Opinion of the Scientific Panel on Plant Protection products and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005[1]

Scientific Opinion of the Panel on Plant Protection Products and their Residues (PPR)

(Question N° EFSA-Q-2006-160)

Adopted on 15 April 2008

PANEL MEMBERS

Damia Barcelo Culleres, Jos Boesten, Claudia Bolognesi, Alan Boobis, Arne Büchert, Ettore Capri, David Coggon, Anthony Hardy, Andy Hart, Herbert Köpp, Matthias Liess, Robert Luttik, Otto Meyer, Stella Michaelidou-Canna, Mark Montforts, Angelo Moretto, Markus Müller, Bernadette Ossendorp, Walter Steurbaut, Maria Tasheva, Christiane Vleminckx.

SUMMARY OF OPINION

In this Opinion the PPR Panel self-tasked to evaluate and possibly refine existing methodologies for assessing risks of exposure to two or more pesticides in combination, particularly in the context of setting MRLs according to Regulation (EC) 396/2005.

The PPR Panel is of the opinion that ideally, risk assessments for chemicals, whether individually or in combination, should consider all sources (e.g., plant protection products, veterinary drugs, human medicines), pathways (e.g., food, drinking water, residential, occupational) and routes (ingestion, dermal, inhalation) of exposure that could contribute materially to a person's total exposure. The PPR Panel noted however, that appropriate data on levels of exposure to pesticides from pathways and sources other than as plant protection product residues in food are not generally available and further work is required in this respect. Therefore, at this stage the PPR Panel restricted its consideration of combined risk assessment to exposures from residues in food that could arise from plant protection products.

[1] For citation purposes: Scientific Opinion of the Panel on Plant Protection Products and their Residues (PPR Panel) on a request from the EFSA evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005. *The EFSA Journal* (2008) 704, 1-85

The combined toxicity of two or more compounds can take three possible forms: dose-addition, response-addition, or interaction. However, having considered the evidence on the different forms of combined toxicity and their potential relevance to risk assessment for pesticide residues at the levels occurring in food, the PPR Panel limited this opinion to the possible impact of dose-addition. In particular, the PPR Panel noted that although toxic interactions from pesticide residues in food cannot be ruled out, there is no empirical evidence for their occurrence at the expected levels of exposure from pesticide residues in food.

The PPR Panel proposes criteria by which to include compounds in a cumulative assessment group (CAG), highlighting the possibility of different levels of refinement in a step-wise approach. The grouping can be based on general criteria like chemical structure, or mechanism of pesticidal action, or more refined criteria like common toxic effect, or ultimately toxic mode of action.

Several methods for cumulative risk assessment are described that use the same underlying data, although expressing the information differently. The PPR Panel concluded that the most useful methods were in increasing levels of complexity and refinement, the hazard index, the reference point index, the relative potency factor method and physiologically-based toxicokinetic (PBTK) modeling.

Acute and chronic exposure scenarios for risk assessments have been considered by the PPR Panel, both in the context of MRL-setting, and also in relation to actual exposures that result from the patterns of usage that occur in practice (i.e. based on monitoring data). Each scenario can be addressed using either a deterministic or a probabilistic approach. The Panel discussed what concentration levels were represented by supervised residue trial data and (targeted) monitoring data, and which data source should be used in each exposure scenario. Proposals were made on how to deal with residues below the Limit of Detection (LOD), Limit of Quantification (LOQ), or Limit of Reporting (LOR). An overview is provided of the food consumption data available at the European level, and how to use them in cumulative exposure assessment. It should be noted that a number of the issues highlighted as of concern in cumulative risk assessment apply to risk assessment in general. However, when the data are used cumulatively their importance is magnified and therefore the PPR Panel considered it important to include them in this opinion.

The available probabilistic models are briefly discussed, as well as factors to consider when assessing the reasonableness of the upper-end percentile estimates.

A critical overview of cumulative risk assessments already performed is also provided in this opinion. These include assessments of organophosphorous (OP) insecticides alone (in USA) or together with carbamates (in UK, DK, NL), triazines, chloroacetanilides, carbamates alone (in USA), and all compounds (in DE). The PPR Panel noted that not all assessments were of the same depth, and that some compounds initially included in a CAG on the basis of toxicological considerations were excluded from the cumulative risk assessment on the basis of exposure considerations. It was also noted that the cumulative assessments for anticholinesterases that have been performed by several bodies did not give materially different results.

General issues on uncertainty as well as those specific to cumulative risk assessment are described in this opinion along the lines of a previous PPR opinion (EFSA, 2006). Uncertainties related to residue data, consumption and toxicity evaluation are presented and a qualitative estimate of their relevance is reported.

The PPR Panel identified criteria for selecting groups of compounds for consideration in a combined risk assessment. These included (a) frequency of detection in monitoring programmes, (b) high use based on surveys or sales statistics, (c) evidence of "high" intake from biomonitoring data for the general population or for sub-populations/geographical areas, (d) compounds with high exposures relative to their reference values, (e) cumulative risk assessment carried out elsewhere showing possible unacceptable exposure, (f) high number of compounds (e.g., 5 or more) in a group, (g) assumptions on future trends in use of pesticides.

In addition the PPR Panel noted that assessment of specific pesticide combinations might be carried out if there were a strong biological hypothesis that certain compounds may interact below their respective No Observed Adverse Effect Levels (NOAELs).

It should also be noted that presence of relevant non-food sources of exposure might require an assessment of the margin of exposure for the food part.

SPECIFIC RECOMMENDATIONS

- The PPR Panel recommends that a tiered approach for both toxicological evaluation and intake estimation be adopted in order to make the most efficient use of the available resources.
- Where possible, advantage should be taken of assessments already undertaken, provided they are of sufficient quality and relevance, thereby avoiding repetition of work. Such global collaboration with sharing of results will require further harmonization of procedures.
- All identifiable assumptions and uncertainties should be evaluated at least qualitatively, and those, which are potentially critical to the outcome of the assessment, should be examined quantitatively (either by sensitivity analysis or probabilistic modeling).
- Risk managers will need to consider what level of cumulative risk would be considered "acceptable".
- A continuing dialogue between toxicologists and exposure assessors, and between them and risk managers is particularly necessary for cumulative risk assessment to identify the relevant issues and to best use available resources.
- It is recognized that in residue monitoring programs, targeted sampling is important for enforcement purposes. However, the degree of targeted sampling should be clearly reported in order to have a better understanding of the available data.
- When designing monitoring programmes, consideration should be given to collection of data more representative of actual exposure to pesticides forming cumulative assessment groups, in order to provide a better basis for cumulative risk assessment.
- Strategies should be developed for dealing with all categories of censored (truncated) data: true non-detects, levels between LOD and LOQ, less than the reporting level.
- It is recommended that when reporting levels are established the needs of cumulative assessments should be taken into account i.e. they should be as close to the LOQ as possible.
- The raw survey data from monitoring programmes of pesticide residues and from national food consumption databases should be accessible for risk assessment purposes.
- It is recommended that a harmonized consumption survey be performed on the European level, e.g., along the lines of the 4 European GEMS/Food cluster diets, and not along the lines of country borders.
- Guidance for performing probabilistic methods should be developed.

- If there is biological plausibility for an interaction between pesticides at low, non-effective doses, a case-by-case approach should be adopted to assess their combined effects.

Following this opinion, a worked example of the proposed methodology is being developed for a group of compounds, and the results will be reported in a separate opinion with any suggested refinements necessary.

Key words: cumulative risk assessment, dietary exposure, MRL, residue monitoring, tiered approach, cumulative assessment group, common mode of action.

TABLE OF CONTENTS

BACKGROUND

Regulation (EC) No. 396/2005 on maximum residue levels (MRLs) emphasises the importance "to carry out further work to develop a methodology to take into account cumulative and synergistic effects of pesticides". In fact, the European Parliament itself has – at the time of the adoption of the Regulation - insisted that such a methodology be developed and applied as soon as possible to estimate the safety of MRLs.

According to the above-mentioned Regulation, EFSA will have to provide – within one year after the entry into force of the regulation – a reasoned opinion on existing or new MRLs, based in particular on the relevant assessment report prepared under Directive 91/414/EEC to the Commission and Member States. All decisions on MRL setting shall take account of any methods on cumulative and synergistic effects as soon as those are available.

As there is currently no internationally agreed methodology to assess risks from exposure to two or more agents, the PPR Panel agrees with the European Commission on the importance to develop such a methodology in order to provide EFSA with the necessary tools to carry out its task in MRL setting and consequently meet the safety standards of the European Parliament. In doing so, the PPR Panel will include consideration of (1) methodologies/approaches which have already been developed by some countries (within and outside the EU), (2) methodologies already developed for compounds other than pesticides (e.g., dioxins and PCBs), (3) the EFSA Colloquium on "Cumulative risk assessment of pesticides in humans: the way forward" in November 2006, and (4) the discussions at the International Workshop on Aggregate/Cumulative Risk Assessment organised by the WHO/IPCS in Washington in March 2007.

TERMS OF REFERENCE

The PPR Panel self-tasked to evaluate the suitability of existing methodologies and, if appropriate, the refinement of new methodologies and/or identification of new approaches to assess possible cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) No. 396/2005.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group for the preparation of this Opinion: Mr. Angelo Moretto, Ms. Bernadette Ossendorp, Ms Ursula Banasiak, Ms. Claudia Bolognesi, Mr. Alan Boobis, Mr. Arne Büchert, Mr David Coggon, Mr. Ian Dewhurst, Mr. Paul Hamey, Mr. Andy Hart, Mr. Otto Meyer, Mr. David Miller, Ms. Stella Michaelidou-Canna Mr. Markus Müller, Ms. Maria Tasheva, Ms. Christiane Vleminckx and the EFSA staff members Luc Mohimont, István Sebestyén, Cinzia Percivaldi, Luisa De Leo.

ASSESSMENT

1. Introduction

This opinion concerns methods for assessing risks from the toxicity of two or more pesticides in combination, particularly in the context of setting MRLs. It takes into account the outputs from two meetings that were recently held on the topic: an EFSA Colloquium on "Cumulative assessment of pesticides in humans: the way forward" that took place in Parma (Italy) in November 2006, and an International Workshop on Aggregate/Cumulative Risk Assessment organised by the WHO/IPCS in Washington, DC (USA) in March 2007. Several members of the PPR Panel participated in these meetings.

Combined risk assessment for pesticides can cover a broad range of issues, and in order to render its task manageable, the PPR Panel first considered what should be the scope of its opinion with regard to:

- sources and pathways of exposure;
- types of combined action; and
- types of risk assessment.

1.1. Sources[2] and pathways of exposure

Human exposure to pesticides can occur via multiple pathways (e.g., food, drinking water, residential, occupational) and routes (ingestion, dermal, inhalation). Historically, exposures to a chemical through the food, drinking water, residential and occupational pathways were each assessed independently and no concerted effort was made to evaluate potential exposures through multiple pathways simultaneously. This may in part be explained by the fact that responsibility for these different pathways of exposure has often resided in different departments or agencies of national governments and international organisations. However, in the USA, the Food Quality Protection Act (FQPA) of 1996 led to research on the assessment of exposure through multiple routes, multiple pathways and multiple chemicals (WHO 2007), and in Europe, Regulation (EC) 396/2005 is now causing the same.

The relative contributions of different pathways and routes to total exposure vary with the pesticide. For example, a recently revised cumulative risk assessment[3] for N-methyl carbamates carried out by U.S. EPA (EPA, 2007b) concluded that exposures through the food pathway predominated, with residential exposures being lower throughout most of the year. Exposures through drinking water were found to be lower than exposures through both the food and residential pathways. This may be explained by the fact that all ten of the carbamates considered by U.S.EPA had agricultural or food uses whereas only three of them were used in homes. However, in U.S. EPA cumulative risk assessment for organophosphates (EPA, 2006a) residential

[2] 'Source' refers to manner of use or intended purpose of the compound

[3] Although the term "cumulative risk assessment" has sometimes been used when referring generally to assessment of the risk from exposure to more than one pesticide (see EFSA colloquium), in the context of this opinion, it refers more specifically to the assessment of risk deriving from combined exposure to compounds that share the same mode of action or that have similar effects but by different modes of action.

exposure was significant, while in a cumulative risk assessment for triazines (EPA, 2006c), drinking water was the main contributor to total exposure.

In Europe, following Council Directive 98/83/EC, the maximum concentration of an individual pesticide that is legally permitted in drinking water is 0.1 µg/L, and the summed concentrations of all pesticides may not exceed 0.5 µg/L. Theoretically, it is possible that exposure to multiple pesticide residues in drinking water could be toxicologically relevant if e.g., five highly toxic pesticides sharing the same mode of action[4] were simultaneously present, at the maximum legally permitted level. In practice, however, this seems a rather unrealistic scenario. The Panel concluded, therefore, that contributions to pesticide exposure from drinking water would not be of toxicological concern.

In addition to exposures resulting from the use of a chemical as a pesticide, the same substance may sometimes also be encountered as a consequence of its use for other purposes – e.g., as a veterinary medicine.

Ideally, risk assessments for chemicals, whether individually or in combination, should consider all sources, pathways and routes of exposure that could contribute materially to a person's total exposure. The Panel noted, however, that appropriate data on levels of exposure from other pathways and sources are not generally available, and that further work is required to develop ways to aggregate risk[5] from exposure via other pathways and from other sources, Therefore, at this stage, the PPR Panel restricted its consideration of combined risk assessment to exposures from pesticide residues in food that could arise from plant protection products. Thus, for example, the contribution of a veterinary medicine would be taken into account only if it produced a residue in food identical to a relevant residue from a plant protection product.

1.2. Types of combined action

The combined toxicity of two or more compounds can take three possible forms: dose-addition, response-addition, or interaction.

Dose-addition, also referred to as simple similar action, similar joint action or relative dose-addition (see glossary), occurs when chemicals in a mixture[6] act in the same way, by the same mechanism/mode of action, and differ only in their potencies. Such compounds are said to belong to a "common mechanism group" (CMG) and dose-addition implies that the effects of exposure to a mixture of such compounds are equivalent to the effects of the sum of the potency-corrected doses of each component compound. For the purpose of this document the term "mode of action" (MOA) rather than "mechanism of action" will be used. "Mode of action" refers to the major steps ("key events") leading to an adverse health effect following interaction of the compound with biological targets whereas "mechanism of action" is a detailed explanation of the individual biochemical and physiological events leading to a toxic effect (Boobis et al., 2006). It should be noted that in U.S. EPA documents relating to cumulative risk assessment, when the term "mechanism of action" is used it implies "mode of action" as defined above. Thus, a common mechanism of toxicity is defined as occurring when "two or more pesticide chemicals …. cause a common toxic effect by the same, or essentially the same, sequence of major (or key) biochemical

[4] See below and glossary for a definition of mode of action
[5] See glossary for a definition of aggregate risk
[6] The term mixture here applies to intake of multiple pesticide residues either in a single food item or in a number of different food items consumed within a relevant timeframe.

events" (EPA, 1999). As the terminology is still not universally agreed, a glossary with the definitions of terms as used in this opinion is provided as an appendix. Groups of compounds considered for a cumulative assessment will be identified in this Opinion as a Cumulative Assessment Group (CAG). This is contrasted to a Common Mode/Mechanism Group (CMG) because for risk assessment purpose it may sometimes be conservatively deemed appropriate to group compounds even if the common MOA has not yet been precisely identified, particularly in lower assessment tiers (see below point 2.1.)

Response-addition, also referred to as simple dissimilar action, simple independent action or independent joint action (see glossary) occurs where the modes of action and possibly, but not necessarily, the nature and sites of toxic effects differ between the chemicals in a mixture, and one chemical does not influence the toxicity of another. The effects of exposure to such a mixture are the combination of the effects of each component compound.

The term, interaction, embraces all forms of joint action that deviate from the two classes of combined toxicity that are described above. It implies that the combined effect of two or more chemicals is stronger (synergistic, potentiating, supra-additive) or weaker (antagonistic, inhibitive, sub-additive, infra-additive) than would be expected on the basis of dose-addition (if the chemicals belong to a CMG) or response-addition (if they do not belong to a CMG).

1.2.1. Relevance to risk assessment for pesticide residues

Exposures to mixtures of pesticides could lead to any of the three types of combined toxicity that have been distinguished. However, with regard specifically to pesticide residues in food, some forms of joint action will be more relevant than others. This is because the doses to which people are exposed through consumption of pesticide residues in foods are relatively low. Regulatory risk management aims to ensure that exposures to residues from individual active substances are well below the levels at which any toxic effect would be expected, and routine monitoring of pesticide residues in foods across the European Union suggests that this objective is largely achieved. As reported in the annual EU-wide monitoring reports[7], available up to 2005, 5% or fewer samples contained residues above the Maximum Residue Limit (MRL), and even where this occurred, estimated intakes were normally below the relevant Reference Value (RV) (see glossary). It follows that the estimated dose for the consumer from an approved use will be at least one order of magnitude lower than the No Observed Adverse Effect Level (NOAEL). As detailed in section 1.2.1.2, at such dose levels no toxicologically/biologically significant interaction is expected to occur and only dose additivity of compounds with a similar mode of action is expected. Indeed, this would be the case also for doses at the NOAEL.

1.2.1.1. Response-addition

By definition, response-addition cannot lead to a toxic effect from a mixture when no toxicity would occur from any of the component compounds individually. Thus, given that exposures to residues from individual pesticides are generally well below the levels at which any toxic effects would be expected, it is anticipated that response-additive toxicity will rarely if ever occur from pesticide residues in food.

[7] http://ec.europa.eu/food/fvo/specialreports/pesticides_index_en.htm

1.2.1.2. Interaction

In theory, the interactive effects of a combination of pesticide residues could lead to adverse effects from a combination of pesticide residues even when the exposure to each component residue individually would be insufficient to cause toxicity. For example, one compound might inhibit a metabolic pathway that normally protects against a potentially toxic effect of another. However, many of the mechanisms that lead to toxic interactions of chemicals at higher doses (i.e. close to or above the doses at which the individual chemicals produce adverse effects) would not be expected to produce toxicity at lower doses. For example, interactions between medicines sometimes occur because one drug induces an enzyme that is responsible for the metabolic activation or deactivation of another. However, significant enzyme induction of this sort normally only occurs at relatively high doses.

To look for empirical evidence on the potential for toxic interaction between chemicals at low doses, the PPR Panel carried out a search of the PUB-MED database from 1980 onwards, using the search terms "toxicity and mixture and (interaction or synergy or potentiation or cumulation)". In addition, reviews on this subject were checked for references to papers not identified otherwise. While there are many papers in the scientific literature concerning the toxic effects of mixtures, both in vivo and in vitro, only a few were found that addressed combined effects from dose levels at or below the NOAELs for compounds when tested individually. The most salient findings are summarised here.

Gordon at al. (2006) reported a deviation from dose additivity for hypothermia and cholinesterase inhibition when administering chlorpyrifos and carbaryl in combination to rats. However, such deviation was observed only when the doses of the individual compounds were at or above their LOAELs, and not at lower doses.

No evidence of synergistic effects was seen on combined exposure of rats to subtoxic doses of nephrotoxicants with either the same or different modes of action (Jonker et al., 1993a, 1993b). However, when compounds with different modes of action were administered at toxic doses, both antagonism and synergy was observed, depending on the combination. Compounds with the same mode of action showed dose additivity (Jonker et al., 1996).

Jonker et al. (1990) treated rats with a combination of eight unrelated substances with different target organs. No interactions were observed at doses at or below the NOAELs of each individual compound, but when the compounds were administered at effect levels, there was some indication of modest antagonism or synergy, depending on the end-points considered.

Crofton et al. (2005) found that in rats, a mixture of thyroid-disrupting polyhalogenated aromatic hydrocarbons showed simple dose addition at low effective doses, whereas at higher doses, their effects appeared synergistic.

