmark dosing.
- With two responding groups it may be possible to define a benchmark dose.
- In vitro: may help on addressing the right end-point in vivo (e.g.: pyrethroids). (all methods)
- Where the necessary data are available it provides a better index of potency than NOAELs.

Criteria for grouping compounds into a common mechanism group

- Criteria should be science based.
- Useful frameworks and guidances are available for determining mode of action (IPCS, ILSI and EPA).
- SAR may give some guide.
- Easy when there is a well established single target (OPs, Carbamates).
- More complicated when there are multiple targets and feed-back mechanisms e.g.: pyrethroids and endocrine disruptors.
- There are options regarding strength of evidence for commonality of mode of action. E.g.: grouping only when the scientific basis are sound enough (US EPA position) or assume common mode of action when no evidence to the contrary.
- As a minimum the compounds must have the same end-effect. This approach opens to a lot more compounds to be grouped.
- Give a higher priority on the compounds for which you have evidence of a common mechanism/mode of action.
- The problem is the lack of information on mode/mechanism of action and there is little possibility of asking for studies (data are mainly from open literature, in-house EPA studies).

Minimum data requirements for including a compound - if not met, what defaults to use

- Minimum data: depends on the criteria set for defining common end-point and mode of action. How refined the risk assessment needs to be?
- TEF/PEF: the most sophisticated would have been PBPK modelling.
- Data that would be ideal to have
  - data for defining key events
  - dose-response for BenchMarking
  - time-course of toxic effects
  - mixture studies
- Information on time-course of effects is essential for acute and longer term exposures.
- Standard studies that are enough to perform risk assessment on that compound are the minimum data requirement.
- Describe uncertainties and missing information for each compound of the group.
- Characterize the uncertainties: qualitative or semiquantitative, use lower and upper confidence limits of TEF/PEF?

Groups of pesticides to be prioritized

Basis for prioritisation

- Public health grounds (i.e.: not "pressure group" driven).
- Screening on all groups of compounds based on
  - Epidemiological evidence (?): unlikely to provide useful information in most instances (OP in US).
  - Biomonitoring data of the general population (agricultural areas vs urban areas).
  - Understanding mode of action or common target with possible same mode of action.
  - "Low" reference dose as compared to the use pattern.
  - Low expected intake vs reference dose (less than few units%?)
- Veterinary drugs? Monitoring of residues and biomonitoring? (practical issue: pattern of use may give more info that monitoring data).
- Availability of data (toxicological and dietary exposure):
  - NO.
  - Rather, lack of data might be the driver for further investigation.
  - So, start with available data, but do not forget the missing information.
- Make use of the existing assessments (e.g.: those made by EPA)
  - Toxicology can be "borrowed", dietary assessment should be done for the European scenario.
  - If cumulative assessment elsewhere showed no problems, this should be a low priority in Europe (Not the case with OPs).
  - Global cooperation needs to be improved.

- Use patterns
  - Compounds found most frequently in certain commodities (monitoring data)
  - Marked analysis (most used pesticides and on what crop)
  - Analysis of the trend of future uses (e.g.: the future of OPs)
  - Compounds appearing in most consumed food items
  - Food items that require most treatments
  - Food mostly consumed by certain age groups (i.e.: children)
  - What about not legal crop treatments? (enforcement, more monitoring data)
- Relevance of sources of exposure other than pesticides in food
  - Biocides
  - Veterinary use
  - Drinking water
  - Occupational
  - Naturally occurring substances (e.g.: anticholinergic compounds)
  - Consumer uses
  - Others (?)
- **Need to take those into account, at least qualitatively**

Compounds to be prioritised (hazard and exposure considerations)

- OPs (plus number of compounds)
- Carbamates
  - only acute exposure
  - Combine with OPs?
- Conazoles (not in the front line in USA because waiting for data from ongoing research)
- Pyrethroids (note the ongoing efforts in the USA)
- Dicarboxyamides (procymidone and iprodione)
- Spindle inhibitors
- Phtalimides (captan and folpet)…
- Dithiocarbamates
  - note that the analytical methods do not distinguish the different compounds – CS2 is measured
  - Exposures other than via food need to be considered

Recommendations

Short-term goals: work-out a tiered approach

Long-term goals: revising the current toxicology paradigm to obtain better and more useful data (see ILSI/HESI tiered approach)

Make use of existing work

Scope for collaboration with EPA and other bodies

DISCUSSION GROUP 2

NON-DOSE-ADDITION EFFECTS

Non-dose-addition effects

Simple dissimilar mode of action, independent action, response or effect addition.

