EFSAscience

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SUMMARY REPORT

EFSA SCIENTIFIC COLLOQUIUM

Cumulative Risk Assessment of Pesticides to Human Health: The way forward

28-29 November 2006, Parma, Italy

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 Discussions

Discussion Group1: 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. EPA1, ILSI2, 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

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[1] Guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity. Office of Pesticide Programs U.S. Environmental Protection Agency. January 2002. http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf

[2] An ILSI Risk Science Institute Workshop Report. A Framework For Cumulative Risk Assessment. 1999. ISBN: 1-57881-055-8. http://rsi.ilsi.org/file/rsiframrpt.pdf

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 Group2: 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).

$$\mathbf{HI = \Sigma_i Exp_i / ADI_i}$$

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.

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

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.

$$\mathbf{CRI = 1 / \Sigma_i Exp_i / ADI_i}$$

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., 99^{th} 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 MS 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.