Walker et al. (2005) showed that the dose-response for hepatic, lung and oral mucosa neoplasms in rats treated with a mixture of dioxin-like compounds could be predicted by assuming additivity of the potency-adjusted doses. No interaction was seen at non-effective doses.

Heindel et al (1994; 1995) assessed the reproductive and developmental toxicity of mixtures of pesticides/fertilizers and other drinking water contaminants in rats when the individual components were below their effective doses. No evidence of synergy was observed.

Cassee et al (1996) exposed rats for 1 or 3 days by inhalation to mixtures of formaldehyde, acetaldehyde, and acrolein to assess their effects on the nasal epithelium. The range of the doses used included the NOAECs for the compound when tested individually. Neither histopathological nor biochemical endpoints changed when the doses were low whereas at high doses both dose addition and synergy were observed.

Groten et al. (1997) exposed rats, by inhalation or via the diet for 4 weeks, to different combinations of nine unrelated compounds. The doses included minimal effect levels, the NOAEC/L and a fraction of the NOAEC/L. It was found that there was no significant effect with doses at or below the NOAEC/L, while at the minimal effect level the effects could not be clearly described and no firm conclusion could be drawn on whether or not dose-additivity or interaction was observed.

Yang and Denison (2007) reanalysed the data of Bae et al. (2001) and Gennings et al. (2002) who tested cytotoxicity on human epidermal keratinocytes by arsenic, chromium, cadmium and lead alone or in combination. The results showed that there was dose-addition at low doses, with evidence of antagonism at higher doses.

Tajima et al. (2002) tested five Fusarium mycotoxins as inhibitors of DNA synthesis in L929 cells. In this system, dose-addition was again observed at low doses whereas at higher doses both antagonism and synergy were observed, depending on the combination.

Rajapakse et al. (2002) used an in vitro system with a yeast reporter gene assay for the human estrogen receptor α to test the effect of a combination of 11 xenoestrogens with 17β-estradiol. They found that the observed responses could be predicted assuming concentration-additive effects and no interaction was observed either at effective or non-effective levels of each individual compound.

Olgun et al. (2004) showed that there was a more than additive effect on apoptosis and necrosis of cultured thymocytes when lindane, permethrin and malathion were tested in paired combinations at doses, which individually caused minimal effect. No combined effects were observed when the compounds were at individually non-toxic doses.

When five organophosphates were administered together to rats, it was found that the doses for 20% or 50% effects were lower than those expected from simple dose addition (Moser et al., 2005). For most endpoints, the doses were about half of those predicted by dose-addition. However, these experiments were conducted at effective doses or at doses just below the effective doses for most of the compounds. The combined effects of lower doses were not determined experimentally. No explanation for the deviation from additivity was established or hypothesised. Subsequently, Stork et al. (2006) re-analysed the data presented in this paper and tested the results statistically for "additivity", with interaction as the null hypothesis. They found evidence in favour of dose addition for three of the four mixtures examined.

In these papers the no-effect dose used was generally less than 10 times lower than the effect level, most frequently between 3 and 5 times lower. The only exceptions were the experiments by Heindel et al (1994; 1995) where effective doses were not tested.

In addition the Panel evaluated several papers published by Abou-Donia and his group over the last 15 years. These studies included treatment of experimental animals with mixtures of compounds, including pesticides, given as either single or repeated doses. However, it was noted

that none of the studies involved the administration of all compounds at doses below their individual effect levels.

The evidence reviewed does not exclude the possibility that interactions could in some circumstances lead to toxic effects from combinations of pesticide residues at doses below their individual NOAELs. Only a limited number of compounds have been tested in combination at low doses; and for those combinations that have been tested, interactions might in some cases have been missed because of the spacing of the dose levels that were employed. However, the available evidence does support the view that significant toxic interactions between chemicals are much less likely to occur at doses below the effect levels for individual component compounds than at higher doses. To this extent, interaction is less relevant to risk assessment for pesticide residues in food.

1.2.1.3. Dose-addition

As indicated above, there is empirical and mechanistic evidence that dose-addition can occur when certain mixtures of chemicals are administered at relatively low doses. With regard to pesticide residues in food, this form of combined toxicity therefore requires further systematic consideration.

It is recommended that a case-by-case approach be adopted to consideration of whether it is biological plausible that interaction might occur between specific pesticides at low, non-effective doses. In some cases, ad hoc tests might then be required.

1.2.2. Implications for scope of the opinion

Having considered the evidence on the different forms of combined toxicity and their potential relevance to risk assessment for pesticide residues in food, the PPR Panel determined that it would limit this opinion to the possible impact of dose-addition when consumers are exposed to combinations of pesticide residues that share (or might share) the same modes of action.

As indicated in Section 1.2.1.1, response-addition would be relevant only where exposures to individual residues were at toxic levels, and this is not expected to occur if products are used in accordance with their conditions of approval, and also on the basis of the overall pattern of consumer exposure reflected by the results of monitoring programmes.

Toxic interactions from pesticide residues in food cannot be ruled out, but there is no empirical evidence for their occurrence, and they are much less likely to occur when exposures are below the effect levels for the individual compounds.

1.3. Types of exposure scenarios in cumulative risk assessment

The EFSA colloquium identified four relevant exposure scenarios in the context of cumulative risk assessment:

- Assessment of actual exposure (i.e. from the patterns of usage that actually occur in practice)
    - acute assessment
    - chronic assessment

- MRL-setting (i.e. a theoretical exposure where the residue of the compound under evaluation is at the level of the MRL)
    - acute assessment
    - chronic assessment

Assessments of risk from actual exposure, either acute or chronic, are based on the distributions of residue levels that are present in food as eaten. These assessments provide a means to check whether the residues from pesticides as used are sufficiently 'safe' for human consumption.

Assessments in the 'acute' MRL-setting context provide an answer to the question: if one ate a commodity with a residue level at the MRL, what would be the risk from cumulative intake on the same day of this pesticide and others with the same mode of action? In other words, can the proposed MRL be accepted? In theory, the 'chronic' MRL-setting assessment could address a number of different questions – for example, what is the risk from exposure through one commodity at the level of the MRL once in a lifetime or once every year? – and decisions on the exact assessment required need to be decided in consultation with risk managers.

In addition to the four scenarios that have been described, the PPR Panel recognised that acute and chronic cumulative risk assessments could also be performed in the context of use authorization. This is a slightly different approach from MRL-setting in that it is not the exact numerical value of the MRL that is assessed, but the residues arising from the proposed use, i.e. the results from the supervised residue trials. Due to the current procedures used in MRL setting, the MRL is normally higher than the highest value found in the residue trials. However, the PPR Panel decided that this opinion should focus on the four scenarios identified by the EFSA colloquium since they will give rise to the highest (MRL-setting scenarios) and lowest (actual exposure scenarios) exposure estimates.

1.4. Summary of scope of opinion

In summary, this opinion focuses on exposure to residues in food of multiple pesticides belonging to a CAG. Where the same residues can occur in food from sources other than from use as a pesticide, these are also taken into account. Acute and chronic risk assessments are considered, both in the context of MRL setting, and also in relation to exposures that result from the patterns of usage that occur in practice.

1.5. Structure of opinion

The first part of the opinion deals with the identification of compounds that comprise a cumulative assessment group, and for which dose-addition might be expected or assumed. The key steps for grouping compounds for cumulative assessment are described, indicating the different levels of refinement that can or need to be achieved. Then methods for assessing cumulation of effects are presented and their strengths and weaknesses discussed.

Next, exposure assessment is discussed in terms of scenarios, choice of data and methodology.

This is followed by a description of cumulative risk assessments that have been performed to date. They include risk assessments performed by the US EPA (organophosphorus compounds, triazines, chloroacetanilides, and N-methyl carbamates), by the UK (PSD and ACP), by RIKILT in

the Netherlands, by the Danish National Food Institute (all on organophosphates and carbamates) and by the Chemisches und Veterinaeruntersuchungsamt Stuttgart (CVUA) in Germany (all compounds). The methods that were used are summarised and discussed. Problem areas and the lessons that can be learned from these earlier experiences are highlighted.

The PPR Panel then considers criteria for selecting groups of compounds for combined risk assessment and the need for effective communication between risk assessors and risk managers in this selection process.

Finally recommendations are presented, including a tiered approach to cumulative risk assessment for pesticide residues in food.

Following this opinion, a worked example of the proposed methodology is being developed for a group of compounds, and the results will be reported in a separate opinion.

2. Existing Methods for Cumulating Toxicity

2.1. Identification of key steps leading to toxic effects and criteria by which to define a cumulative assessment group (CAG)

The criteria for grouping substances to CAGs have been discussed in several papers and meetings. There are several ways and different levels of detail that can be required, according to the circumstances, to define a group of substances as having a common mode of action. What follows is the description of a step-wise approach that is based mainly on US EPA documents (EPA, 1999; 2002) and an ILSI report (ILSI, 1999). This approach includes:

1. Preliminary identification of a candidate set of substances that might cause a common toxic effect by a common mode of action. This preliminary grouping is based on one or more of the following criteria:
    a. chemical structure. This can be explored by substructure searches in databases for toxophore[8] (or a metabolic precursor of a toxophore), core molecular structure, functional groups;
    b. mechanism of pesticidal action. This is considered informative because it is not uncommon that pesticides are toxic to humans through a mechanism that is similar to that of their activity against their target pests;
    c. general mode/mechanism of mammalian toxicity;
    d. a particular toxic effect. It is conceivable that similar toxic effects by different compounds might be caused via a common mode/mechanism. This criterion might allow the identification of structurally unrelated substances that act by the same mode of action. It is emphasized that non-specific effects such as body weight changes or death can result from many unrelated factors and consequently are of limited value in identifying potential candidate substances for a common mode/mechanism group.

[8] A structural feature or moiety contained in substances causing the same toxic effect. The toxic effect is attributed to the interaction of such a feature or moiety with the molecular target.

2. Definitively identify those substances from Step 1 that cause a common toxic effect(s). This step allows a first refinement of the preliminary grouping described above. This is performed by detailed evaluation of available toxicology data for each substance and those not causing a common (i.e. concordant in both site and nature) toxic effect are excluded.
3. Determine the toxic mode/mechanism of action by which each substance causes a common toxic effect. While desirable, not all of the specific biochemical events leading to toxicity need to be known or completely characterised. A minimum set of data is required to identify those events that are most crucial in causing the toxicity (mode of action). All available reliable sources of information should be used, including published literature, and textbooks.
4. Compare the mechanisms of toxicity/modes of action of the different substances.
5. Refine groupings by excluding substances that cause a common toxic effect by a different mechanism/mode of action.

The PPR Panel agrees that full consideration of all of these criteria will provide the most sound and robust grouping. However, as will be discussed later, such a detailed evaluation up to the last step might not be necessary or even possible in all cases. For the purposes of risk assessment, compounds might be grouped even in the absence of such detailed data, on the basis of a less refined evaluation of the mode of action (e.g., based only on target organ toxicity). To embrace this possibility, a group of compounds for which a cumulative assessment is thought to be required will be defined as a common assessment group (CAG). Hence, a common mechanism group, as defined above, comprises a CAG, but the reverse is not necessarily the case.

An additional consideration arises from evidence in the literature that certain endocrine disruptors show dose-additivity even if they do not share the same primary molecular target (Kortenkamp, 2007 and papers there reviewed). Therefore, the issue is the definition of the concept of common MOA, and what this would mean for endocrine disruptors. For instance, compounds affecting male sexual development via interference with steroid synthesis and not by antagonism of the androgen receptor would not be grouped according to a narrow definition of MOA whereas it has been shown that a mixture of such compounds results in a dose additive effect (Gray et al., 2001; Hotchkiss et al., 2004). Similar considerations can be applied to estrogenic or estrogen-like chemicals (Picard, 2003). Therefore, it appears that in these cases the criterion for grouping should rather be that of a common phenomenological effect (e.g.: altered ano-genital distance for anti-androgens) (Kortenkamp, 2007).

2.2. Methods for cumulation of effects caused by substances sharing the same mode of action

There are a number of methods that can be used to assess the risk of cumulative exposure to chemicals (ILSI, 1999; EPA, 1999; Wilkinson, 2000, Feron and Groten, 2002; Jonker et al., 2004). In general, the methods address this issue by determining the combined risk from the individual chemicals by summing the doses or exposures normalised according to the potency of the compounds. Most of these methods have been developed in response to certain regulatory needs and each has advantages and disadvantages.

The combined risk can be determined using either the respective reference points (RfPs) (see glossary) or the reference values (RVs). The latter include the application of uncertainty factors for the individual chemicals whereas in the former the uncertainty factors are applied to the end-result.

The method of addition after normalising the potency of each compound to a reference chemical was first developed for dioxins and is known as the Toxic Equivalency Factor (TEF) method (Haws et al., 2006; Van den Berg et al., 2006). The Relative Potency Factor (RPF) method (EPA, 2000a) is a generalized form of the TEF method, and has been used for classes of pesticides and other chemicals and is also known as the Potency Equivalency Factor (PEF) method. With this method, risk characterisation occurs after the process of toxicological evaluation.

Most of this section is based on an ILSI report (ILSI, 1999) and on a paper by Wilkinson et al. (2000) that described the different methods that can be used to assess cumulative risk.

The methods are presented with the assumption that evaluations will be performed using existing data, since new data will not be produced specifically for cumulative risk assessment, contrary to what was done by EPA when assessing OPs (see below section 4.1.1.).

2.2.1. Hazard index and adjusted hazard index

The Hazard Index (HI) is the sum of the Hazard Quotients (HQ), i.e. the ratios between exposure and the RV for each component to be evaluated. When the RV of a certain compound is based on an effect that is not the group effect (common toxic effect) or the assessment factor applied includes adjustments not related to the endpoint of concern then the HQ can be refined by identifying the RV for the group effect and adjusting the Hazard Quotient, accordingly. In this situation an adjusted HI (aHI) is then calculated.

$$HI = \frac{Exp1}{RV1} + \frac{Exp2}{RV2} + \frac{Exp3}{RV3} \quad \text{etc.}$$

When the HI is less than 1, the combined risk is considered acceptable. In this method, extrapolation of the no-effect level for the toxic endpoint to an acceptable exposure in humans is taken into account in determining the individual RVs.

2.2.2. Reference Point index

The Reference Point Index (RfPI) represents the sum of the exposures to each pesticide expressed as a fraction of their respective RfPs for the relevant effect (e.g., the dose that causes a 10% effect, BMD10; or the NOAEL). When the RfPI multiplied by the chosen group uncertainty factor (UF) is lower than 1, the combined risk is considered acceptable.

$$RfPI = \frac{Exp1}{RfP1} + \frac{Exp2}{RfP2} + \frac{Exp3}{RfP3} \text{ etc.}$$

In this method, extrapolation of the no-effect level for the toxic endpoint to an acceptable exposure in humans is taken into account using a common UF, applied to the combined exposure.

2.2.3. Combined margin of exposure

The Margin of Exposure (MOE) is the ratio of the RfP to the level of exposure in humans (measured or estimated). As such it is the reciprocal of the RfPI. The combined MOE is called the MOET, and is calculated as the reciprocal of the sum of the reciprocals of the individual MOEs. If the MOET is greater than 100 or other alternative value specified for the MOE by the risk manager, the combined risk is considered acceptable.

For instance, if the BMD10 is used as RfP:

$$MOE = \frac{BMD10}{Exposure}$$

$$MOET = \frac{1}{(1/MOE1) + (1/MOE2) + (1/MOE3)} \text{ etc.}$$

In this method, extrapolation of the RfP for the toxic endpoint to an acceptable exposure in humans is taken into account by considering what an acceptable combined margin of exposure is.

2.2.4. Cumulative risk index (CRI)

The risk index (RI) of a chemical is the MOE divided by the UF for that chemical or simply the RV divided by exposure. It is the reciprocal of the HQ previously discussed. The Cumulative Risk Index (CRI) is the reciprocal of the sum of the HQs. As such, when the CRI is greater than 1 the combined risk is considered acceptable. If the RV is used, similar considerations with respect to the toxicological basis of deriving the HQ apply here.

$$RI = \frac{RfP}{Exposure \times UF} = \frac{RV}{Exposure} = \frac{1}{HQ}$$

$$CRI = \frac{1}{\frac{Exp1}{RV1} + \frac{Exp2}{RV2} + \frac{Exp3}{RV3}} = \frac{1}{HQ1 + HQ2 + HQ3}$$

In this method, extrapolation of the RfP for the toxic endpoint to an acceptable exposure in humans is taken into account in determining the individual RVs.

2.2.5. Toxic equivalency factor/potency equivalency factor/relative potency factor methods

The Toxic Equivalency Factor (TEF) method was developed initially for dioxins and other Ah receptor agonists (Haws et al., 2006; van der Berg et al, 2006), whereas the Potency Equivalency Factor (PEF) or Relative Potency Factor (RPF) is a more generalised method that has been used for compounds such as polycyclic aromatic hydrocarbons and certain pesticides (organophosphorus compounds). Both these methods require the identification of a so-called "index compound" (IC) and the potencies of all chemicals of the group are normalized to the IC. Usually the potencies are derived from dose response curves, using the same benchmark response (e.g., 10%) for each compound, but NOAELs have also been used. The activity of the mixture is then determined by the sum of the potency-normalised doses to yield a total equivalent exposure expressed as IC equivalents. An example of the calculation is given in table 1 below. This total equivalent exposure is then compared to the RV of the IC. If the total equivalent exposure is lower than the RV of the IC, the combined risk is considered acceptable. Alternatively, the MOE of the total equivalent exposure is calculated from the RfP of the IC. In this case, if needed, additional UFs are applied to the individual RPFs before calculating the MOE.

In this method, extrapolation of the no-effect level for the toxic endpoint to an acceptable exposure in humans is taken into account in determining the RV for the index compound.

Table 1 Example of the application of the RPF method

COMPOUND	BMD10 (mg/kg/day)	RPF relative to IC (A)
I	100	5/100 = 0.05
II	500	5/500 = 0.01
III	25	5/25 = 0.2
IC (index compound)	5	5/5 = 1.0

COMPOUND	Exposure (mg/kg/day) (B)	Exposure in terms of IC (A×B)
I	0.5	0.025
II	0.5	0.005
III	0.01	0.002
IC (index compound)	0.01 (RV)	0.01
Total equivalent exposure to be compared to the RV of the IC		(0.042)

2.2.6. General comments on the approaches

The methods described above do not differ in the underlying data used but in the different ways of expressing the data. In particular the CRI and the MOET are the reciprocal related to the HI and the RfPI, respectively. These, in turn, differ because the former uses the existing RV whereas the latter is based on the RfP. The RfPs are generally less readily available than the RVs and UFs need to be applied to the RfPs and this requires an additional effort. The RPF method uses a different approach since all compounds of the group are normalised to an IC and exposure considerations are applied at the end of the process. More detailed comments follow. It should also be noted that confidence in the outcome may diminish when RVs or RfPs are based on or derived from studies differing in species and design, or when different methodologies are used in the RfP determination (e.g., NOAEL vs BMD).

HAZARD INDEX and CUMULATIVE RISK INDEX: The HI has the advantage of relating directly to the RV, which is a long-used and well-understood index of acceptable risk, and as such it is transparent, understandable and can be (relatively) rapid and simple to apply (since individual RVs are readily available). It can accommodate the application of chemical-specific adjustment factors (CSAFs) earlier in the process.

Among the possible disadvantages it should be noted that RVs are obtained by application of an uncertainty factor (UF) that may incorporate policy (e.g., default extra UF for children or severity of effect) and scientific (e.g., on the quality of the database that might not be directly related to the relevant toxic effect) judgments. As such, it does not necessarily represent a true measure of relative toxicological potency of the different compounds. Moreover, there is the need to identify the basis for the RV for each compound; however this might be necessary only if refinement of the assessment is required.

The CRI is conceptually more difficult to understand than the HI, but in essence the same considerations apply to this method.

In conclusion, the HI may be suitable as an initial screening method.