- No interactions (none of the compounds in the mixture influence the toxicity of the others)
- The mechanisms of actions will always differ and the toxic effects (types, target organs) are possibly (but not necessarily) also different.

Complex dissimilar mode of action
The compounds will interact, producing either antagonism, potentiation or synergism

- Interactions in the *toxicodynamic* phase:
  - e.g. combination of an agonist and a neurotransmitter uptake inhibitor, endocrine disrupters.
- Interactions in the *toxicokinetic* phase:
  - e.g. one compound can inhibit the binding of another to transport proteins in the blood,
  - or reduce the effect of another compound by inducing its detoxification,
  - or potentate the effect of another compound by increasing its bio-activation.

1. Combined effects of concern

- Effect/response addition
  - Effect/response addition not relevant for mixtures where the exposure is below the NOAELs for each individual compound.
- Synergism, potentiation
  - May be relevant even for mixtures where the exposure is below the NOAELs for each individual compound.
- Antagonism
  - Although it may occur in some cases it is not of public health concern and cannot be used in the risk assessment.

2. Toxicological effects of concern from combined exposures of pesticides and their prioritization

- Reproductive, neurodevelopmental, and neurobehavioral effects
- Neurotoxicity
- Acute effects, multiple targets
- Short-and long-term systemic toxicity
- Immunotoxicity
- Carcinogenicity
- (Genotoxicity)
- To be further developed!

3. Compound groups for such consideration

- Should be chosen based on toxicological profile and mechanisms of action.
- It should be plausible that the compounds would interact at effect levels for the relevant end-points; for instance having the same target organs. Then the possibility for synergism at lower doses should be explored.
- Where co-exposure is likely to occur with special attention to e.g. intentional use-combination. As an example, piperonyl butoxide enhance the toxicity of pyrethroids.
- Are impurities/metabolites an issue as relevant residues?

4. Default assumptions to be used

- Although available studies have not shown interaction leading to toxicity when exposure is below NOAELs for each compounds operating by simple dissimilar action, this have not been adequately demonstrated for potential mixtures of pesticide residues:
- OP and pyrethroids not predicted to interact at low residue levels.
- Interactions (and/or additivity) possible to occur if exposure is at the LOAEL for each compound.

5. Study design necessary to enable such assessments and ways to distinguish combined effect

- There is no standard study design.
- (Partial) factorial designs have been used in animals but are expensive.
- Try to start with end-point and mode of action. In vitro studies if endpoint (marker) can be measured reliably.
- The isobole method useful *in vitro* for distinguishing between synergy, additivity, and antagonism. Expensive to perform *in vivo* due to the need for multiple combinations of test compounds.
- Potential for kinetic interactions (induction/inhibition) of concern (nature of interaction) should be addressed. Usefulness of PBPK modelling should be explored. Such information should in special cases be obtained from the applicant.

6. Methods and their advantages and disadvantages to be used to estimate combined hazard

- Point of Departure Index (PODI)
- Sums the exposures of each compound expressed as a fraction of their respective PODs (NOAEL or BMD) instead of the ADI/TDI. These POD fractions (PODF) are reciprocals of the individual margin of exposures (MOE) of each compound. This approach sums the exposures to the compounds in terms of their relative potencies expressed as risk units.
- **In case interaction foreseen an additional UF may be used.**
- **Literature search for range of synergies to determine a common extra UF?**
- The hazard index is the sum of the hazard quotients (HQ) of the individual chemicals, i.e. the sum of exposure to each chemical expressed as a fraction of its ADI/TDI.
- $HI = HQ_I + HQ_{II} + HQ_{III} + HQ_{IV}$, or
- $HI = Exp_I/ADI_1 + Exp_{II}/AD_{III} + Exp_{III}/ADIIII + Exp_{IV}/ADI_{IV}$
- The HI should not exceed 1.
- The HI method is transparent, easily understandable and directly relates to the ADI/TDI.
- The major disadvantage is that the ADI/TDI is not an appropriate metric to use for cumulative risk assessment, since it is normally derived by using NOAELs and uncertainty factors, which are not data based, but may incorporate significant policy-driven assumptions.
- TEFs are derived as the ratio of the POD of one of the chemicals, the "index compound", to that of each member in the group. The exposure to each chemical is then multiplied by the respective TEF value to express exposure in terms of the index compound. Summation of these values result in the combined total equivalent exposure (TEQ) expressed in terms of the index compound.
- **Assumes dose additivity**
- **Not to be used for simple dissimilar action**

- The MOE is the ratio of the NOAEL (or BMD) to the level of exposure.
- MOE = NOAEL/Exposure
- The combined MOE (MOE_T) is the reciprocal of the MOEs of each compound in the mixture.
- $MOE_T = 1/(1/MOE_1 + 1/MOE_2 + 1/MOE_3 + 1/MOE_4)$
- There are no established criteria for magnitude of an acceptable MOE_T for mixtures of chemicals.
- The Cumulative Risk Index CRI has been suggested by US EPA to combine MOEs for chemicals with different UF. The risk index (RI) of a chemical is the MOE divided by the UF or simply the ADI/TDI divided by the exposure and is the reciprocal of the hazard quotient (HQ).
- $CRI = 1/(Exp_1/ADI_1 + Exp_2/ADI_2 + Exp_3/ADI_3 + Exp_4/ADI_4)$

7. Point of departure to be used in estimating hazard in combined risk assessment

- POD Index based on BMD or NOAEL.
- However, BMD may not always be applicable.
- ADI/TDI of lower priority (Hazard Index), but may be practical for screening purposes.
- BMD/NOAEL from testing of relevant mixture.

8. Minimum data for including a compound - if not met, what defaults to use (overlap with 3)

- Exposure information suggesting the possibility of co-exposure (if not exposed to each compound within a reasonable time-frame there is no issue of interaction)
- The availability of a plausible hypothesis for interaction of two or more pesticides
- Could be already available data, data to be produced, or predictions.

Risk characterisation

- Integrating combined exposure assessment and hazard assessment:
- Dose-response range should be explored for potential interactions possibly by using probabilistic methods.
- If data from testing of mixture is available: BMD/NOAEL to be compared with exposure assessment.
- Point of departure index could be used in the risk characterisation.
- If all compounds in mix have ADI use the lowest.
- In case of minimum data on interaction and very low residue levels explore the usefulness of threshold of toxicological concern (TTC) approach.

Joint actions (MS, EFSA, non-EU-MS, international organisations): Prioritization

- The subject for Group 1 more important than that for group 2.
- Co-operation always important and should be advocated in developing approaches for better harmonisation in risk assessment (e.g. IPCS). Potential hazards may be very local.
- Co-operation between MS and EFSA a priority.

Conclusions for non-dose-additon

- Simple dissimilar actions not of concern at levels below the ADIs of all the compounds.
- Complex dissimilar actions considered to be rare at levels of regulated residue exposure (below MRL).
- Assessment should be performed where co-exposure is likely to occur with special attention to e.g. intentional use-combination.
- Discriminate between acute and chronic effects of exposure in the risk assessment. Timing in exposure essential, influence kinetic interactions.
- In case of concern for interactions it is the risk manager to decide what to do. This has not to do with changing ADI/ARfD.

Recommendations

- Consider potential non-dose-addition effects even for chemicals with common mechanism of action.
- As examples of synergy are obtained read-across will help in hypothesis generation.
- For the assessment of interactions the use of probabilistic methods in the hazard assessment should be explored.
- If concern persists as regards co-exposure and plausibility of interactions more data to be requested.
- Testing of pesticides should focus more on generating data useful in exploring potentials/mechanisms for interactions during kinetics and dynamics, and to establish BMDs.
- Research to explore low-dose (below the NOAEL) non-dose-addition effect/synergy of pesticides to be supported.
- More "real" exposure data to be used in risk assessment. Helpful for probabilistic modelling.
- In case interaction foreseen, an additional UF may be used.
- Literature search for range of synergies to determine a common extra UF?