REFERENCE POINT INDEX and COMBINED MARGIN OF EXPOSURE: The RfPI has the advantage that it sums the exposures to the different pesticides in relation to their relative potencies, expressed as the RfP. It is intuitively more straightforward and mathematically simpler than other methods. It is also more transparent because UFs are not used prior to calculating the RfP. A single group UF can be applied as the last step in the process.

The use of the RfPI does not allow the application of chemical specific adjustment factors (CSAFs) (for interspecies differences), including those associated with the availability of data in

humans, unless this is done earlier in the process, if needed. For these reasons, study design should preferably be comparable for all compounds.

The MOET is conceptually more difficult to understand than the RfPI, but it is only a different expression of the same approach.

RELATIVE POTENCY FACTOR: This method is transparent, and easy to understand because it also separates potency correction from exposure considerations. Thus, it provides a better basis for standardising toxic dose metrics for the various chemicals. When RPFs are based on BMDs, this method can potentially be used for assessments of risks at or above the RV.

However, it should be noted that determination of the risk posed by the combined exposure places great emphasis on the quality of the toxicology database of the IC. The IC would normally be chosen among the compounds with a toxicological database that provides the lowest uncertainty and clear criteria need to be established for selecting the IC.

Moreover, as reported by EPA this method can be quite labour intensive.

The TEF/REF/RPF approach is somewhat different from the others in that it relies on expressing the different potencies of the entire group on the toxicology database and UF of the IC. However, it has been shown (Wilkinson et al., 2000) that, if all of the pesticides in the group have a common data set (i.e., the toxicology data all use the same end-point and type of RfP in the same test species) and all are associated with the same UF, the final result is the same irrespective of which method is employed. However, in general, the types of toxicity data available, as well as the overall quality of the data, are likely to differ from one chemical to another.

With all of these methods, it is necessary to take account of possible differences in time-course of effects when choosing the RV or the RfP. For instance, in performing cumulative acute assessments, it is possible that the use of single day consumption data for comparison against an ARfD will under-estimate the risk from compounds that have a long half life (kinetics) or a long-lasting effect (dynamics). In the former case, there are a significant proportion of the active substances (or relevant metabolites) present on the following day, whereas in the latter there might be effects carried over into the next day (e.g.: inhibition of acetylcholinesterase by an OP). An exposure to another compound(s) from the CAG on the next day could result in a cumulative systemic exposure above that predicted. In such instances a case-by-case approach is recommended.

It should be noted, also, that all of the methods assume that compounds have parallel dose-response curves, which is not necessarily true (for example see Moser, 1995) and hence is a source of uncertainty. It is not possible to determine a priori whether this will result in more or less conservatism in the assessment, this will vary on a case-by-case basis. It should be noted that this applies to both the NOAEL and the BMD approach. A further complication is that whilst the dose-response curves may be non-parallel in the range of observable responses, it is not possible to determine how the curves relate to each other at lower levels of exposure.

When using the RfP or RV, one should be aware that NOAELs/LOAELs may represent varying risk or response levels for different compounds, depending on dose-spacing. In fact, it may happen that for one compound the NOAEL is lower than the NAEL (no adverse effect level = biological threshold for the effect in the relevant experimental system) because of sensible choice of dose spacing whereas for another, the NOAEL defined on the basis of a statistically insignificant or borderline effect may be above the NAEL. In the former case, the margin to reach the effective

dose is much higher than in the latter. In contrast, BMDLs represent a uniform level of response across chemicals, since they take into account the shape of the dose-response curve and of the variation of the data (Filipsson et al, 2003).

2.2.7. Physiologically-based toxicokinetics (PBTK) and toxicodynamics (PBTD)

Physiologically-based modeling could be used for a higher tier assessment, if this were considered necessary. Whilst most emphasis to date has been on modeling toxicokinetics (PBTK), it is also possible to model toxicodynamics (PBTD) and to link the two. PBTK permits an estimate of the concentration of the compound at the target site for a toxicological effect. In cumulative risk assessment, the concentrations of each component of the combined exposure would need to be corrected for potency, for example by using potency equivalency factors. It is also possible to use PBTK and PBTD approaches to investigate other types of combined effect.

The general approach has been described by Teuschler et al (2004), for the assessment of combinations of disinfection by-products. Whilst PB approaches have been outlined for cumulative assessment of pesticides (Conolly et al, 2005; Lowit et al, 2004), to date they have not been utilised in the final assessments. PB approaches provide a highly refined methodology, they are resource intensive and demanding of specialised expertise therefore are unlikely to be routinely used in the near future.

3. Cumulative exposure assessment

3.1. General issues on exposure

This section reviews methods of exposure assessment that can be applied in the context of combined risk assessment for pesticide residues in food belonging to a CAG.

As described in section 1.3, the focus is on assessment of the risk from combined exposures associated both with the patterns of usage that occur in practice, and on MRL-setting. According to the toxicological properties of the group of pesticides under consideration, the relevant exposures may be acute, chronic or both. These (24-h or lifetime exposure) are the usual timeframes considered for the risk assessments of individual chemicals. In addition, intermediate timeframes could be important both from the exposure and toxicological perspective (see 2.2.6). Therefore, before an exposure assessment is carried out, the relevant time period(s) of exposure should be determined from the toxicological database as a guide to the type of exposure assessment required.

To date, U.S. EPA has the most extensive experience on cumulative risk assessments for pesticides. However, the exposure assessments performed by U.S. EPA simulated only actual exposures, not exposures that may occur when one commodity is at the level of the MRL. Therefore the methodology to do this had to be developed anew.

In the actual exposure scenarios, residue levels from monitoring programmes should be used for all commodity/pesticide combinations in the assessment and the group of consumers considered should be the total population of interest, i.e. including non-consumers.

In the acute cumulative MRL-setting scenario, residues at the level of the MRL should be taken into account only for the commodity/pesticide combination for which the MRL is to be set. For all other commodity/pesticide combinations in the assessment, background levels (e.g., from

monitoring programmes) should be used. Furthermore, the group of consumers considered should only be those who consume the commodity of interest.

With regard to chronic risk assessment for MRL-setting, it should be noted that over a lifetime it is very likely that patterns of pesticide usage will change. Therefore the chronic assessment cannot be more than a snapshot. Furthermore, the starting assumption (how many times in a lifetime is one likely to be exposed to a pesticide at the level of the MRL) is hard to define. The PPR Panel recognizes that for assessments of individual chemicals, the assumption is that in the worst case, consumption could be at the MRL (or Supervised Trial Median Residue (STMR)) for a lifetime. However, for a cumulative assessment where multiple residues are summed this is considered to be unrealistic, even if exposure at the STMR for a commodity/pesticide were to be combined with background exposure for other commodities/pesticides. Given these limitations, the PPR Panel considered that perhaps the actual chronic cumulative exposure assessment would provide all the information necessary, i.e. 'what is the risk in the long run from being exposed to multiple pesticides in a group with the same mode of action?" As a first tier though, an assessment combining lifetime exposure at the STMR for a given commodity/pesticide combination with background exposure for all other commodities/pesticides could be performed, while recognizing that this tier may often show a cumulative exposure higher than the RV.

For dietary as for other routes of exposure, an important question is whether differences are to be expected with time of year or region. U.S. EPA assumes that exposure to pesticide residues in foods is uniform across the nation. This assumption is based on the knowledge that, to a large extent, food is distributed nationally and consumption is independent of geographic region and season. In Europe, this assumption may not be appropriate. European Member States are not so uniform in their production and import of food, and certainly not in consumption behaviour. Thus, Europe had to be characterized by four of the thirteen WHO/GEMS-Food cluster diets (WHO, 2006b) whereas all of the USA could be covered by a single cluster diet. However, regional differences can be addressed by performing separate risk assessments using national consumption databases from each of the four clusters. Moreover, seasonal differences can be incorporated in the exposure modelling if food consumption surveys cover all seasons (see also section 3.3.1).

In the remainder of this chapter, data sources and requirements (residues and consumption) are discussed as well as the methodology available to assess the different types of exposure. It should be noted that a number of the issues highlighted as of concern in cumulative risk assessment are common to risk assessments of individual chemicals. However, the fact that the data are used cumulatively magnifies the issues identified, therefore the PPR Panel considered it important to include them in this opinion.

3.2. Residues Data

3.2.1. General requirements

A pesticide residue can be defined as the pesticide and/or a combination of its metabolites and derivatives. Ideally, a pesticide residue should include substances of toxicological interest for dietary intake estimations and risk assessment and be suitable for monitoring compliance with Good Agricultural Practices (GAP).

The two requirements are sometimes not compatible and, as a compromise, different definitions of residues are possible. For some compounds there may be separate residue definitions for MRL enforcement and dietary risk assessment purposes. The residue definition for dietary risk assessment purposes should include metabolites and degradation products of toxicological concern whereas the residue definition for compliance with MRLs needs to be a chemically simple definition (i.e. indicator molecule) suitable for practical routine monitoring and enforcement of the MRL at a reasonable cost (FAO, 2002). It is also noted that, residue definitions (especially those for risk assessment) can change with time because of changing views on the toxicological importance of certain metabolites or degradation products.

For cumulative risk assessments, parent compounds, metabolites and degradation products are of concern only when they have the same common effect/mode of action being considered within the CAG.

Cumulative risk assessments may be conducted for scenarios that assess either acute or chronic risks. For both these scenarios, the ideal is to characterise the distribution, i.e. occurrence and representative concentrations in the food supply, of residues of each substance to be included in the cumulative assessment in foods as consumed[9]. However, in reality such ideal data are rarely available, but rather data from supervised residue trials and targeted monitoring data, although less suitable, can be used.

The details of the approaches for characterising residue distributions may differ between scenarios assessing acute and chronic intakes. In the former it is of particular interest to characterise the upper portions of the residue distributions, while for chronic assessments information on the average levels is required.

3.2.1.1. Supervised Trials and Other Residues Data

To support both plant protection product marketing authorizations (Directive 91/414/EEC) and the establishment of MRLs (Regulation (EC) 396/2005) notifiers have to provide data from supervised trials.

Guidance on the conduct of such trials has been set out by the European Commission (EC, 1997). This guidance requires that data reflect the critical GAP that is expected to leave the maximum residue at harvest, or at the end of any mandatory withholding interval, for post-harvest treatments.

It should be noted that residues data may not be required, and therefore will not be available, for every edible crop on which use is permitted. This is because plants or plant products where residue behaviour is regarded as comparable have formally been identified, and in these cases knowledge about the residue data in one commodity can be transferred, or "extrapolated", to another (EC, 1997). Therefore, the cumulative assessment should consider if any uses are permitted on the basis of such agreed extrapolations and where they are, the available residues data for both the tested and extrapolated commodities should be used.

Supervised trials should include analyses for substances of toxicological relevance for dietary intake estimations and subsequent risk assessment. Therefore, in that regard, the data are appropriate to use in cumulative risk assessments. However, a limitation is that the residue is

[9] In the MRL-setting context, these distributions provide the background residue level to which a residue at the level of the MRL will be added

determined in the raw agricultural commodity, which is not necessarily the portion of the commodity consumed.

In some instances, processing studies (e.g., peeling, canning, and cooking) are reported to support risk assessments for authorisation or MRL setting that allow a more realistic estimate of residues in the edible portion of the commodity after simple processing. Where available and appropriate (EC, 1997; BfR, 2007), such data should be used to provide more appropriate residue concentration estimates.

Typically, data from supervised trials are expected to overestimate the levels and particularly the occurrence of residues in market samples. This is because in supervised trials all the commodity sample will have been treated at the maximum dose, with the minimum time elapsing between treatments and sampling[10]. In actual use, not all of the commodity will have been treated and even when the commodity has been treated, lower doses may have been used, with longer intervals between treatment and sampling. Comparison of trials and monitoring data can reveal wide differences in the residue distributions. This is most relevant when estimating chronic intakes, but can also be an issue for acute intake estimates. However, with acute intakes it is not unreasonable to assume that occasionally, foods will contain residues at the concentrations observed in supervised trials (or even the MRLs estimated from the trials).

The PPR Panel noted that even residues data from monitoring samples might overestimate the real exposure of the consumer. This is due to the fact that sampling can be done at several points in the distribution chain (e.g., farm gate, retailer, supermarket) and that at the time of consumption the residue may have declined. Residues data from food on the consumer's plate is almost never available. This is an additional source of uncertainty.

In addition to residues on directly treated crops, residues of substances of concern may occur in crops grown in previously treated areas (rotational crops). Where, after 100 days, tests show that in soil less than 10% of applied active substance or bioavailable metabolites can be detected, current procedures for single compound assessment usually assume the residues to be negligible. In other situations a theoretical estimate of the residue in rotational crop may be made and then model or field tests may be required (EC, 1997). When performing a cumulative assessment, the evaluation according to Directive 91/414/EEC, or if not available a similar review, of the active substance should be examined for information on possible rotational crop residues of concern. Where such residues are possible, their impact on the assessment should be considered and the associated uncertainties should be discussed.

Residues of concern may also occur in animal products (e.g., meat, milk and eggs) where residues in animal feedstuffs are passed on to products. The possibility of this occurring is investigated mainly when significant residues (0.1 mg/kg of the total animal diet on a dry basis) occur in the animal diets and where metabolism studies in domestic animals indicate significant residues (typically above 0.01 mg/kg) occur in edible tissues (EC, 1997). When performing a cumulative assessment, the evaluation according to Directive 91/414/EEC, or if not available a similar review, of the active substance should be examined for information on possible residues of concern in animal products. Where such residues are possible their impact on the assessment should be considered and the associated uncertainties should be discussed.

[10] EU Guidance actually allows +/- 25% variation in a single parameter around the "worst case".

3.2.1.2. Monitoring data

Member States operate national monitoring programmes that generate residues data in marketed commodities. The sampling procedures followed are those specified in Commission Directive 2002/63/EC. The majority of the residues data come from official monitoring plans corresponding to random sampling procedures, with some targeted sampling based on e.g., the violation rate in previous years. The validity of the analytical results is governed by a quality assurance system complying with ISO/IEC 17025 Standard (General requirements for the competence of testing and calibration laboratories) in all countries. However, while the EC Directive refers to random sampling within a selected lot so as to obtain a representative sample, it is also important for the design of the sampling programme to ensure that the lots selected are representative of the available supply. Specifically, it is important that a sampling frame be developed in which each potential sampling location (e.g., food distribution facility) is assigned a probability proportional to the throughput and the locations are sampled in such a way as to ensure the commodities sampled are representative of the supply. The U.S. follows this procedure as part of its Pesticide Data Program (PDP) (under the U.S. Department of Agriculture). As stated in the PDP Annual Summary for calendar year 2006 (USDA, 2007), the goal of the PDP is to obtain a statistically defensible representation of the U.S. food supply. In this manner, PDP data reflect actual pesticide residue exposure from food.

Directives 90/642 and 86/362 and from 1st September 2008 Regulation (EC) 396/2005 (will) require Member States to check regularly the compliance of foodstuffs with maximum residue levels (MRLs). Besides national monitoring programmes, coordinated community monitoring programmes are adopted following a multi-annual strategy. The choice of commodities includes the major components of the Standard European Diet of the World Health Organization. In most cases, sampling follows annual national plans that are usually established taking into consideration consumption, production, and share of imported and exported products as well as risks.

In addition to official monitoring data, monitoring data from industry may also be available. Such data may be collected by retailers (e.g., Supermarkets), growers, and processors. Provided the quality control aspects can be transparently demonstrated to support the validity of such data, this information can be a useful adjunct to official programme results. When using these data it should be assessed whether they are representative of the general food supply.

Monitoring programmes often involve a degree of targeted sampling so that commodities with known or suspected residue issues may be over-sampled, and therefore the residues distribution may not be representative of the whole food supply. In addition, the degree of targeting within a MS's programme is not usually explicit. It is recommended that in future this should be clearly reported.

On the other hand, it should be noted that monitoring programmes never include all pesticides present in the worldwide market. For cost and efficiency reasons, choices have to be made each year.

As discussed above, the residue definition used for the MRL, and therefore the analyte(s) sought in the programme, may not include all substances of toxicological concern for the cumulative assessment. Occasionally, a conversion coefficient may have been determined so that it is possible to estimate the total quantity of the residue(s) of concern from the amount of residue detected

during monitoring. This will introduce additional uncertainty the effect of which should be considered.

Finally, like supervised trials, monitoring programmes sample raw agricultural commodities, not foods as consumed. Again, if processing data are available it may be possible to make some limited estimates of residue concentrations in foods as eaten. This is of particular concern for commodities like citrus fruits, banana, pineapple, melon, kiwi fruit, etc, which are usually peeled before consumption.

Despite the reservations mentioned here, monitoring data provide potentially the most representative and realistic residue values for use in cumulative assessments of actual exposure, and the most realistic background level for MRL-setting scenarios. Where potential for residues in rotational crops and animal products has been established (see above) and provided relevant commodities and products are sampled, monitoring data will include information on these contributions.

However, there are two additional aspects that should be considered. Monitoring data typically do not include the whole range of commodities consumed. The uncertainties from uses on unmonitored crops and their contributions to the diet should be considered.

As discussed above (3.2.1.1), in some situations residues data are "extrapolated" between commodities. Where MRLs have been set on this basis for commodities that have not been monitored for residues, it is possible similarly to extrapolate the monitoring results from the commodity used as the basis of the MRL. It is proposed in such cases that a sensitivity analysis be performed, modeling intakes with and without such extrapolations.

Further extrapolations may be considered from analysis of monitoring data. For example, patterns of occurrence of multiple residues (or the absence of multiple residues) present in commodities from the same crop group may justify extrapolation of the findings to non-monitored commodities. Another approach would be to determine if there are patterns of actual residues compared to MRLs, e.g., ratio of different residue percentiles to the MRL, that can be extrapolated to infrequently monitored commodities.

When making extrapolations, the following should be considered:

- Choice of pesticides that could be used on the crop,
- Agronomic reasons for use (including likelihood of using more than one pesticide for the control of a same pest considering possible applied strategies preventing pest-resistance)
- Application patterns (doses, timings, and methods)
- Pattern of co-occurrence within monitoring programme
- Geographical and temporal variation in pesticide usage

Also, monitoring data are often censored (truncated), with the lowest values being unknown or unreported. While this is not usually significant when considering residues of a single pesticide it can be problematical when considering multiple residues as the assumptions made regarding censored concentrations can affect the distribution of estimated high intakes. This is a significant issue and is discussed below.

3.2.1.3. Using censored data

In the context of results, censored (truncated) data can typically fall into three categories:

- In monitoring programmes and supervised trials, residues may not be found above the detection limit of the analytical method – these are true non-detects.
- In monitoring programmes and supervised trials, residues may be found above the detection limit, but below the lower concentration qualification limit (limit of quantification, LOQ or lowest calibrated level, LCL) validated for the method.
- In monitoring programmes a standard reporting level may have been assigned with concentrations below this level, even when quantified, being simply reported as "not found" or more correctly as less than the reporting level.

Strategies should be developed for dealing with data from all of these categories. In the case of supervised trials, residues less than the detection limit of the method can be regarded as zero if this can be substantiated by consideration of the plant metabolism studies that are required to support authorisations and MRL setting. If not, one of the strategies described below would need to be adopted.

Dealing with non-detects in monitoring data may be more problematical, as it cannot be ascertained if these are the result of non-treatment or not[11]. However, in the situation where no residues above the limit of detection have been found, such non-detects could be treated as zero. A sensitivity analysis should be done assuming such values are zero or are equal to the limit of detection. If this shows the impact of the assumption does not significantly affect the outcome, there is no need to modify the assumption. Otherwise, evaluation of the evidence to support the assumption is required. This may include: the plant metabolism studies and supervised trials data discussed above; data showing that only a very low proportion of the commodity is treated; or where a secondary processed commodity is sampled, data showing that relevant processing procedures are likely to remove residues (e.g., crystallization during refining of sugar). In addition, information on the level of consumption of the commodity and the toxicology of the potential residue should be considered and the uncertainties discussed.