DISCUSSION GROUP 3

CHOICE OF DATA FOR COMBINED EXPOSURE

Initial reflections and decisions (1)

Combined exposure assessments should (for reasons of feasibility) at the moment be limited to:

- plant protection products (not including biocides or veterinary drugs)
- food (not including drinking water)
- oral intake (no other routes of exposure)

Initial reflections and decisions (2)

Four exposure scenarios were distinguished which might require different sets of data:

- MRL setting
  - *acute assessment*
  - *chronic assessment*
- Assessment of actual exposure
  - *acute assessment*
  - *chronic assessment*

cumulative risk assessments could in principle be considered for all four scenarios

Data required (acute, actual)
Cumulative assessment of actual exposure

Acute assessment

- *Residue:*
  - monitoring data, focus on edible portion, conversion tables (have to be developed)+ processing factors (preferably measure the edible portion)
  - use whole range of data
  - variability/homogeneity factor?
  - for refinement: measurements in individual units
  - measure according to residue definition for risk assessment (not acc. to residue definition for enforcement) or apply conversion factor
  - LOQs for all compound in the group considered should be in the same range and fit for purpose
- *Consumption:*
  - "all foods together": could be only done probabilistically
  - "one food, multiple pesticides from the same mechanism group": PRA (see above) or deterministically using LP (already done in enforcement), both for consumers only and for the whole population (this means the relevant subgroup in this context)
  - single days (use dietary records, 24 h recalls, not data from FFQ questionnaires)
  - standardized portion sizes are not suitable for LP estimates
  - give consideration to number of days and respondents
  - use randomized data to cover whole year and all days of the week
  - care should be taken to cover relevant subgroups

Recommendations

Monitoring residues in food as eaten (edible portion, processed…)

Dietary surveys: separate days rather than consecutive days

Decide on how to handle non-detects

Data required (chronic, actual)
Cumulative assessment of actual exposure

Chronic assessment

- *residue:*
  - monitoring data, focus on edible portion, conversion tables (have to be developed)+ processing factors (preferably measure the edible portion)
  - mean cumulative level per commodity (for common mechanism compound group). Method to cumulate the levels and to average in time needs to be developed
  - measure according to residue definition for risk assessment (not acc. to residue definition for enforcement) or apply conversion factor
  - LOQs for all compound in the group considered should be in the same range and fit for purpose
- consumption:
  - could be done either deterministically or probabilistically (as a refinement)
    - deterministic: mean consumption level per commodity
    - probabilistic: see acute; possible to extrapolate survey data from few days to long time
  - give consideration to number of days (in this case really more than one day) and respondents
  - use randomized data to cover whole year and all days of the week
  - care should be taken to cover relevant subgroups

Data required (acute/chronic, MRL)
Cumulative assessment for MRL setting

- check wether existing authorisations give acceptable cumulative exposure (see actual exposure)
- for new registrations: assess contribution of the new compound to the existing assessments
  - ▷ residue:
    - combination of monitoring data and supervised trials residue data (whole distribution for acute; STMR for chronic), the latter for the commodity/compound combination you want to set the MRL for
    - revise these assessments from time to time to adopt it to the range of pesticides on the market
  - ▷ consumption:
    - see actual exposure, but focus on RACs

Initial reflections and decisions (3)

Should "all foods eaten together" and "more pesticides on one commodity" be considered for MRL setting and for actual exposure?

- yes

Should both chronic and acute exposure be addressed?

- yes, focus was seen on chronic assessment by some members of the group (consumers more concerned about that), while others tend to put the focus on acute assessment
- chronic assessment should focus on RACs (including meat, eggs, milk…); processed commodities could be considered in a refined assessment
- acute assessment should focus on the food as eaten (large portions, whole meals, processed food as appropriate)

Consumption data
Available sources of information

EFCOSUM

- gives good overview of existing consumption data but has some limitations:
  - level of aggregation will not meet needs for cumulative RA
  - is the use of 24 h recalls adequate?
  - portion size not precise enough
  - is the number of recalls (2 days) adequate?

EFSA Collection of National Consumption Models

EFSA Concise Data Base (under construction)

- limitation: aggregated to 16 food classes

EFSA Comprehensive Data Base

- guidance to MS to conduct food surveys in a comparable manner

SAFE FOODS Project

- 6 national consumption surveys ready to use in PRA

Recommendation:

Provide access to all raw data from consumption surveys

Consumption data
What is needed for cumulative RA?