Where residues are detected above the limit of detection, but below the limit of quantification, a commonly used approach is to assign these results a value of one half of the limit of quantification. If this is done, it is recommended that a sensitivity analysis be performed to evaluate the effect of this assumption. Where the outcome of the assessment is not sensitive to this assumption, modification of the assumption is not warranted. In other cases, a more sophisticated analysis (e.g., maximum likelihood estimation) can be used to estimate likely levels of such values from the distribution of values above the quantification limit, if there are both a sufficient number and proportion of results above the quantification level (this requires an assumption about the underlying distribution (log normal) of residues. However, because of the small numbers of samples in supervised trials such approaches are unlikely to be feasible with trials data.

It should be noted that in monitoring programmes, reporting levels are often established at relatively high concentrations, as historically these programmes have been used to monitor compliance with MRLs. A consequence of dealing with censored data with high reporting levels

[11] Checking the MRL for a given crop-pesticide combination provides no information on authorized uses, since the MRL can be set at the LOQ because there is no use of the pesticide on this crop, OR because there is a use resulting in residues below the LOQ.

for several substances in several commodities may be significant uncertainty in the intake estimates. Lower reporting levels sometimes increase the cost of analysis, but the need to do cumulative assessments and the introduction of a default MRL of 0.01 mg/kg justify considering routine application of lower reporting levels.

One possible approach to help produce more realistic estimates would be to take into account the proportion of the commodity that had not been treated with the substances under consideration. The U.S. EPA does take account of the percentage of domestic crop treated in their cumulative assessments (EPA 2000a) and also has developed an approach for predicting this parameter (EPA, 2002a). In Europe, data to reliably estimate this percentage exist for some crops in some countries[12]. However, data are not currently available to reliably estimate the percentage of commodities imported into the EU that have been treated when growing or after harvest.

3.2.2. Residue data in acute intake assessments

It has been suggested that for acute risk assessments it is desirable for residues data to be provided for single items rather than for the composite samples required by current protocols for both supervised trials and monitoring. This is to avoid difficulties in having to estimate the consequences of possible uneven distributions of residue concentrations in the individual units that comprise composite samples. However, in reality such data are unlikely to be available so the variability of concentrations in individual units will need to be considered.

The results of limited modeling conducted for a previous Opinion of the PPR Panel on acute dietary intake assessment (EFSA, 2007c) showed that changing the way the variability factor was represented in the probabilistic models used by the Panel (fixed factors of 1, 5 and 7 versus a range of values in a distribution) had little effect on the distribution and uncertainty of estimated intakes for the total population. This implies that for the specific models considered the estimated intakes for the total population were more strongly influenced by other factors (e.g., extreme values in the consumption and residue monitoring data). Therefore, in some cases it may not be critical to have residues data for single commodity units. However, this is unlikely to be true for all models. For instance, models that use parametric distributions to describe the concentrations may sample values from the upper tails of the distributions of composite sample concentrations that are similar in frequency and magnitude to values that may be sampled from the upper tails of distributions of single unit concentrations. On the other hand, in models that bootstrap the measured concentration data, the upper values will be limited to the maximum observed.

It is therefore necessary to consider the possible influence of variability of residue concentrations in individual units that make up the composite samples analyzed, and it is recommended that a sensitivity analysis be performed to determine the influence of various assumptions.

[12] The UK undertakes very detailed surveys of all commercially grown crops, with surveys of arable crops, representing about 90% of all pesticide use. These data will allow percentage of crop treated with any pesticide to be derived but also allow the actual level of tank mixing or multiple applications of different actives to the same crop to be determined as well. Similar detailed surveys are undertaken by the Netherlands and by Sweden, though Sweden only covers major arable crops. Of the twelve new member states, detailed surveys have been undertaken by Malta and Poland, and surveys of at least two vegetable, fruit and arable crops have been undertaken in pilot areas by all the others except Cyprus. Information on times treated and % crop treated for any active on crops grown in the UK can be found at: http://pusstats.csl.gov.uk/ Detailed information from individual UK surveys can be found at: http://www.csl.gov.uk/pus

In the context of cumulative assessments, when establishing MRLs the approach should be based on the MRL value for the contribution of the active substance/commodity combination under consideration and if available use monitoring data for the background contribution from the active substance in other commodities plus the background contribution of other active substances in the same CAG. Where monitoring data are not available, supervised trials data may be an alternative coupled with a sensitivity analysis of realistic use assumptions. See also chapters 3.4 and 7.

3.2.3. Residue data in chronic intake assessments

For chronic assessments, composite residue samples are adequate, and variability between individual units is not a concern. How representative the monitoring data are of the actual food supply should be considered: this is in terms of seasonality and global sources of the monitored commodities as well as the range of commodities monitored.

In the context of cumulative assessments when establishing MRLs, the approach should use the STMR value from the supervised trial data for the contribution of the active substance/commodity combination under consideration with average concentrations from monitoring data for the background contribution from the other active substance/commodity combinations plus the background contribution of other active substances in the same CAG. Where monitoring data for the background contributions are not available, averages derived from supervised trials coupled with a sensitivity analysis of assumptions on realistic uses should be considered.

For actual chronic cumulative assessments, supervised trial data could be used only as a first tier.

3.2.4. Sources of information

As discussed above, some information on supervised trials, plant metabolism and rotational crops will be provided in the Directive 91/414/EEC evaluations of active substances. The more recent evaluations are published by EFSA after peer review and the relevant information is therefore available. However, these evaluations do not consider all authorised uses, as additional uses and MRLs may be established. These other evaluations, and evaluations for MRLs of active substances not used in the EU, but used outside the EU on imported commodities, have not historically been published. Under Regulation (EC) 396/2005, MRL proposals will be reviewed by EFSA, and uses will not be permitted until the MRLs are in place.

Information on monitoring programmes and their results are published in varying details by member States, and the EU publishes annual EU-wide reports[13] on the results of the monitoring of pesticide residues in products of plant origin in the European Union, Norway, Iceland and Liechtenstein. Regulation (EC) 396/2005, when it comes into force, will place a requirement on individual member States to publish on the internet details of their monitoring annually. In addition, they also have to report the results to the EFSA annually. The EFSA intend to develop a standard reporting format for the individual sample results (including information such as sampling strategy, sample origin, LODs). This should result in a database that will aid cumulative assessment. This initiative will be invaluable in applying the methodology described here and should be actively encouraged.

[13] http://ec.europa.eu/food/fvo/specialreports/pesticides_index_en.htm

It is recommended that when reporting levels are established the needs of cumulative assessments should be taken into account, i.e. the reporting level should be as close to the LOQ as possible.

3.3. Consumption data

3.3.1. General requirements

Dietary consumption data take many forms and may be collected by several different methods. They reflect what either individuals or groups consume in terms of solid foods, drinking water, beverages and supplements. Dietary consumption can be estimated through food consumption surveys at an individual or household level or approximated, more coarsely, through food production statistics. Food consumption surveys can be performed through one or more of prospective records/diaries, retrospective dietary recall, and food frequency questionnaires. Food production statistics (food balance sheets) represent consumption data of foods available for consumption for the whole population, typically in the raw form as produced. These can be adjusted to account for food losses or waste.

The way in which the food consumption data are collected, or organized after collection, determines to some extent the nature of the dietary intake estimate that may be calculated. The same food consumption survey could provide data for different scenarios, but depending on the question addressed (e.g., MRL setting or cumulative risk assessment) and the methodology (e.g., deterministic or probabilistic methods) different inputs to the assessment could be extracted from the database. Therefore, the raw survey data from these databases should be accessible.

Ideally, food consumption data used at the European level should take into account the differences in food consumption patterns that may exist in different regions. They should include information on factors that influence consumption patterns and the dietary exposure. Such factors include: demographic characteristics of the individuals sampled, body weight, the geographic region, the day of the week and the season in which the data are collected.

Food consumption data should be representative of consumption over the whole year, as well as the sex, age, race/ethnicity and socioeconomic characteristics of the population. This information is essential to provide a reliable estimate of the distribution of consumption in the overall population. Special attention should be given to consumption situations of relevant subgroups of interest (e.g., different age groups, especially young children and women of child bearing age) and consumption patterns for individuals at the upper ends of the distribution. Approaches for food consumption data collection at the international level, and further information on the different methods including references, data format and modeling are described in detail in the report of the 2005 FAO/WHO Workshop on Exposure Assessment for Chemicals in Food (WHO, 2007). An example of design and methods for a national food survey is the Belgian National Food Consumption Survey (De Vries et al., 2005).

Data requirements differ depending upon whether one wishes to estimate one-day (for acute or short-term assessments) or multi-day (for longer-term and chronic assessments) food consumption. These are discussed further below in greater detail. It is important that reliable information on the identity of the actual food items consumed be included, and thus the original survey database in which the specific food items are identified (in contrast to aggregated consumption figures) must

be available. Such information would ideally include cooking and other food form information (e.g., baked, boiled, fried, canned, bottled).

In addition, the food items should be described in a transparent and explicit food coding system to avoid misinterpretation of the data and to simplify computations of consumption estimates. Several food-coding systems exist e.g., LanguaL[14]. Initiatives to establish a harmonised European food coding system are currently underway. Since dietary consumption surveys collect data on foods "as eaten" (e.g., pizza, hamburger, beef stew) and not on their component parts (i.e. ingredients) and pesticide residue monitoring programmes generally collect residue data on raw agricultural commodities (e.g., apples, oranges, maize oil, etc.), it will also be necessary to translate food consumption from an "as eaten" food basis to a food commodity basis. More specifically, it will be important to use standard recipes to develop consumption estimates of the food commodities which are consumed and for which the majority of pesticide residue data are available. For instance, the U.S. obtains its consumption data from the U.S. Department of Agriculture's Continuing Survey of Food Intakes by Individuals (CSFII), 1994-96/1998[15]. This was translated by means of standard recipes to food commodities and is available from the National Technical Information Service of the U.S. Department of Commerce on CD-ROM as the Food Commodity Intake Database (FCID). The FCID reports consumption on a food commodity basis (e.g., milk, wheat, flour, tomato paste, beef, etc.) rather than on the food "as eaten" basis which serves as the basis for (CSFII) data collection.

At the supra-national European level, no such food intake database is available. However, on the national level such databases are available from UK, Netherlands, Germany (children only) and others, but often instead of the complete original databases only summarized data (97.5% and median consumption figures) are available. It is recommended that a consumption survey be performed on the European level, e.g., along the lines of the 4 European GEMS/Food cluster diets (WHO, 2006b), and not along the lines of country borders. This would allow a consistent exposure assessment for the whole EU in 4 regional diets, instead of performing different assessments at the Member State level. Such a survey could be coordinated by EFSA. The results and experiences of both SAFEFOODNET[16] and EFCOSUM (Brussaard et al., 2002) projects should be considered. The former research project was sponsored by the Chemical Food Safety Network for the enlarging Europe, and was designed to help harmonize and integrate the chemical food safety infrastructures and activities of Europe and to identify for EFSA an expert network in food safety. The project was completed in the years 2005-2006 for 17 countries; the latter project (EFCOSUM -- European Food Consumption Survey Method project) is concerned with defining a method for the monitoring of food consumption in Europe and for harmonizing the methodology for collecting comparable food consumption data across Europe.

3.3.2. Food consumption data in acute intake assessments

One goal of a dietary consumption survey can be to obtain a statistically defensible representation of the consumption estimates of one-day food intakes. Not all available consumption databases allow probabilistic assessments of acute intake. The minimum data needs are:

[14] LanguaL "Language for food" is a food description thesaurus. http://www.langual.org
[15] http://www.ars.usda.gov/Services/docs.htm?docid=14392
[16] SAFEFOODNET. Chemical Food Safety for the enlarging Europe. Final report on country profiles on existing national diets. 28/03/2007. http://www.safefoodnet.net

- Dietary records on a single day (24 hour) basis. These data may be collected over multiple (consecutive or non-consecutive) days, but individual day (unaggregated) data must be available. In addition, data should be collected in such a manner that (ideally) the exact times of consumption or the names of the meals (e.g., breakfast, afternoon snack, lunch) at which the food is consumed are recorded.
- Data on exact quantities of all raw, cooked or processed food consumed in g per day on an individual basis. Also needed are each individual's body weight, sex, and demographic characteristics (e.g., age, race, ethnicity, geographic region) and information on special eating behaviours or diets (e.g., vegetarian).

Combined with recipe files, the consumption survey data can be converted to a food commodity (or ingredient) basis, which is important in order to be able to link this with data that are available on pesticide residues. Also important are data on processing or preparation of food at the household level which would include such information as food form (e.g., fresh, canned, dried) and cooking method (e.g., baked, broiled, fried) since this information can be used to adjust levels of pesticide residues to account for cooking and commercial processing.

It is important that food consumption data be collected in a way that is representative of day of the week and of season. That is, data collection should be such that all days of the week and all seasons of the year are covered.

To measure both intra-individual and inter-individual variability in consumption on single days, data should be collected in at least two non-consecutive time periods, and within each, from more than one day (e.g., a 2 periods x 3 days per period dietary record) for each individual.

Not essential, but useful information to include would be detailed food descriptions, sources of the food items consumed (e.g., organic grown, home grown, import country of origin, location at which the food was consumed).

Ideally, any Europe-wide survey would be conducted using statistically-based sampling procedures and incorporate sample weights, over-sampling of certain population subgroups, and stratification so as to provide representative data and to permit valid estimation of results for various subpopulations of interest.[17]

The goal of the data analysis in the deterministic approach is to estimate the Large Portion (LP), 97.5th percentile of "consumers only" in g food/day (for individual commodities only). The 97.5th percentile was chosen by a Joint FAO/WHO consultation in Geneva in 1997 (WHO, 1997a). The LP should be matched to the raw agricultural commodity (RAC) to which the residue data relates. In the case of commodities that are eaten predominantly fresh as for fruit and vegetables, the LP

[17] The USA has developed a set of statistical guidelines for reporting data (including the issues of variance estimation and statistical reporting standards) from statistical surveys. These recommendations are presented in Table A.3.of the document "Third Report on Nutrition Monitoring in the United States". The report recommends that the sample size requirements shown in this table for prevalence estimation be used for all surveys and surveillance systems conducted by the U.S. government. A minimum sample size of 30 is recommended for reporting any mean, proportion, percentile, and variance under the simple random sample assumption. When complex multi-stage survey designs are used, minimal sample sizes for reporting statistical data are increased depending upon the survey design (more specifically, its estimated "design effect") and the percentile which is to be estimated. As indicated in the table, proportions (or prevalence) that are large (or small) require a much larger sample size to achieve the same degree of reliability as the mean or median. The guidelines are not meant to be absolute. As stated in the document, "they represent conditions that yield the most sound statistical conclusions" and "violating these sample size guidelines (or other criteria included in the larger report) introduces a greater degree of uncertainty about the soundness of the analytic conclusions, but does not necessarily mean that a particular analysis is invalid."

should be derived for the raw commodity. When a high proportion of the commodity, such as cereal grains, is consumed in a processed form, the LP should relate to the processed commodity e.g., bread, flour, providing matching residue concentration data are also available for the processed food. Since the residue data can differ substantially between RAC and processed commodity, one should not calculate back everything to RAC (e.g., orange juice, cooked potatoes). Furthermore, it is necessary to obtain information on the edible portion in the raw versus the processed commodity[18].

In some cases, the number of consumers of some commodities, which are only occasionally consumed, is too small to derive a statistically valid 97.5 percentile level of consumption. If available, other percentile data (the 90th, 95th percentile or the maximum) could be used instead of 97.5th percentile but one must be aware of the uncertainty.

Travis et al. (2004) recommend in such cases the use of

- pooled data from a single food from a wider commodity group,
- consumption data from a similar commodity that has higher consumer numbers.

The limitation is that consumption of the related commodity may overestimate actual consumption of the commodity in question. However, it allows a calculation to be undertaken, providing that note is taken of the assumptions used.

There are in principle two options to find the 97.5th percentile when the survey consists of more than a one-day dietary recall. First option: Use all days as one single day and calculate 97.5%. Second option: Calculate maximum consumption amount of each person over the several days and take the 97.5th percentile afterwards. In the first case protection of exactly 97.5 percent of the population cannot be assured. The percentage could be lower because of not taking into account intra-individual variability. The differences might not be very large but the second is the more exact approach. Therefore, if the survey consists of more than a one day dietary recall, it is recommended that only one day per person is used. The maximum daily intake of each person over the survey period would then be used to calculate the 97.5th percentile of the distribution of all persons. All 97.5% single day values should be lower than the final 97.5%

The choice of percentile will influence the conservatism/level of protection of the assessment overall and therefore choosing one involves a risk management judgement. The degree of conservatism of deterministic assessments will also be influenced by the percentiles taken for all other inputs, including concentrations.

The goal of the data analysis in the probabilistic approach is to obtain a distribution of consumption using the available data, with the aim of estimating the full distribution of exposure per day and person. It will then be possible to determine an estimated exposure at any desired percentile and vice versa. For acute intake assessments, in principle survey data collected on single days suffice. When data are collected over more than one day, care should be taken that only one day per person is used in the calculations (see above). A probabilistic cumulative intake

[18] Information on chemical-specific processing factors obtained from JMPR reports, selected EU Draft Assessment Reports etc. is available in a German database (in English) http://www.bfr.bund.de/cd/579. Generic (non-chemical specific) processing and food preparation factors for a variety of commodities are available in a handbook entitled "Food Yields Summarized by Different Stages of Preparation" (Handbook # 102) published by the U.S. Department of Agriculture. The handbook can be obtained at: http://www.nal.usda.gov/fnic/foodcomp/Data/ Classics/ah102.pdf. While this handbook does not discuss factors associated with specific chemicals, it does discuss various factors associated with various food preparation processes (e.g., peeling, coring)

assessment allows identification of the crop-pesticide combinations that contribute most to the cumulative exposure.

3.3.3. Food consumption data in chronic intake assessments

The goal of any survey to collect long-term dietary intake information should be to collect appropriate information that can be used to develop consumption estimates, which are representative of multi-day food intakes, by individuals. The data collected in such a survey should be sufficient to estimate the mean consumption over a defined long-term period.

Ideally, these data would be collected from a statistically representative group of individuals for whom daily records of food consumption would be collected over a long period of time (i.e. collected longitudinally)[19]. The period of time would be sufficient to cover all seasons and all days of the week. From this information – along with information about pesticide residues in foods – the risk assessor could develop a distribution of *long-term exposure averages* which were representative of exposures expected from multi-day food intakes. However – methodologically -- such an approach can be very difficult to do well: individuals recording food intakes over long periods of time can change eating patterns and recording of food intake may become less accurate as time goes on. Thus, for practical reasons, longer-term, average, and "usual" dietary intake (and exposure) estimates will likely of necessity rely on shorter-term consumption information, which will be extrapolated to longer-term periods[20].

Clearly for a long-term assessment the average intake is the key measure for an individual person. However, that average will vary between individuals. For deterministic assessment, one might choose to regulate on the average of averages, or on some percentile of the distribution of averages. This is a risk management choice and requires further consideration.

The goal of the data analysis in the probabilistic approach is to determine the distribution of consumption, with the aim of calculating the mean individual daily exposure within a specific period of time (e.g., one week, month or year). A specific percentile of that distribution will need to be selected. This could be the distribution of average individual consumption across the population (variability), or the uncertainty distribution for the average of the averages. Again, this is a risk management choice and further consideration is needed.

[19] It should be noted that it is entirely inappropriate to use single-day or short term food consumption estimates directly in estimating long-term food consumption estimates as it is well known that these estimates produce high-end intakes which are biased. Specifically, long-term exposure estimates produced in this way will be biased high and will show greater variability than truly exists. There are, however, methods which have been and are being developed in which food frequency questionnaire (FFQ) data is combined with short-term dietary recall data to produce estimates of "usual dietary intake". (see e.g. Tran et al 2004). The US National Cancer Institute has developed statistical methods for evaluating usual dietary intake by combining FFQ and dietary recall data (see http://riskfactor.cancer.gov/diet/ usualintakes/method.html for more information). There also exist a variety of statistical models and procedures which can take into account correlation between days and produce estimates of long-term or usual dietary intakes from survey data containing only several repeated day intakes.

[20] The U.S. currently relies on the CSFII for its dietary consumption estimates, and will be transitioning to the NHANES dietary consumption survey in the future. However, both surveys contain only 2 (non-consecutive) days of intake. The US's National Institute of Child Health and Human Development (NICHD), the National Institute of Environmental Health Sciences (NIEHS), the Centers for Disease Control and Prevention (CDC), and the U.S. Environmental Protection Agency (EPA) are collaborating on a multi-year prospective study in which 100,000 children will be followed from birth through 21 year so age. Information on dietary intakes will be collected and could be performed longitudinally. The program is currently in the planning stages with a variety of Vanguard centres established and pilot studies expected to commence in 2008. For additional information, see http://www.nationalchildrensstudy.gov. Thus, this study may allow long-term multi-year longitudinal data on dietary consumption by children to be collected, albeit not in Europe.

3.3.4. Available sources of information

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 all up-to-date, and cover different population subgroups as described above.

EFCOSUM provides an overview of existing consumption data, but the level of aggregation will not always fulfil the needs for a cumulative assessment, and the authors question whether the information on the portion size was sufficiently precise enough, and whether the duration and number of recalls were adequate (TNO Nutrition and Food Research, 2001).

EFSA has started to set up a Food Consumption Data Base and will provide guidance to Member States on the collection of consumption data in a consistent manner. In a first step, the so-called "EFSA Concise Database" was constructed and was published in 2008[21]. The database contains aggregated consumption information for 16 classes of food items for adult populations from all European countries where data are available. For the future, a more comprehensive database is planned which will provide comparable information for more detailed food groups and other population groups (e.g., children). In addition and more specifically for pesticides residues, EFSA/Pesticide Risk Assessment Peer Review Unit (PRAPeR) has collected national consumption models from EU Member States and created an EFSA model for risk assessment of pesticide residues. The model is based on 19 national acute and 22 national chronic diets, provides deterministic calculations and is under continuous development. It was used for the first time to perform the risk assessment of the temporary MRLs to be included in Annex III of Regulation EC 396/2005 (EFSA, 2007d).

Work Package 3 of SAFE FOODS, a project under the 6th Framework Programme, has compiled data from 6 national consumption surveys, which are in a form ready to use in a probabilistic cumulative assessment[22].

The 13 WHO/GEMS/Food consumption cluster diets are based on food balance sheets and can be used for chronic dietary exposure estimates by a deterministic approach (WHO, 2006b).

The GEMS/Food short-term diets are based on consumption data submissions by 8 countries and can be used for acute dietary exposure estimates by a deterministic approach (WHO, 2008b).

3.4. Cumulative exposure: methodology

As stated in 1.3, four relevant exposure scenarios in the context of cumulative risk assessment can be identified:

- Assessment of actual exposure (i.e. from the patterns of usage that actually occur in practice)
    - acute assessment
    - chronic assessment

[21] These data, together with the Guidance document for the use of the concise database in exposure assessment are at the following link <http://www.efsa.europa.eu/EFSA/ScientificPanels/DATEX/efsa_locale-1178620753812_ConciseEuropeanConsumptionDatabase.htm> under the DATEX section.

[22] http://www.safefoods.nl

- MRL-setting (i.e. a theoretical exposure where the residue of the compound under evaluation is at the level of the MRL for acute assessments and the level of the STMR for chronic assessments)
    - acute assessment
    - chronic assessment

Exposure assessment calculations can be performed either deterministically (to give 'point-estimates', in essence: multiplying a residue value with a consumption value) or probabilistically (in essence: multiplying a distribution of residue values with a distribution of consumption values). In theory, when the *same assumptions* are used for both deterministic and probabilistic acute intake calculations, where the aim is to calculate a high exposure, the outcome of the point estimate should be at the high end of the intake distribution as calculated by the probabilistic method. The main advantage of a deterministic method is that it is relatively easy to perform, and does not require sophisticated software. The main advantage of a probabilistic method is that it provides information on the probability of the outcome of the calculation.

In general, a refined cumulative exposure assessment (including multiple commodities and multiple pesticides belonging to a CAG) cannot be done without using probabilistic methods. However, for one commodity containing multiple residues of pesticides belonging to a CAG a deterministic assessment can be done based on the IESTI equations as used for assessments of individual chemicals. This has been done in the UK, Denmark and Germany, see chapter 4.2, 4.4 and 4.5. The assessments were done in the context of evaluating monitoring data (actual exposure assessments).

Although all three examples used deterministic methods to evaluate monitoring data, the calculation methods were different. For the acute cumulative exposure assessment, the UK and Denmark considered only pesticides of the same CAG present at the same time on the commodity, while the German CVUA considered *all* pesticides present at the same time on the commodity, regardless of the toxic effect or mechanism/mode of action. In the Danish example, a cumulative calculation using RPFs was subsequently carried out, while in the UK and German examples the % of ARfD was determined separately for the individual pesticides and the individual results then summed. In the German example, as a final step an assessment of the plausibility of a cumulative effect was made based on the toxicological effects involved.

A deterministic chronic cumulative exposure assessment was reported only in Denmark. The calculations involved mean consumption values and mean residues from the monitoring programme as well as RPFs for summing the contribution of the different pesticides.

In Table 2 an overview is given of the current experiences in cumulative exposure assessments. For detailed description of the assessments see chapter 4.

Table 2 Available experience in cumulative exposure assessments

Scenario	Deterministic methods	Probabilistic methods
Acute exposure		
MRL setting	none of which the PPR Panel is aware.	none of which the PPR Panel is aware.
Actual exposure	UK evaluation of application for	- U.S. EPA : OPs, N-methyl

	authorisation and evaluation of multiple residues in monitoring samples DE: evaluation of multiple residues in monitoring samples.	carbamates - UK : OPs and N-methyl carbamates - NL : OPs and N-methyl carbamates
Chronic exposure		
MRL setting	none of which the PPR Panel is aware.	none of which the PPR Panel is aware
Actual exposure	DK: OPs and N-methyl carbamates.	- EPA: chloracetanilides, triazine (but in this case exposure from food was not considered, as it was estimated to be negligible in comparison with exposure from water).

Several models are available to perform probabilistic exposure assessments. All have their pros and cons, and it is not the intention of the PPR Panel to advice on the selection of the 'right' model. 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 is linked to the percentile of the exposure distribution (e.g., 97.5, 99 or 99.99 percentile) selected by the risk managers for decision-making.

The PPR Panel agrees with the U.S. EPA criteria for models that can be used to perform a probabilistic exposure assessment: the model should be transparent, peer-reviewed and freely available[23]. At the moment, the PPR Panel is aware of eight models that could be used. USA models DEEM/Calendex, CARES, Lifeline and SHEDS have been the subject of a comparative exercise in the USA and produced similar results. Four European models were used in the EFSA opinion on the IESTI equation (EFSA, 2007c) and also produced similar results: MCRA 5.1 (RIKILT, Netherlands), CREMe 2 (CREMe, Ireland), Uni HB (University of Bremen, Germany), CSL (CSL, United Kingdom).

All four European models use the same basic approach, but there are also differences because they were developed in different circumstances. An overview of the most relevant differences is given in Table 3.

[23] Note that freely available is not identical to 'free'.

1 Table 3 Summary of differences between the European models used in the IESTI Opinion (EFSA, 2007c).

	MCRA 5.1	CREMe 2	UniHB	CSL
Concentration data	actual measurements + # nondetects	actual measurements + # nondetects	empirical distribution summarised by # <LOD, # <LOQ, some percentiles, maximum, N	actual measurements (with uncertainty from errors in the measurement process) + # nondetects
Model fit to concentration data	binomial + lognormal	use empirical data	Lognormal or censored log-normal	binomial + censored log-normal
Variability factor (field trial)	From EFSA lognormal distribution (Trials)	fixed 3/1	Fixed or from EFSA lognormal distribution (Trials)	-
Variability factor (monitoring)	Fixed 6.83/5/1 (from EFSA lognormal distribution for model comparison run)	fixed 7/1	Fixed 6.82/5/1 or from EFSA lognormal distribution (from EFSA lognormal distribution for model comparison run)	from EFSA lognormal distribution (from trials data), with uncertain parameters
Monte Carlo	Monte Carlo sampling from concentration distributions; Monte Carlo resampling of 100,000 person-days from consumption data	Monte Carlo sampling from concentration data, Monte Carlo re-sampling of 10,000 person-days from consumption data	Monte Carlo sampling from concentration distributions, repeated consumption set	sample from concentration distributions, keep consumption set fixed
Uncertainty intervals for exposure percentiles	bootstrap concentration data and consumption data	Intervals describe uncertainty of Monte Carlo sampling of concentrations	bootstrap concentration data (only for trial data, not for monitoring data) and consumption data	from Bayesian posterior distribution, allowing for uncertainty in concentration data and variability factor distribution parameters

2

In some respects, all models are the same:

- Intake is calculated per kg body weight, and the body weights were available for each individual from the food consumption survey data.
- All models convert food-as-eaten to primary agricultural products using recipe data.
- Concentrations for individual units are sampled from a lognormal distribution around a sampled batch mean (with the variability factor determining the width of this distribution).
- Concentrations are corrected by fixed values of processing factors when such information is available.

The PPR Panel considered that conceptually there is no reason to prefer one model to the other. However, a key issue is that European consumption data should be linked to the model of choice. Presently this rules out the USA models. One model could be coupled to consumption survey data from more than one European country. However, multiple models (validated and giving similar results) each with one consumption database could also be used. An advantage of using two or more models in one assessment would be that anomalies would be detected more easily.

It should be noted that most current Monte Carlo models have the limitation that they provide only an estimation of the fraction of person-days, not of the fraction of the individuals, i.e., the calculations provide the probability that *a* certain consumption pattern of an unknown individual on *a* certain day will lead to exceeding the (acute) RV used. They do not estimate what fraction of the population exceeds the limit value on at least one day over a longer period nor do they estimate the frequency with which such exceedances occur in individuals. In other words they do not provide an answer to the question *how many people* will exceed the limit value *how often*. For example, when 5% of person-days are above the limit value, it is not known whether this means that 5% of persons exceed this value every day, or whether it means that, all persons exceed it on 5% of days, or something in between. Depending on the toxicological profile of the CAG, one scenario may be more relevant then another. It is possible to estimate distributions to model between and within individual variation and then use them in a Monte Carlo simulation of intakes, which will give the fraction of the population exceeding limit values and frequency per individual (Slob 2006). However, further work is needed to address this issue.

The variability factor is the factor applied to the composite residue to estimate the residue level in a high-residue single unit. It is defined as: the residue level in the 97.5th percentile unit divided by the mean residue level for the lot. EU models take this factor into consideration either by using a distribution of variability factors or a fixed value. US models do not consider this factor.

In a probabilistic risk assessment, the handling of non-detects can be crucial, especially when most of the samples are 'non-detects'. There are several ways how to include non-detect samples (see 3.2). One could treat these samples as being zero (containing no residue at all). In reality one does not know what fraction of the samples represent true zeros and what fraction represents residues < LOQ (but greater than zero). One way to handle this is to assume that the fraction of non-detects being a true zero is similar to the percentage of crops not treated. This is frequently done in the USA (see 3.2.1.3) but not in Europe. In fact, in Europe such statistics are not available (or probably only to a limited extent). In addition, the high turnover of imported and exported foodstuffs makes it very difficult to attach any percentage of the crops (un)treated to monitoring data. Even at local regional scales very large differences can occur.

A draft guideline on probabilistic exposure assessment has been provided to the European Commission following the Fifth Framework Monte Carlo project (Institute of European Food Studies, 2003). It addressed the running of the models and generating the output, but does not currently cover interpretation of results/output or risk management. The output of probabilistic models might not be clear to risk managers, for example when there is a low probability of exceeding an acute reference dose (ARfD). It is recommended that the draft guideline will be evaluated and finalized

Uncertainty (the unknown) and variability (variation of the known) would both apply to the output of the model. If the model indicated that there was an exceedance of a RV by some population subgroups, sensitivity analysis could be used to indicate the degree to which certain inputs or default assumptions contributed to that exceedance.

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

Deterministic models produce a single value, taken by some to mean that there is no uncertainty in the result. This of course is not true, but it is harder to estimate the uncertainty. Nevertheless, an attempt should be made (at least qualitatively) to assess whether the outcome is likely to be under- or overestimating the exposure.

Probabilistic models produce a distribution of predicted exposures, often with a long tail. The choice of the appropriate percentile of the distribution to use for decision-making is ultimately the responsibility of risk managers. At present there is no agreement on how much of the tail to include in an assessment. U.S. EPA usually regulates at the 99.9th percentile. It should be noted that the selection of the 99.9th percentile by U.S. EPA was only partly due to the increased uncertainty at higher percentiles, but was primarily based on the "reasonable certainty of no harm" standard of FQPA. The issues that should be considered in choosing the relevant percentile are: what is the risk manager willing to accept, and: what are the limitations of the residue and consumption databases at hand? It is possible that the percentile could vary between similar assessments, depending on the supporting data and also on other risk management considerations (e.g., legal, economic, social and other considerations – see definition of risk management in the EU Food Regulation). 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.

The PPR Panel recommends that the risk manager be provided with a full and adequate characterization of the risk estimates that should at least include a review of the following factors which were described by the U.S. EPA (EPA 2000b) (in approximate order of relative importance):

- Whether a "high-end" consumption value actually acts as a "driver" in the risk assessment. (*in many cases, high-end consumption values may not be actual "drivers" (i.e., significant contributors) in the risk assessment and thus may not be the primary reason behind high estimated exposures at the tails of the distribution*)
- How extreme the upper tails of the consumption curve are. (*for example, is the 95th percentile consumption value greater than four times the mean consumption? Is the 99th percentile value greater than six times the mean consumption?*)

- How far the presumed high-end consumption value is from where it would be expected to be given the pattern (*or distribution) of reported consumption values in the lower percentiles. (e.g., if a distribution can be reasonably established for the reported consumption values in the lower percentiles (e.g., 70th through 95th percentiles), how extreme would the suspected outlier be in an appropriate Q-Q or other statistical plot*) .
- The size of the affected subpopulation and how likely exposure estimates for the subpopulation would be subject to undue effects of outliers. (*a high-end value would be expected to have more influence on the upper end exposure estimates in a small subpopulation than it would in a large subpopulation*).
- From a dietary standpoint, how likely the high-end value is to be a valid reported consumption event. (*for example, although they may be equally extreme from a probabilistic standpoint, consumption of three gingko fruits in a day might be considered more reasonable than consumption of 10 apples*).
- The nature of the inputs both in the overall assessment and (particularly) for the drivers. (*this would include, for example, whether input residue data included field trials vs. monitoring data; the use of default vs. actual processing factors; the extent to which single-serving values are measured vs. established by applying the variability factor, the nature and degree of percent crop treated data, etc*.)

In sum, the PPR Panel agrees that the risk assessor should adequately characterize the nature of the assessment (including any biases and uncertainties) and perform a sensitivity analysis, where appropriate, such that the reasonableness of the upper-end percentile estimates can be properly gauged. Risk assessments should characterize the effect of any high-end points (on the consumption) on the percentiles of possible regulatory interest. Likewise, it is important for the risk manager, in turn, to consider the entire set of data and information available in deciding if the chosen percentile is an appropriate demarcation point for use in regulation. In particular, risk management decisions should consider the effect of any high-end data values (consumption or residue) or other relevant factors and, when appropriate, be flexible with respect to the regulatory threshold selected. See also chapter 5.

4. Review of methods and cumulative risk assessments performed by different bodies[24]

In order to gain knowledge from the efforts already undertaken in this field, cumulative risk assessments already performed have been reviewed. Most of the assessments have dealt with OPs or anticholinesterase compounds in general, therefore allowing useful comparisons. The available documents on cumulative risk assessments included those of the US Environmental Protection Agency (EPA), of the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) and Advisory Committee on Pesticides (ACP), of the Dutch RIKILT, of the Danish Veterinary and Food Administration[25], the German *Chemisches und Veterinaeruntersuchungsamt* Stuttgart (CVUA) and of ILSI. These have used different methodologies and are discussed in some detail below.

[24] The Norwegian Scientific Committee has recently published a comprehensive opinion on combined effects of multiple chemical exposures. However, the Norwegian opinion was published only a few days before the adoption of the present PPR opinion for which reason the Norwegian opinion was not considered by the PPR-panel

[25] Today "The National Food Institute, Technical University of Denmark

4.1. US EPA approach

The US EPA began the development of a guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity as a consequence of the Food Quality Protection Act (FQPA, 1996). FQPA requires assessment of the cumulative risk deriving from exposure to pesticides and other substances that are toxic by a common mechanism. The final guidance document was published in 2002 (EPA, 2002b). This document sets forth the basic assumptions, principles, concepts, and analytical framework associated with aggregate (multi-pathway) and cumulative (multi-chemical and multipathway) risk assessments. For the purpose of this opinion, only the procedure for cumulative exposure deriving from residues in food will be considered.

When such substances that act by a common mechanism of action have been identified, the next step is to gather available hazard and exposure information for each chemical and to conduct a preliminary evaluation of their hazard potency and exposure potential. To screen for the potential magnitude of exposure and co-occurrence, a variety of factors are considered: the percent of the reference value occupied by each pesticide, the frequency and magnitude of detections in exposure (e.g. NHANES) and food (e.g. USDA and FDA) monitoring programmes, registered uses, tolerances, use patterns, and % crops treated usage information are considered. This evaluation may suggest that at a screening-level there is no risk concern for the group of chemicals and no further detailed assessment will be necessary.

Once such substances have been identified, the next step is to determine the time-course of effects, and evaluate the quality of the dose-response data for each compound and recommend endpoints/species/sex that can serve as a uniform basis for determining relative potency (EPA, 1999).

Then those pesticides that have the potential exposure and hazard to result in cumulative effects are selected.

Subsequently, an appropriate dose-response method to determine the relative toxic potencies of the substances is selected and applied, and then the RfP(s) for extrapolating the risk is (are) determined.

The next steps include assignment of route/duration-specific risk metrics, conduct of trial run and sensitivity analysis, and assessment of subpopulations of concern, group uncertainty and FQPA safety factors.

The final step is the risk characterization, which includes: a) a description of the confidence in the toxicity and exposure data, b) a description of the variability and of the areas of major uncertainty, c) the magnitude and direction of likely bias, d) the identification of the major risk contributors (pesticide, food item, e) the basis for the group UF, and f) the application of the FQPA UF

This approach is very comprehensive and resource intensive, and may not necessarily be completed for all groups of compounds when simpler assessments indicate no relevant risks.

So far US EPA has conducted cumulative risk assessments for organophosphorus compounds, N-methyl carbamates, triazines, and chloroacetanilides.

4.1.1. Organophosphorus compounds

Methamidophos was selected as the Index Compound (IC) to calculate the relative potency factors for each OP. Toxic potencies for the OPs were determined using brain acetylcholinesterase inhibition from female rats measured at 21 days of exposure or longer, on the basis of the known toxicokinetic and toxicodynamic characteristics of these compounds.

The relative potency was calculated on the central estimate of the BMD10 (benchmark dose causing 10% brain acetylcholinesterase inhibition) using an exponential dose-response model using multiple rat ChE studies, so that the RfPs for all OPs were normalised to the chosen IC, methamidophos. This combining of ChE data provided a more robust estimate of toxicological potency and incorporated variability across studies. EPA elected to use the central estimate of BMD10 instead of the BMDL10 for methamidophos on the basis of the complexity brought to the analysis by the joint consideration of multiple studies for multiple chemicals and the high quality of the toxicity database. However, the BMDL10 was used to select the RfP for the IC. Once the RPF had been calculated, if needed and according to the USA FQPA, the appropriate UF, additional to the standard 100, was applied to the RPF of each OP. Finally, estimated exposures were compared to the RfP and the target MOE was 100 to account for the standard 10X factors for intra- and inter-species differences (see figure).