Data on <u>combination</u> of food which is consumed

- on single days
- by one individual consumer
- with a known individual body weight
- at each separate meal (breakfast, dinner...)
  to make further refinements possible

The same data base might be used for different exposure scenarios by specifically extracting different data

Consumption data
Food codes

- not yet harmonized
- LANGUAL, used by EUROFIR (work ongoing), detailed enough?
- CODEX Codes (e.g. used in SAFE FOOD project)
- EU Food Classification according to Annex I of Regulation (EC) No 396/2005
- Translation table for CODEX codes to transform them to EU codes is available, could be provided by EFSA/COM

Consumption data
Food Surveys (General)

Food surveys

- lack of data for many MS (especially the new MS)
- EFSA initiative to harmonize the conduction of food surveys (EFSA Comprehensive Data Base; guidance to MS to conduct food surveys in a comparable manner)
- food surveys applied different methodologies and covered different population subgroups, not all surveys up-to-date, interdependance of consumption data (raw data required!)

Recommendation:

EFSA to conduct a new European food survey which is representative for all MS

not necessarily within the borders of each MS, but rather for regions with comparable diets (diet clusters)

Residue data
Sources of information

Existing information:

- supervised field trials residue data
  - reflecting critical or realistic GAP, often available for Northern and Southern EU
  - processing data
- monitoring/enforcement residue data
  - may be biased
  - not all MS are measuring the same substance/commodity combinations, expand EU coordinated monitoring progr.
  - analytical methods, LOQs may differ
- models to calculate residue data from application conditions and substance properties
  - should such models be applied? opinions were divided
- market shares
  - to be considered? (in order to derive % crop treated)

Residue data
Desired information

Information additionally desired:

- monitoring data representative for food consumption and country of origin (random sampling)
  - EU monitoring programmes to be checked for their appropriateness and to be amended accordingly
- explore methodologies for deriving actual usage data
  - e.g. from farmers records
- more data on individual unit basis
  - e.g. in the frame of additional modules supplementing existing monitoring programmes

DISCUSSION GROUP 4

METHODOLOGY FOR COMBINED EXPOSURE

Day 2

What scenarios to be addressed? Starting point

MRL setting/chronic and acute

- Granting authorisations/chronic and acute

Actual exposure assessments/chronic and acute

- Cumulative analysis/trade monitoring/acceptance of lots in trade

Use US approach as starting point

- Risk cup for individual chemicals (probabilistic modelling)
- Then cumulative exposure using probabilistic modelling
- Revisit individual chemicals when cumulative exposure shows problems

but limitations for EU are

- EU view of %CT (sensitivity analysis?)
- Use of the variability factor prevents the risk cup approach using deterministic models (overly conservative – to be discussed?)

Agreed not to include drinking water at present

What kind of cumulative exposure analysis do we want to do?

When should cumulative exposures be used?

When should cumulative exposure analysis be used?

Baseline assessment for groups of chemicals

Authorisation of pesticide uses

Not to solve MRL exceedances in traded lots/lot acceptance

1. Deterministic or probabilistic methods to be used to assess consumer exposure?

- Data and model needs are different between acute and chronic scenarios
  - How to use cumulative risk assessment in the MRL setting process – amount of data points available from supervised field trials
- Can deterministic modelling be used for acute cumulative assessments?
  - Yes if only single unit food item is being addressed (e.g. one bunch of grapes with multiple OP residues)
  - Not possible for composite samples? Can be done for single food items
  - Over-estimate exposure with many compounds in cumulation group
- Can probabilistic modelling be used for acute cumulative assessments?
  - Yes if samples are not pooled/mixed lots (use of variability factor/tiered approach)
  - Single unit data? Cost? Modelling? (see Q3)
  - Model from composite sample to individual unit (possible with MCRA/MaxLIP)
  - Can you do a meaningful cumulative assessment for risk managers without using probabilistic modelling? Interpretation of ARfD exceedances/meaningful assessment