It was concluded that the total exposure to OPs through food was dominated by a few uses of OP pesticides on food crops. However, evaluation of the total risk from exposure to OPs in foods indicated that the cumulative MOE (99 to 300) did not raise concerns about repeated exposures. Even when considering the single day exposures compared to the RfP based on a 21-day exposure, which was a clear overestimate of risk, the MOEs reach the target of 100 for >99.3th percentile for different subpopulations, including children (EPA, 2006a).

4.1.2. Chloroacetanilides

This group of compounds includes acetochlor, alachlor and butachlor, which were considered a common mechanism group on the basis of their ability to cause nasal turbinate tumours via the generation of a common tissue reactive metabolite that leads to cytotoxicity and regenerative proliferation in the nasal epithelium. Butachlor was excluded from the assessment because there were no registered uses in the USA. The PPR Panel has previously also concluded that the strength of the evidence suggests that a mode of action other than genotoxicity is involved in the occurrence of nasal turbinate tumours observed in the rat carcinogenicity studies with such compounds (EFSA, 2004). In this case, the RfP was considered to be the NOAEL for tumour formation and alachlor was used as the IC. Since tumour formation was attributed to a non-genotoxic and hence non-linear mode of action, a MOE of 100 was considered adequate. Evaluation of the total risk from exposure to chloroacetanilides in foods indicated that the cumulative MOE (13,000 to 53,000) did not raise concern (EPA, 2006b).

4.1.3. Triazines

Three triazines (atrazine, propazine, simazine) and three of their metabolites were identified as a common mechanism group because of their ability to cause neuro-endocrine and endocrine-related developmental, reproductive effects. Carcinogenic effects of triazines were not considered relevant

to humans.[26] Other triazines were excluded because they did not share this toxicity profile. Hence, the combined risk for drinking water was based on the NOAEL for LH suppression and a 90-day rolling time frame. The combined risk from drinking water and residential uses was based on the NOAEL for delay in puberty and a 28-day rolling time frame. It should be noted that one of the triazines (i.e. propazine) was excluded from the analysis because of the expected very low exposure that would have contributed insignificantly to the total exposure. The NOAEL on which the MOE was derived was based on the relevant adverse effect (neuroendocrine and neuroendocrine-related developmental effects due to changes in the hypothalamic-pituitary-gonadal axis) in the triazine toxicity database, for which all compounds were as a default considered as potent as atrazine, although some of them showed a somewhat lower potency for some end-points. The most important source of exposure was found to be drinking water and the determined MOE was always >300. It should be noted that this CRA is being revised and thus, the estimated MOEs may change (EPA, 2006c)

4.1.4. N-Methyl carbamates

Oxamyl was selected as the IC to calculate the RPFs for the remaining 9 N-methyl carbamates (NMC) (aldicarb, carbaryl, carbofuran, formetanate HCl, methomyl, methiocarb, pirimicarb, propoxur, thiodicarb). Toxic potencies for the NMC were determined using brain acetylcholinesterase inhibition in male (or both sexes when data provided statistically similar BMD10s) rats measured after a single exposure for all three routes of exposure of interest (oral, dermal, inhalation). Based on the toxicological characteristics of NMC (rapidly reversible effect), only short-term (one-day exposure) risk assessment was performed. An exponential dose-time-response model was developed to derive BMD10s for determination of RPFs (EPA, 2007a).

The BMD10s for the NMC ranged over several orders of magnitude.

When data on juvenile rats were available, a chemical-specific FQPA UF was used instead of the default 10x. For three compounds (aldicarb, methomyl and oxamyl) studies in humans were used and the standard inter-species UF of 10x was not applied. The interspecies and FQPA UFs were directly applied to the RPFs for each NMC. Thus, only the MOE for intra-species differences needed to be taken into account and the target MOE was set at 10.

EPA concluded that a few uses of NMC pesticides on certain food crops were the major contributors to the cumulative risk (i.e. aldicarb on potato, carbaryl on peach and strawberry, methomyl on cantaloupe, watermelon, peach, spinach, and strawberry). The target MOE of 10 was reached at 99.848th and 99.870th percentiles of the most exposed age groups (children 1-2 and 3-5 year old, respectively). The 99.9th percentile MOE was 7.9 and 8.6 for the same age groups, whereas in the other age groups of the population it ranged from 12-42.

[26] The carcinogenic effect in rodents are due to a species (and strain) specific consequence of the endocrine effects of the compounds, and are therefore considered not relevant to humans, although the endocrine changes themselves do have other consequences, which are potentially relevant to humans.

4.2. UK approaches

4.2.1. Working Group on the Risk Assessment of Mixtures of Pesticides and similar substances (WIGRAMP)

A Working Group of the UK Committee on Toxicity reported a general consideration of risk assessment for mixtures of pesticides and similar substances, WIGRAMP (COT 2002).

The WIGRAMP group made a number of recommendations applicable to the PPR considerations including:

- The default assumptions should be that chemicals with different toxic actions will act independently (response addition), and those with the same toxic action will act with dose addition;
- A framework for performing combined risk assessments should be developed;
- Combined assessments will probably require changes in the methods used for risk assessment, including, in some cases, the use of probabilistic exposure assessment. This might require residue surveillance programmes to be modified to provide more representative data for this purpose.
- In specific instances the possibility of interaction, particularly potentiation (synergy), may have to be considered.
- There should be research work to investigate: biomarkers of combined exposures; human variability in response to mixtures; identification of groups of compounds having common modes of action.

Some of these recommendations have been followed up by specific research projects (FSA, 2005; FSA, 2007; FSA, 2008)

A specific consideration of compounds such as benzimidazoles that inhibit tubulin polymerisation as the mechanism for their aneugenicity was performed by the UK Committee on Mutagenicity (CoM, 2007). The CoM report included a decision tree for determining whether a benzimidazole should be included in the common mechanism group and recommended that potential combinations of benzimidazoles that meet the CMG criteria and other aneugens that interact with tubulin should be investigated using an in vitro micronucleus assay.

4.2.2. Assessment of combined exposures to cholinesterase-inhibiting pesticides.

In 1998 the UK initiated a review of national authorizations of all anticholinesterase pesticides. One of the Ministerial requirements was that a cumulative assessment should be performed at the end of the process. By the time the UK review was coming to an end, the US EPA were well on the way to completing their cumulative/aggregate assessment of OPs and an EPA officer was invited to the UK to discuss the EPA approach and the lessons learned.

The cumulative assessment included both OPs (n=26) and carbamates (n=12) that inhibited acetylcholinesterase. Although the kinetics are very different there was the potential for co-exposures from the same meal or to a carbamate after an OP, and the potential for combined toxicity from OPs and carbamates could not be discounted. The common mechanism group

included some low potency inhibitors (e.g., the fungicide tolcofos-methyl), a morpholine fungicide with a cholinesterase-inhibiting metabolite as well as the more potent cholinesterase inhibitors used as insecticides. Initially the CMG contained only UK authorized pesticides but was expanded subsequently to include all those found during residue surveillance exercises.

Various options for assessing relative potency were discussed. These included deriving RPFs from NOAELs for erythrocyte or brain cholinesterase inhibition in studies of various durations and species; estimations of BMD10s; or a HI approach using the ADI or ARfD corrected if necessary to exclude non-cholinergic end-points. The exposure model was run using two different approaches. The first one was a RPF type approach using the NOAEL for erythrocyte cholinesterase inhibition in acute and 90-day rat studies (or for some carbamates a modern acute study that minimized reactivation) with chlorpyrifos as the reference compound. Chlorpyrifos had the best database of the compounds authorized in the UK. For the second approach, the plan was to perform a HI assessment to determine exposures as percentages of the RV and then sum these, but this approach did not work successfully with the modeling software available[27] so a RPF approach based on ADIs and ARfDs was adopted to complement that based on NOAELs (Table 4). A comparison of RPFs determined by EPA and PSD is shown in Table 7.

The exposure assessment was completed in 2004 using probabilistic software (Monte Carlo Risk Assessment, MCRA) from RIKILT in the Netherlands. This used Dutch consumption data (data from recent UK surveys were not in a suitable format and would have taken a lot of resource to load into the model) and some relatively old UK residues data (1993 – 1997) for 10 commodities. The old residue data were used as they were derived from an extensive dataset looking at individual units and thus avoided issues associated with composite sample data. On investigating the early results some problems were identified e.g., high residue levels in individual units before processing being matched with high consumption data for processed commodities e.g., fruit juices (other data show residues in fruit juice are routinely very low). A sensitivity analysis showed that the method of determining the RPF had minimal impact on the overall outcome. The main contributors to cumulative risk were the absolute potency, residue levels and consumption values. The results from the modeling were reassuring, and in line with findings in other countries, showing that acute exposures on only about 0.1% of consumer days might exceed the acute reference dose.

Table 4 Acute Intakes (µg/kg bw/day) estimated for each of the four different methods of residue conversion (based on relative toxicity) (acute reference dose is 100 µg/kg bw)

Method	Acute RPFa	ARfD RPFb	90 day RPFc	ADI RPFd
95.00th percentile	12.1	6.7	0. 9	1.5
97.50th percentile	26.1	13.6	3.8	5.0
99.00th percentile	51	29	17	17
99.90th percentile	178	100	87	79
99.99th percentile	390	219	279	234
maximum	829	467	741	838
mean	2.46	1.39	0.69	0.72

a NOAEL for red cell cholinesterase inhibition in a single dose or short-term study in rats relative to chlorpyrifos
b ARfD corrected if necessary for non-cholinergic end-points relative to chlorpyrifos
c NOAEL for red cell cholinesterase inhibition in a 90-day study in rats relative to chlorpyrifos

[27] There is no inherent reason why a HI approach could not be made to work with probabilistic modeling software, but no solution could be found within the time and resource allocations available.

d ADI corrected if necessary for non-cholinergic end-points relative to chlorpyrifos

Data limitations included the consumption and residue issues mentioned above; plus difficulties in determining RPFs for pesticides not authorized in the UK but present in imported produce, due to the limited availability of toxicity data. The latter was crucial to the outcome, as one of the main contributors to exposure was an active substance, which had never been authorized in the UK, and there was a need to rely on third party summaries of the toxicity data.

Now that the EU reviews of anticholinesterase compounds have been completed, future work includes rerunning the modeling using updated RPFs, new UK consumption data, and contemporary data on residues from UK surveillance schemes, and to include some assessment of uncertainty.

4.2.3. Assessing Combined Toxicity and Risks when Evaluating Applications for Authorisation and Multiple Residues in Monitoring Samples

In 2005, the UK authorities described (PSD 2005)[28] an approach for applicants for authorisation to use to evaluate the risks from exposures to two or more compounds in the same plant protection product or an intentional mixture that might result in combined toxicity. During the evaluation for authorisation where there is potential for combined toxicity, simple limited cumulative risk assessments are done for consumers (and other exposed groups). These follow a tiered approach.

In the first instance the estimated exposure to each of the active substances is expressed as the HQ for that substance. If the HI is ≤1 (or ≤100%), exposure is acceptable. If the HI >1 a more refined assessment will be required.

The next tier, involves calculating an aHI for each active substance of concern. If the sum of the fractions is ≤1 (or ≤100%), exposure of the consumer is acceptable.

If estimated exposure is not shown to be acceptable following the aHI approach, further specific data will be required to address the risk. This might include in vitro testing of the combination, or in vivo testing of the combination.

The same approach is also followed by the UK when evaluating health implications of findings of multiple residues found in individual composite samples during the monitoring of residues in food[29], although, to date such assessments have only employed the first tier of the scheme.

4.3. Dutch approach (anticholinesterase compounds)

In The Netherlands a short-term cumulative risk assessment for OPs and carbamates was addressed in two reports. The RPF approach was used by Boon and van Klaveren (2003) of the Dutch RIKILT for 40 OPs and carbamates using two index compounds, acephate and phosmet. For the 18 OPs addressed by EPA, RPFs were derived from the reported BMD10s, using either acephate or phosmet as index compound. For the 22 compounds that had been addressed by EPA, data were obtained from a literature search. RPFs from acute NOAELs for either brain or RBC AChE inhibition in any species, including humans were used. For phosmet the NOAEL was independent

[28] PSD and ACP approach to assessing the mammalian toxicity (and consumer/operator risk assessment) of two or more compounds in a pesticide product (formulation), PSD Regulatory Update 05/2005, 12/04/2005 http://websrv1/approvals.asp?id=1556

[29] Pesticide Residues Committee Pesticide Residues Monitoring Report Third Quarter 2004 July to September 2004, Published 10 March 2005, http://websrv1/uploadedfiles/Web_Assets/PRC/PRC_2004_Q3_Text.pdf

of the endpoint, whereas for acephate, the NOAEL for brain AChE was 5 times higher than that for RBC AChE. For this reason the RPF when using acephate as IC was 1.8 times lower than that using phosmet as IC when RBC AChE inhibition was used as end-point, whereas it was about 9 times lower when brain AChE inhibition was used as end-point. When no acute NOAEL was available, it was assumed to be 10 times higher than the NOAEL from repeated dose studies. This was also applied to 4 carbamates. On the basis of the Dutch diet a MCRA was conducted and it was found that, although dependent on the choice of the IC[30], about 0.1 % of the calculated person-day exposures to the AChE inhibitors would exceed the ARfD. The most relevant commodities were grape and orange juice, where parathion and monocrotophos were the most relevant compounds.

As was discussed in a subsequent report by RIVM (Van Raaij et al, 2005) the cumulative risk assessment described above could be refined. For instance, the EPA BMD10s are based on 21-day repeated dosing studies and not on single dose studies. For the OPs the assumption that the acute NOAELs are 10 times higher than their NOAELs in repeated dose studies increases the uncertainty of the estimation because of toxicokinetic and, to a lesser extent, toxicodynamic differences. For carbamates, the assumption that the acute NOAELs are 10 times higher than the NOAELs in repeated dose studies cannot be deemed sound, since the inhibition of AChE caused by carbamates does not accumulate over repeated dosing due to its rapid reactivation. Thus, this results in an underestimation of the toxic potential of carbamates. Furthermore, in view of their differences in kinetics cumulating OPs and carbamates will probably overestimate the chronic risk.

Since the residue data used were obtained from inspection monitoring programmes they are likely to be biased by non-random sampling. As such, the risk assessment will result in a worst-case estimate. Furthermore, the Monte Carlo approach used for the probabilistic exposure assessment provides an estimation of the fraction of person-days, i.e. the probability that a certain consumption pattern of an unknown individual on a certain day will lead to an exceedence of the (acute) limit value. However, this cannot be translated into a fraction of the population exceeding the limit value at some time over a longer period.

4.4. Danish Veterinary and Food Administration[31] (anticholinesterase compounds)

In the early 2000s the Danish Veterinary and Food Administration estimated dietary cumulative exposure to 35 OPs and carbamates that inhibit acetylcholinesterase (Jensen et al, 2003). The aim of the study was to assess the risk from chronic as well as from acute exposure, but only the chronic assessment was performed (see below). The estimates were based on Danish consumption data and results from the Danish monitoring programme of pesticide residues in food on the Danish market. RPFs were compiled from the literature, respectively from the Dutch RIKILT report of 2000 (Boon and van Klaveren 2003) and from a U.S. EPA study (EPA, 2002c). The Dutch values were based on NOAELs using chlorpyrifos as index compound, while the US study was based on BMDs using methamidophos as the IC as described above. Due to the different bases for determining the RPFs, the Dutch and US-values should not be compared directly.

Cumulative chronic exposure was calculated deterministically. Using the National Estimated Daily Intakes (NEDI equation) (WHO, 1997b), of the OP's and carbamates were calculated on the basis

[30] For instance, the 99.5th %ile of the general population had an estimated intake of anticholinesterases of 61% or 21% of the ARfD of acephate or phosmet, respectively. At the 99.9th %ile the percentages were 268 or 45%, respectively.

[31] Today "National Food Institute, Technical University of Denmark

of the mean food consumption data and mean pesticide residues data from the Danish monitoring programme. An important factor for calculation of the cumulative chronic exposure is how the monitoring results of residues below the limit of quantification (LOQ) are handled. In the Danish study, the LOQs of the index compounds were chosen to represent the levels below the LOQ for all individual residues, and 2 sets of calculations were carried out using either 0 or 50% of the LOQ of the index compound for samples without any detected residues. In either case, the NEDI's were multiplied by using the RPFs to convert the intake of the different pesticides into equivalents of the index compounds, and the total intake - being equal to the cumulative intake - was then derived by adding up all the individual intakes. The final risk assessment was made by comparing the calculated total intake with the ADI-value of the index compound.

The estimated dietary intakes were well below the ADI (up to 2% of the ADI when samples below the LOQ were considered to be = 0 and 2-11% of the ADI in adults and 5-27% of the ADI in children when samples below the LOQ were considered to be 50% of the LOQ). It was also determined that 7 different commodities accounted for 75-83% of total exposure depending of the RPF used or the treatment of samples below the LOQ (as 0 or as 50% of the LOQ). Seven of the pesticides contributed to 74-98% of the total exposure (Jensen et al., 2003). Furthermore, differences were found between intakes based on the Dutch and the US EPA RPF, in particular when the samples below the LOQ were considered as having residues at 50% of the LOQ.

An attempt was made to estimate acute or short-term intakes using the JMPR equations (FAO/WHO, 2001) for the National Estimated Short Term Intake (NESTI). The calculations were only made using chlorpyrifos as the index compound since acute TEF-values were only available for this compound. It was noted that the calculated individual intakes could not be added up since they were based on such large portions that it was considered very unlikely that an individual will consume 2 large portions of different commodities within a short period. The acute exposures, which were estimated for an adult and for a 5 year old girl, were all below the ARfD-value for the index compound.

It is noted that the method described, which is based on a deterministic model, is considered a preliminary exposure estimation. A more refined and realistic estimation when needed should be based on a probabilistic model where all available data are used.

4.5. German CVUA approach

Within the framework of food surveillance in Germany, simple deterministic approaches are used for the acute dietary risk assessment of multiple residues in composite samples or single units. For example, the 'Chemisches und Veterinaeruntersuchungsamt Stuttgart' (CVUA, 2007), the governmental food control laboratory of the Federal State Baden-Wuerttemberg, started a project in 2005 to develop a feasible approach to short-term dietary risk assessment for multiple residues from data generated in routine pesticide residues analysis .

The CVUA Stuttgart used the hazard index approach applied deterministically to each sample separately. All the residues found in a sample were considered irrespective of their toxicological characteristics. When the HI was <1 no other action was taken. When the HI was >1 the process was repeated only for those compounds judged to belong to a CAG.

This method was used by the CVUA Stuttgart to evaluate multiple residues in sweet peppers from 2004 – 2005, in table grapes from 2005 and in strawberries from 2002 - 2005. The HI for sweet

peppers was 0.29 and for table grapes 0.24. The strawberry project is described in detail by Looser (Looser et al, 2006). Between 2002 and 2005, 593 conventionally grown strawberry samples were collected from the market and analyzed by the CVUA. Pesticide residues were detected in 98% of the samples and 93% of all strawberry samples were found to contain multiple pesticide residues. The average number of pesticides per strawberry sample was 4.7 and the highest number of different pesticides found in a single sample was 14. The HI was 0.054 in 2002, 0.047 in 2003, 0.037 in 2004 and 0.037 in 2005. Only one strawberry sample had an HI >1 and was further evaluated on the toxicology of the individual substances in a next step (taking into account only residues belonging to a CAG).