- Further Qs?
  - Where to start
  - Practical experience of models increases acceptance
    - Single chemical, move to cumulative?
    - Criticism from NGO groups about not considering whole diet
    - Can you model occurrence/co-occurrence of residues?
      - Do you need data? Probably yes
      - What level of uncertainty can the risk manager accept?
  - Possibilities of tiered approach?
    - Ideas for specific tiers
    - One commodity, all pesticides?
    - Probabilistic modelling to predict likelihood of event occurring?
- Chronic
  - Possible to do, no intrinsic difficulties
  - Data/questions on longitudinal assessments
    - Decisions on how to use short term consumption data
  - Need to start somewhere – acute is priority

2. Criteria for a model to estimate combined exposure

- Use experience of US to address some of the challenges in developing models/guidelines etc
- Define criteria
- Model design affects output? Complex models produce complex results/ multi-faceted questions – a bad thing?
- Use of guidelines on probabilistic modelling (running models, reporting inputs/outputs etc?)
  - Draft being considered by EFSA (good practice for running models and generating output, not interpretation/risk management guidance – still required)
- Further development of draft guidelines on cumulative assessment
  - Probabilistic modelling guidelines needed first
- How to handle new uses?
  - Practical experience shows unlikely to be an issue until cumulative assessment carried out with existing uses (US experience)

3. Data requirements for the model

- Must be able to be compatible with as many EU consumption databases as possible
  - Pooling databases
  - Able to focus in on regional differences
- Must be transparent
  - Modeling outputs accepted more easily when you have experience of using model
- Model must be able to required number of iterations (power of model)
- What level of exposure is acceptable to risk manager?
  - They must be able to examine end of tail distribution (what are drivers? Examine in detail)
- % crop treated
  - Difficult issue

Further requirements of model

- Replicate results
- Availability of model
- Module based
  - First model exposure through food, later other exposures (water, household uses, pet uses etc)
  - Confidence in the model
    - Peer review/verification/validation

4. Uncertainty and variability?

- Sensitivity analysis to determine whether exposure/RfD exceedance is real when differences occur between consumer/population groups
- Uncertainty in data of all parameters
  - How to handle?
- Models needs to separate uncertainty (CL around MOE) and variability (MOE at any percentile)
- Uncertainty analysis may inform where new data are required/assess data gaps
- Risk characterisation
  - MOE/severity of effect
  - Uncertainty in estimated value
- Modelling can be used to address uncertainty
  - Iterative process

5. Interpretation of the results, when should safety concerns be raised?

- Decision on acceptable exposure based on a certain percentile?
  - 99.9^{th} centile as guideline? (Use 97.5^{th} for acute at present)
  - What percentile appropriate?
  - Ultimately down to the risk manager?
- Consider
  - What foods and chemicals contribute to the risk? Sensitivity analysis
  - Quality of simulations e.g. number of food items contributing
  - Quality of data used in simulations e.g. field trials, monitoring data
  - Results expressed as margin of exposure
    - Risk characterisation
- **Other options?**

6. Models now available and the lessons learnt: Do we have an appropriate model or do we need a new one?

- Are existing software appropriate to answer the cumulative modelling question now?
  - MCRA
    - SAFEFOOD project – to introduce further consumption data
  - CREMe
  - (DEEM/Calendex)
  - (CARES)
  - (Lifeline)
  - (SHEDS)
- US experience – 4 US models give similar results

- Should further models be developed?
  - Possibility for MS to generate their own models (not necessarily software)
  - Costs? Experience/work done so far
  - Availability of consumption data to be introduced into models
- Need to have models available for prospective assessment of new uses

Recommendations

Start the process as soon as possible but in a stepwise manner

Start with acute cumulative exposure assessment

Start with post-registration uses

Identify priority chemicals

Guidelines needed for probabilistic modelling (draft available) and cumulative exposure (no draft available)

Make the best use of the models available

Organise additional training in use of models

- Improves understanding/acceptance of modelling techniques
- Helps risk managers improve process
- Make best use of available data
- Use sensitivity analysis to inform data gaps and prioritise future data collection/
- use existing knowledge from monitoring data (targeted/random – improve reporting/sampling strategy/sampling at farm gate) – DG3
- Suitability of supervised field trial data?
- US EPA RPFs etc

Need to make progress on how to advise risk managers/framework for risk management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