4.6. ILSI

The ILSI report on "A framework for cumulative risk assessment" (ILSI, 1999) does not address the cumulative risk assessment of specific compounds. However, it addresses some issues related to the assessment of OPs and pyrethroids. For the OPs it was pointed out that they fulfil the three criteria for considering them as a common group (i.e.: structural alerts, pesticidal action, toxic effect), that there are issues related to toxicokinetics (e.g., direct acting vs activated OPs, rapidly vs slowly eliminated compounds) and toxicodynamics (e.g., rates of spontaneous reactivation and aging of phosphorylated AChE). For the pyrethroids it was pointed out that type II, but not type I, pyrethroids seem to interact with γ-aminobutyric acid (GABA) receptors in vitro, the significance of this interaction in vivo being unknown. It was also pointed out that pyrethroids do not interact covalently with their target. Therefore, unlike the OPs, they do not produce a chemically altered target molecule. Hence, the consideration of the rate of recovery of the target is not an issue for pyrethroids. In addition, pyrethroids do not require bioactivation and are effectively detoxified by cytochromes P450 and carboxylesterases. Therefore, it was concluded that it is improbable that at very low levels of exposure there would be "exacerbations" of effects by the presence of multiple pyrethroids.

4.7. General comments

The EPA experience with 4 groups of compounds gave some useful indications for further progress. First, not all assessments need to be of the same depth. For instance, the TEF/PEF/RPF approach was not always used, for triazines the assumption was made that all compounds were equally potent, and for chloroacetanilides the NOAEL was used instead of the BMD to characterise potency.

To address the use of different UFs for inter-species extrapolation and for age-related differences (FQPA) depending on availability of data, in the assessment of NMC, EPA chose to apply these UFs directly to the RPFs and only the intra-species UF was considered after cumulation of the potency-normalised exposure, giving as target a MOE of 10.

EPA reported that the cumulative risk assessment for OPs required significant resources, especially for the derivation of the TEF/PEF/RPF.

It should also be noted that in the EPA work, some compounds initially included on the basis of toxicological considerations were excluded from the cumulative risk assessment on the basis of exposure considerations. For instance, propazine was excluded from the analysis of the triazine group because exposure was estimated to be very low and it would have contributed insignificantly

to total exposure. Butachlor was excluded from the assessment of chloroacetanilides because there were no registered uses in the USA. This indicates the need for a continuing dialogue between toxicologists and exposure assessors, and between them and risk managers. This is necessary to identify the relevant issues and to best use available limited resources.

The UK efforts were reported to have been made less difficult by exchanges and discussions with other bodies, especially EPA, who had experience of performing CRA.

It was reported by UK that BMD approaches are not well suited to standard regulatory toxicity study designs (3 dose groups and control) and the 95% confidence intervals were often very large and hence NOAELs were used. The PPR Panel noted that, in contrast, EPA combined multiple studies for AChE inhibition to increase the reliability of the modeling; this generally resulted in smaller confidence intervals around the BMD10 (and consequently the RPFs). However, it is noted that other than for the index compound, in deriving RPFs, the BMD rather than the BMDL is often used. In addition, the NOAEL in a study is not necessarily a reliable marker of the true No Adverse Effect Level because of limitations related to e.g., dose spacing and group size, whereas the benchmark approach is more explicit about uncertainty and is based on a fixed response (e.g.: 10%).

The modeling outputs should not simply be taken at face value. Rather it is important to check the plausibility of the output with respect to predicted major and minor contributors. For example, according to the UK results for OPs, the use of the RV or the NOAEL to derive a RPF resulted in a <3-fold difference in the predicted intake at the 99.90 %ile level. Thus, choice of comparator for derivation of RPF was not critical in this case. In addition, the methods used are not always directly compatible with the available modeling software.

The cumulative assessments for anticholinesterases that have been performed by several bodies did not give vastly different results. Although the residues data used were different, it should be noted that only some European countries were considered, the consumption data as well as the supporting toxicology database were partly overlapping, and the uses of the RPF approach were comparable.

It should also be noted that from the exposure perspective, although most national assessments dealt with actual exposure scenarios one dealt with use authorization scenarios (see 4.2.3, UK)

It should be noted that US EPA derived RPFs for OPs from a set of specially commissioned studies with a standard design and a consistent end-point (brain cholinesterase inhibition at steady state). The assessments for cholinesterase inhibitors carried out by other bodies made use of studies of different design and the end-point was sometimes inhibition of RBC acetylcholinesterase. In these cases, there were greater uncertainties in the derived RPFs.

When using routine surveillance data there is a need to find a way to handle inter-unit variability within composite samples.

There is a need to ensure a reliable match between residue source and consumption data (raw versus processed)

5. Dealing with uncertainty.

All risk assessments are subject to uncertainty. Because cumulative assessments consider exposure and toxicity for multiple pesticides, they are affected by more potential sources of uncertainty than

assessments of individual pesticides. It is important to characterise the degree of uncertainty associated with risk estimates, so that it can be taken into account in risk management (Madelin 2004, Codex 2007). US EPA considers the uncertainties in its risk assessment part of its risk characterization.

This section summarises guidance published by EFSA (2006) for dealing with uncertainty in exposure assessment. In principle, these approaches are general in nature and therefore applicable to cumulative risk assessment, including both exposure and toxicity. Readers are referred to EFSA (2006) for more detail.

Each element of a cumulative assessment should be examined systematically for potential sources and types of uncertainty, to maximise the likelihood that important uncertainties are recognised. EFSA (2006) suggests a tabular approach to help with this task. Table 5 lists some types of uncertainties that are likely to be relevant in cumulative risk assessments.

It will be efficient to use a tiered approach to analysing uncertainties (EFSA 2006). Each individual source of uncertainty may be analysed at one of three levels: qualitative, deterministic or probabilistic. Note that it is not necessary to treat all uncertainties in an assessment at the same level; on the contrary, it is likely to be more efficient to quantify only the most substantial uncertainties. Initially, all significant uncertainties may be analysed qualitatively. This may be sufficient, if the outcome is clear enough for risk managers to reach a decision. Otherwise, those uncertainties that appear critical to the outcome may be analysed deterministically or probabilistically. For example, EPA conducts extensive sensitivity analyses designed to evaluate the degree to which key areas of the risk assessment may or may not under- or over-estimate the risk. In these sensitivity analyses, EPA varies the values selected for a variety of input parameters or datasets and evaluates the degree to which its risk estimates may change. To the extent that these changes in input parameters or datasets result in minimal changes to estimates of risk, EPA develops greater confidence in its risk estimates. To the extent that these changes in input parameters or datasets result in substantively meaningful changes in its risk estimates, EPA may attempt to obtain additional data to refine its risk estimates. Treating the most significant uncertainties at higher tiers (deterministic and probabilistic) progressively refines the characterisation of uncertainty, and provides an increasingly clear picture of the likelihood of adverse effects. An example of an opinion employing all three levels of uncertainty analysis is provided by EFSA (2007a).

It is important to communicate the strengths of the assessment (what is known) as well as the uncertainties. The aim should be to provide a balanced picture of what is known and what is uncertain, and avoid giving an exaggerated impression of either certainty or uncertainty.

Table 5 Qualitative evaluation of influence of uncertainties on cumulative risk assessment when consuming commodities containing two or more CAG compounds. Key to direction and magnitude: +, ++, +++ = uncertainty with potential to cause small, medium or large over-estimation of risk (i.e.: over-estimation of the ratio of exposure to ADI or ARfD, hence increased conservativism); -, --, --- = uncertainty with potential to cause small, medium or large under-estimation of risk (i.e.: under-estimation of the ratio of exposure to ADI or ARfD, hence reduced conservativism). The relative importance of these and also of other uncertainties not listed here may vary from one cumulative assessment to the next, and should be considered case by case.

Source of uncertainty/variability	Direction and magnitude
Residues	
Monitoring programmes do not cover all relevant commodities	-/- - - (if no attempt is made to extrapolate from monitored commodities)
Sampling uncertainty due to limited monitoring data. This uncertainty will be large in many cases, where the number of samples (especially positive samples) is small.	- - -/+++
Sampling uncertainty due to limited number of units per composite sample	- - /+ +
Measurement uncertainties in pesticide concentrations	-/+
Handling of data below the LOD, LOQ or LOR	- - -/+++
Extrapolation to unmonitored commodities	-/+
Residue data from monitoring samples may overestimate the real exposure of the consumer, due to the fact that sampling can be done at several points in the distribution chain (e.g., farm gate, retailer, supermarket) and that at the time of consumption the residue may have declined	+/+++ (only for actual exposure scenario's)
Monitoring programmes never include all pesticides present in the worldwide market. Therefore not all compounds in the CAG may be included in the assessment	-/- --
Data on the effect of processing (e.g., peeling, canning, cooking) on residues are rather limited, incomplete and frequently based on a limited number of measurements. Most frequently they will/can not be used.	+/+++
Concentrations in edible and non-edible parts of commodities may differ, and could cause over- or underestimation of intakes if the non-edible parts were included in the residue analysis.	- /++
Relation of supervised trial data to residues in the marketplace	+/+++ (only for actual exposure scenario's, early tier assessment)
Omission of potential contribution of residues from preceding rotational crops	- (only relevant when supervised trial data are used)
Omission of potential contribution of residues in animal products	-

Source of uncertainty/variability	Direction and magnitude
Selection of commodities for monitoring is sometimes targeted on those thought likely to contain high residues. This will tend to overestimate the general distribution of residues.	+/+++
Use of residue as defined for MRL/enforcement to represent all residues of toxicological concern	- - -/+
Using a conversion factor to correct residues as defined for MRL/enforcement to represent all residues of toxicological concern	-/+
Treatment of unit-to-unit variation (e.g., choice of variability factor)	- -/++
Future change of pesticide usage/residue levels	- - -/+++ (for chronic exposure)
Field trial data will tend to overestimate concentrations in treated produce, because field trial conditions are supposed to tend towards a worst case (e.g.maximum number and rate of applications, minimum intervals between and after treatment). This will tend to overestimate intakes, although due to the limited number of trials per commodity (4 or 8) the opposite (underestimation of residues and hence intakes) may also occur.	- / ++ (only for scenario's using field trial data)
Consumption data	
Influence of survey design (method used, season, days of week, etc)	- --/++
Use of old food consumption survey data	- - /++
Statistical uncertainty due to limited number of persons surveyed (especially for rarely-consumed commodities)	- /+
Measurement/reporting uncertainty in consumption surveys.	-/+
Extrapolation from short-term surveys to long-term average consumption check	-/+
Ambiguity in food coding descriptions	-/+
Extrapolation from food as eaten to commodities: the recipes used for this may include both underestimates and overestimates in different cases.	- -/++
Uncertainty in estimation of food weights	-/+
Estimation of large portion size, e.g., 97.5th percentile (when used)	- -/+ (for first tier exposure assessment)
Relation of consumption to body weight	+
Differences between probabilistic models	-/+
Toxicology	
Use of NOAEL from standard toxicity studies as a RfP might either over- or underestimate the true NAEL, depending on dose spacing and on the sensitivity of the toxicological end-point that is assessed.	- -/++
Use of BMD/BMDL gives an estimate of potency, with lower uncertainty than the NOAEL.	-/+
Time-course of effects may differ between compounds. Since acute exposure is assessed	-/+++ (for acute

Source of uncertainty/variability	Direction and magnitude
as 24-hours exposure, for compounds showing effects that are reversible in a few hours such an assessment would overestimate the effects. Alternatively there could be carry-over from consumption on a previous day	exposure)
All of the methods assume that compounds have parallel dose-response curves, which is not necessarily true. It is not possible to determine a priori whether this will result in more or less conservatism in the assessment, this will vary on a case-by-case basis. A further complication is that whilst the dose-response curves may be non-parallel in the range of observable responses, it is not possible to determine how the curves relate to each other at lower levels of exposure	-/+
Refinement of grouping can reach different levels of precision, depending on available data and needs. According to the step-wise approach described, "unrefined" CAGs will include more compounds than refined CAGs. Therefore, the lower tiers of refinement lead to an overestimation of expected toxicological effects.	+/+++ (for lower tier assessments)

The PPR Panel notes that sources of uncertainty rated +++ or - - - warrant sensitivity analysis and provide the greatest scope for refinement of the assessment.

6. Criteria for selecting and prioritising cumulative assessment groups (CAG)

In Regulation (EC) 396/2005, which will come into force in September 2008, cumulative effects are addressed several times. In (6) it is stated: '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 effects on human health, MRLs should be set after consultation of the European Food Safety Authority (…).'

In Article 14 it is stated that: '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 sources other 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 article 36 it is stated that: 'Support measures relating to harmonised pesticide MRLs shall be established at Community level, including: (…) (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'.

The interpretation of this legislation by the PPR Panel is that all pesticides that could potentially be present in food marketed in the EU should be assessed for their possible inclusion in a CAG. Furthermore, that besides cumulative assessments carried out in the context of MRL-setting, the periodical evaluation of monitoring data should consider an assessment of the actual cumulative exposure.

The PPR Panel, in agreement with others, identified a number of possible criteria for deciding on when to perform a cumulative risk assessment. These include toxicological and exposure criteria:

- Pesticide groups including compounds frequently detected in monitoring programmes or with high use based on surveys or sales statistics
- Evidence from biomonitoring data for the general population or for sub-populations/geographical areas of "high" intake,
- Groups including compounds with high HQ (e.g., > 0.25-0.5)
- cumulative risk assessment carried out elsewhere showing possible unacceptable exposure
- CAG that includes a large number of compounds (e.g., 5 or more)
- Assumptions on future trends in use of pesticides

Priority setting of CAGs should be based on these criteria, although not all need to be fulfilled at once.

It should also be noted that presence of relevant non-food sources of exposure might require a cumulative and aggregate assessment to determine what is the margin of exposure for the food part.

In addition, assessment of specific pesticide combinations might be carried out when there is a strong biological hypothesis that certain compounds may interact below their respective NOAELs.

The Panel noted that existing cumulative risk assessments include OPs and carbamates, either separately or together as anticholinesterases, triazines, and chloroacetanlides. In addition, it is aware that evaluation of pyrethroids is ongoing in EPA. Although EPA conducted aggregate risk assessment, whereas the UK, the Danish National Food Institute and the Dutch RIKILT assessed cumulative risk only from residues in food, no assessment of actual cumulative exposure (see 1.3) conducted so far has indicated any significant risks from exposure to multiple chemicals belonging to a CAG where the individual compounds presented no unacceptable risks.

7. Conclusions and Recommendations

The PPR Panel recognises that the issue of exposures to multiple pesticide residues needs to be addressed. It also recognises that exposures to a single pesticide occur at levels that are (well) below the effective dose when the active ingredient is applied according to the regulations. Monitoring data throughout the European Union, available up to 2005, confirm that less than 5% of the tested samples have residues that are above the MRL[7]. The Panel noted that for a number of pesticides, even intake at the legal limit is often well below the toxicological reference values for the compound.

From the available data there is no evidence that exposure to a mixture of pesticides with different modes of action poses any substantially greater risk than that of exposure to the individual pesticides in the mixture, when exposure occurs below the respective RV. In other words, the risk associated with the exposure to such a mixture is determined primarily by the component that poses the highest risk (e.g., the highest HQ). Therefore, the PPR Panel did not further address the combined risk of exposure to pesticides with different targets and different modes of action, when they occur as residues in food.

The methodology used to assess the MRL-setting cumulative exposure scenarios can also be used to assess the risks associated with exceedence of MRLs.

The PPR Panel benefited from the work that has already been done in Europe and in the USA. This includes methods and criteria to identify CAGs and methods to perform their cumulative risk assessments. Although the analyses performed in Europe and the USA on organophosphates and carbamates cannot be considered fully independent because they used similar data and partly comparable approaches, they all point to cumulative exposure to organophosphates that is below the RV of the index compound for >99%ile. Also, the EPA cumulative risk assessments for triazines and chloroacetanilides point to estimated exposures that are well below the relevant RV.

There are several methods to cumulate risk that use essentially the same metrics, although expressing the data differently. They all have their own strengths and weaknesses, related to different levels of uncertainty and refinement that can be achieved. Some are more quickly performed and easily understandable (e.g. the HI); others require thorough analysis of the toxicological data (e.g., RPI) or additional calculations (e.g. RPF based on BMDs). The CRI and the combined MOE are reciprocally related to the HI and the RPI, respectively. As such they are conceptually more difficult to understand, but possibly the combined MOE is simpler to communicate to the public. All these methods can be refined, to a varying extent, by analysis of the toxicological database to identify the relevant end-point for the CAG (HI/CRI), to apply CSAFs (all methods), to refine the RfP from NOAEL to BMD (RPI and RPF). A possible tiered approach is described in the figure below.

With respect to cumulative exposure assessment, 4 scenarios were described

- Assessment of actual exposure (i.e. from the patterns of usage that actually occur in practice)
    - acute assessment
    - chronic assessment
- MRL-setting (i.e. a theoretical exposure where the residue of the compound under evaluation is at the level of the MRL, or, for chronic exposure, at the level of the STMR)
    - acute assessment
    - chronic assessment

Each scenario can be addressed using a deterministic or a probabilistic approach, the requirements on both residue and consumption input data lead to some recommendations as listed at the end of this chapter.

The PPR Panel identified a number of issues that need to be taken into account when performing cumulative risk assessment.

One of the major problems is how to deal with the UFs of the individual pesticides in the group and how to accommodate them in the overall assessment. In particular, it is important to bear in mind that there are UFs for animal-to-human extrapolation (usually 10x), human intraspecies variability (usually 10x), quality of the database, and LOAEL to NOAEL extrapolation. There may also be information on toxicokinetics and toxicodynamics such that chemical-specific adjustment factors can be determined. It may be that the group database can be helpful in reducing the UF applied for the quality of the database.

It is possible that the end-point that brings a chemical into a CAG is different from that of major concern driving the RV for that compound. This should be taken into account, although not necessarily at a first tier initial screening.

Differences in toxicokinetics between compounds belonging to the same group are generally not taken into account. However, the PPR Panel points out that on-going efforts for improving the testing paradigm for pesticides should also allow the acquisition of data that are more useful for carrying out cumulative risk assessments, especially when better information on toxicokinetics becomes available.

Sensitivity analysis needs to be performed with inclusion/exclusion of certain compounds,

The PPR Panel discussed the criteria for prioritization between CAGs. These include toxicological characteristics and information and/or estimation of intake (exposure). The PPR Panel points out that the focus should be on specific groups that are prioritised on the basis of the potential risk and not simply on hazard. To this end, a dialogue is necessary not only within the risk assessment community (toxicologists, experts in residues and food consumption) but also between them and risk managers. Available data and expert judgement will need to be used.

Of the methods for cumulating toxicity that were described in Chapter 2, two can be eliminated from further consideration. The combined margin of exposure is very similar to the reference point index, but marginally more complex mathematically, and therefore less easy to understand. Similarly, the cumulative risk index is similar to hazard index, but more complicated mathematically and with no compensatory advantages.

This leaves, in increasing levels of complexity and refinement, the hazard index, the reference point index (which, depending on the choice of reference point and uncertainty factors can be equivalent to the adjusted hazard index), the relative potency factor and PBTK modeling.

In the same way, exposure assessment can be addressed at increasing levels of refinement ranging from standard deterministic methods through to probabilistic characterisation of exposures for individual members of the relevant population.

The general concept of a cumulative risk assessment using tiered approaches both for exposure and hazard assessment is explained in Figure 1. The options for toxicological and exposure evaluation when setting MRLs are summarised in Figures 2 and 4, the arrows indicating increasing refinement. In theory, any of the toxicological methods could be combined with any of the approaches to exposure assessment. We suggest that a tiered approach be adopted to cumulative risk assessment in which the risk assessor starts with a combination of methods near the top of the figure (the choice of starting point will depend on the data that are readily available). If a lower tier assessment does not give adequate reassurance of safety, then the risk assessor should progress to a higher tier method, jumping by one or more steps for either or both of toxicological and exposure assessment, and if necessary proceeding eventually to use of PBPK modelling with probabilistic assessment of exposure based on individuals rather than person-days.

In the same way, a tiered approach can be adopted to assess the risk from actual exposures by progressing through one or more combinations of the methods set out in Figures 2 and 3. It should be noted that a cumulative risk assessment for actual exposure requires less resources then for MRL-setting scenarios. For actual exposure, all pesticide/commodity combinations are included in one model-run. However, for MRL-setting scenarios, the model should be run anew for each pesticide/commodity combination for which an MRL needs to be set, because only for that

pesticide/commodity combination will a value other than background (monitoring) level be used. For a new compound, there will be no monitoring data available to determine the background level. This problem should be addressed on a case-by-case basis. For example, for a compound used post-harvest, residue trial data could represent the background level. In contrast, for a compound that is used early in the season before the crop is present, the background could be taken to be zero. It should be realised that a cumulative risk assessment will always be a 'moving target' since besides potential new authorisations for new members of the CAG, also new authorisations for additional uses of an existing member of the CAG can be granted.

If a lower tier deterministic assessment (e.g., based on the hazard index) proves satisfactory, the risk manager can be assured that the margin of safety is at least that which would normally be required for an individual pesticide. If a lower tier assessment does not meet the criteria for acceptability, this does not imply that there is unacceptable risk, but rather that a more refined assessment is needed. Deterministic methods based on the hazard index are normally highly conservative when applied to combinations of compounds.

Where higher tier methods are employed, using probabilistic methods, results will take the form of percentages of person-days or people with exposures exceeding a specified 'RV'. When interpreting such findings, risk managers may be assisted by the PPR Panel's earlier opinion on the IESTI equation, which shows percentages of person-days with exposures exceeding ARfDs for a number of individual plant protection products that have been used in the EU (EFSA, 2007c).

A tiered approach of this type has been described for chemicals in general by a WHO/IPCS working group (WHO, 2008a).

Figure 1. Proposed cumulative risk assessment process, using a tiered approach both on exposure and hazard assessment

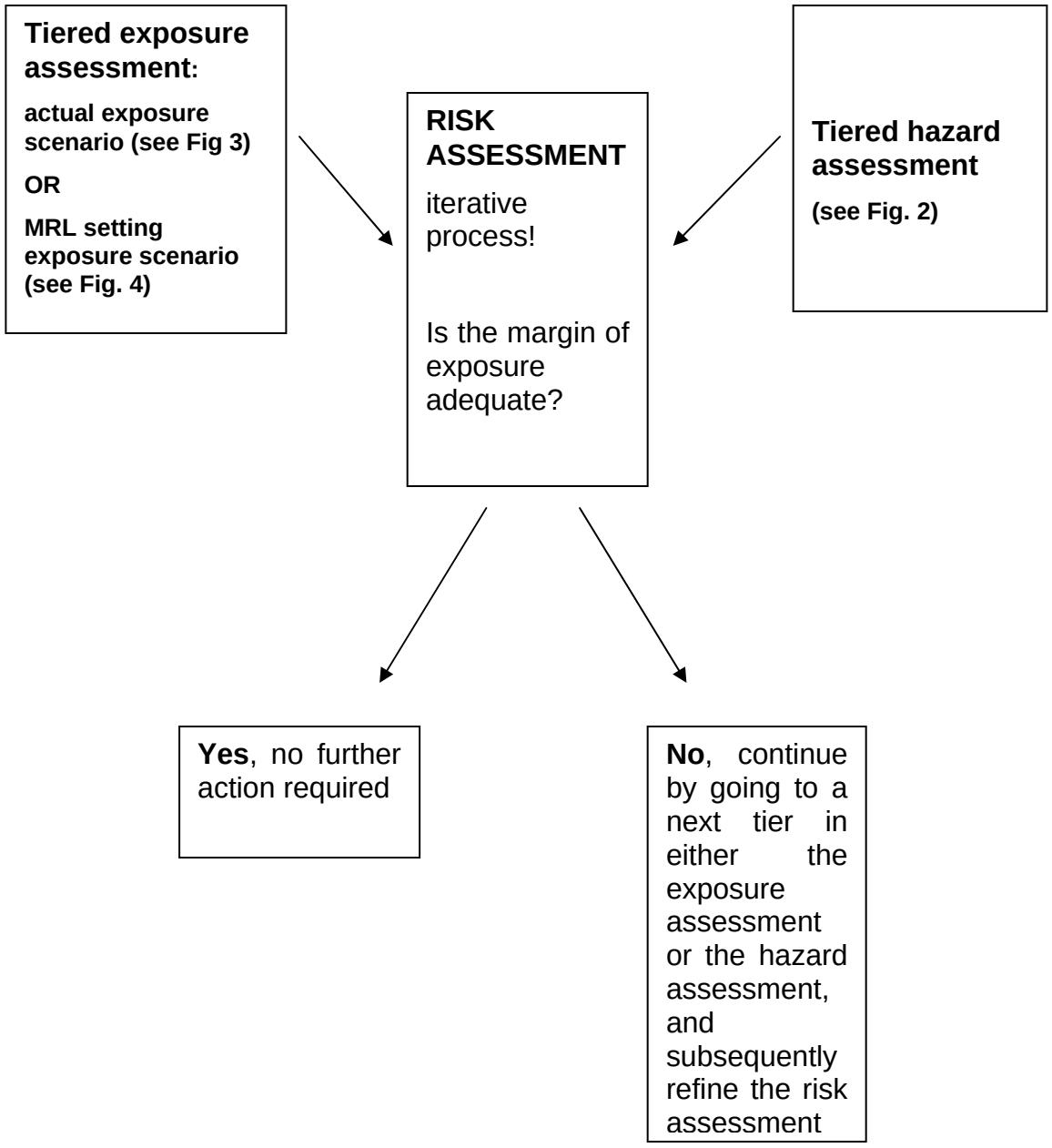
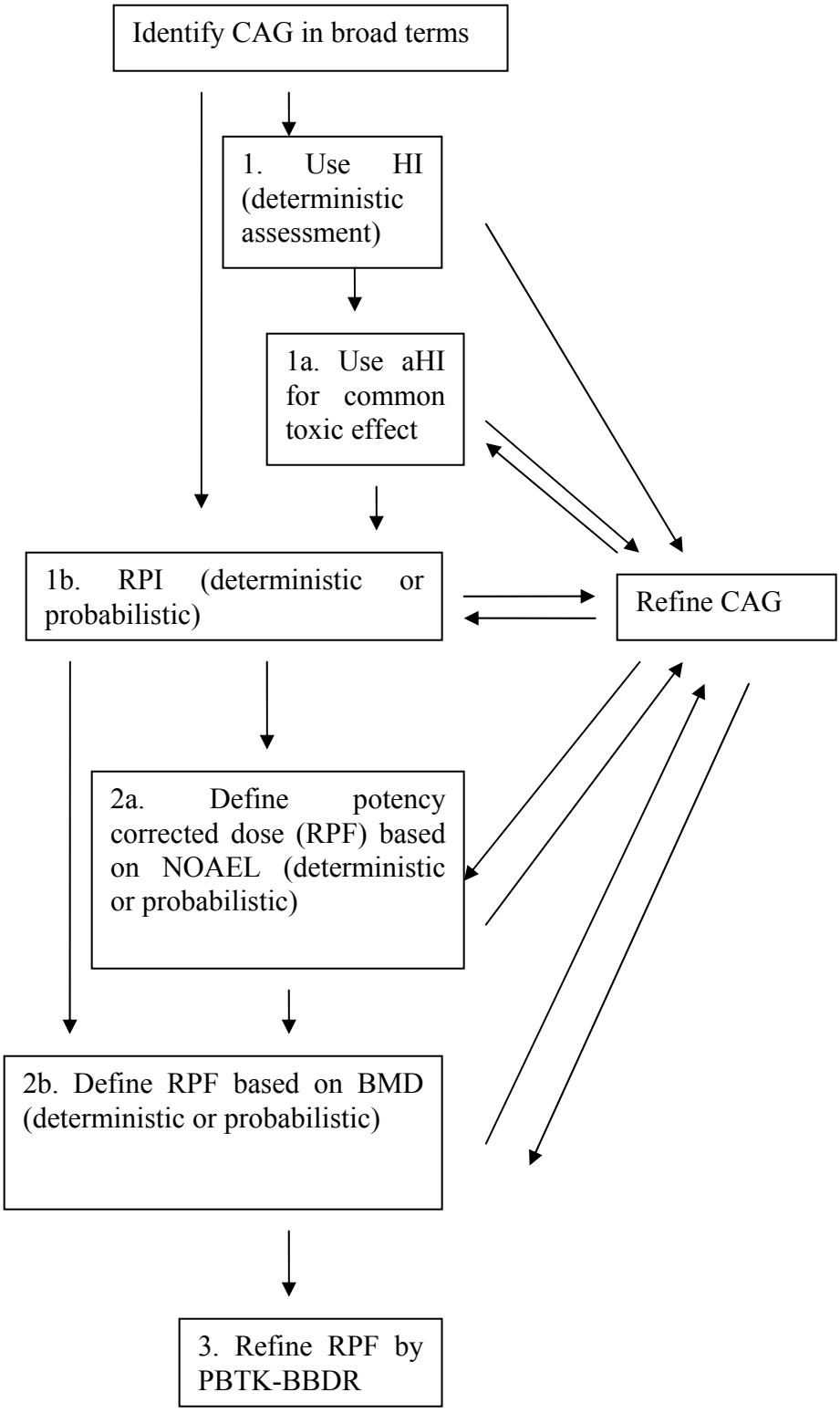
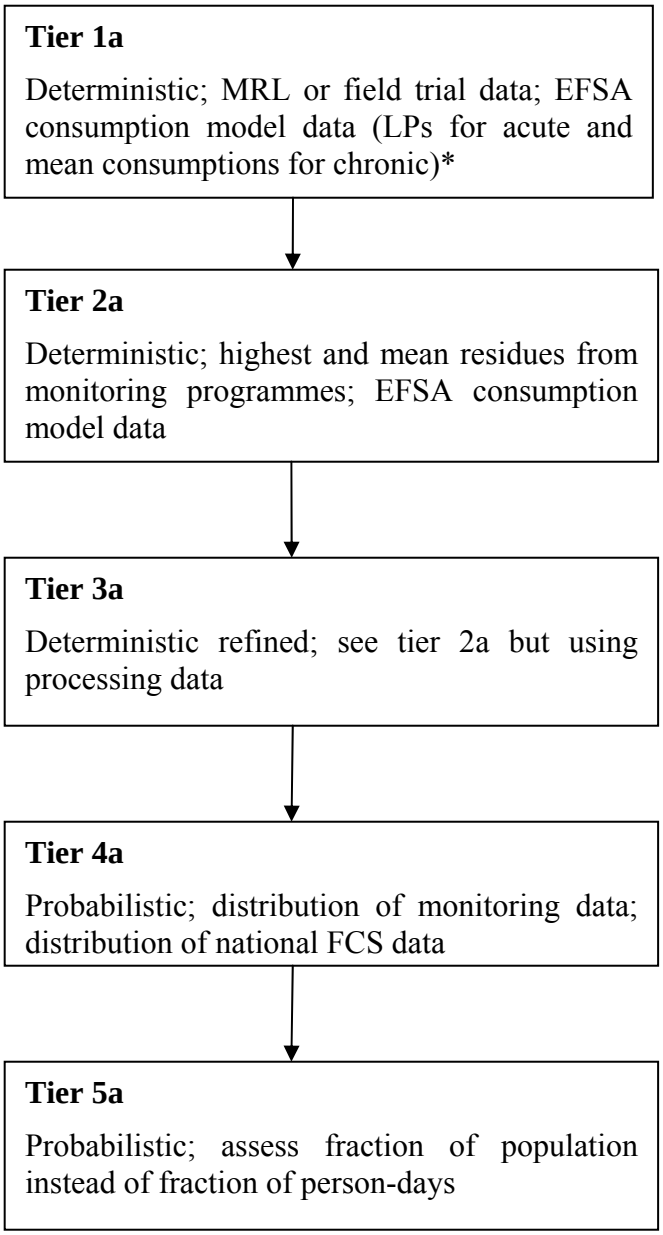


Figure 2. Tiered hazard assessment



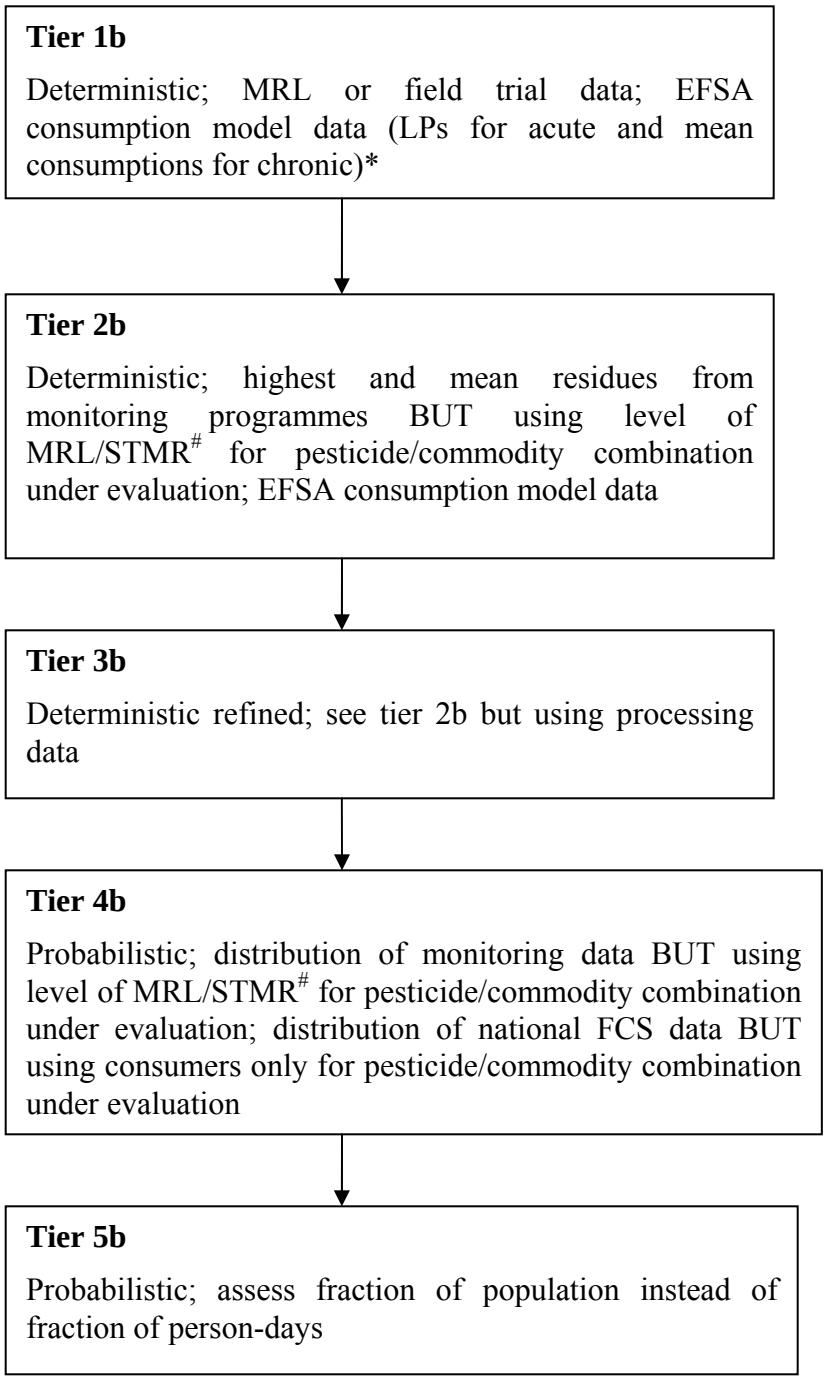
BBDR=Biologically-based dose-response modeling

Figure 3. Tiered exposure assessment, actual exposure scenarios



* EFSA consumption model data when performing a European assessment, on the national level national consumption data may be used

Figure 4. Tiered exposure assessment, MRL setting exposure scenarios



* EFSA consumption model data when performing a European assessment, on the national level national consumption data may be used

\# use MRL or STMR depending on scenario (acute vs. chronic)

The PPR Panel will use the tiered approach that has been described in this opinion in its forthcoming opinion on conazoles and will refine the procedure in the light of the results.

RECOMMENDATIONS

- The PPR Panel recommends that a tiered approach for both toxicological evaluation and intake estimation be adopted in order to make the most efficient use of the available resources.
- Where possible, advantage should be taken of assessments already undertaken, provided they are of sufficient quality and relevance, thereby avoiding repetition of work. Such global collaboration with sharing of results will further harmonization of procedures.
- All identifiable assumptions and uncertainties should be evaluated at least qualitatively, and those that are potentially critical to the outcome of the assessment should be examined quantitatively (either by sensitivity analysis or probabilistic modeling).
- Risk managers will need to consider what level of cumulative risk would be considered "acceptable".
- A continuing dialogue between toxicologists and exposure assessors, and between them and risk managers is particularly necessary for cumulative risk assessment to identify the relevant issues and to best use available resources.
- It is recognized that in residue monitoring programmes, targeted sampling is important for enforcement purposes. However, the degree of targeted sampling should be clearly reported in order to have a better understanding of the available data.
- When designing monitoring programmes, consideration should be given to collection of data more representative of actual exposure to pesticides forming CAGs, in order to provide a better basis for cumulative risk assessment.
- Strategies should be developed for dealing with data from all categories of censored (truncated) data: true non-detects, levels between LOD and LOQ, and levels less than the reporting level.
- It is recommended that when reporting levels are established the needs of cumulative assessments should be taken into account; i.e. they should be as close to the LOQ as possible.
- The raw survey data from monitoring programmes of pesticide residues and from national food consumption databases should be accessible for risk assessment purposes.
- It is recommended that a harmonized consumption survey be performed on the European level, e.g., along the lines of the 4 European GEMS/Food cluster diets (WHO, 2006a), and not along the lines of country borders.
- Guidance for performing probabilistic methods should be developed.
- If there is biological plausibility for an interaction between pesticides at low, non-effective doses, a case-by-case approach should be adopted to assess their combined effects.

DOCUMENTATION PROVIDED TO EFSA

- Letter of 11 July 2006 with ref. D/530753, from R. Madelin from the Health & Consumer Protection Directorate-General to EFSA.
- Regulation (EC) 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. Official Journal of the European Union, No. L70 of 16/3/2005, p. 1-16.

REFERENCES

BfR (Federal Institute for Risk Assessment, Germany), 2007. BfR programme on processing factors. http://www.bfr.bund.de/cd/579#dok

Boobis, A.R., Cohen, S.M., Dellarco, V., McGregor, D., Meek, M.E., Vickers, C., Willcocks, D., Farland, W., 2006. IPCS framework for analyzing the relevance of a cancer mode of action for humans. *Critical Reviews in Toxicology*, 36, 781-792.

Boon, P.E., van Klaveren, J.D., 2003. Cumulative exposure to acetylcholinesterase inhibiting compounds in the Dutch population and young children. Toxicity equivalence approach with acephate and phosmet as index compounds. RIKILT, Wageningen. http://www.rikilt.wur.nl

Brussaard, J.H., Löwik, M.R.H., Steingrimsdottir, L., Moller, A., Kearney, J., De Henauw, S., and Becker, W., 2002. A European food consumption survey method – conclusions and recommendations. *European Journal of Clinical Nutrition*, 56, Suppl 2, S89-S94.

Cassee, F.R., Groten, J.P., and Feron, V.J., 1996.Changes in the Nasal Epithelium of Rats Exposed by Inhalation to Mixtures of Formaldehyde, Acetaldehyde, and Acrolein. *Fundamental and Applied Toxicology*, 29, 208-218.

Codex (Codex Alimentarius Commission Procedural Manual), 2007. 17th Edition. Available at http://www.codexalimentarius.net/web/procedural_manual.jsp

COM (Committee on Mutagenicity of Chemicals in Food, Consumer Products and The Environment), 2007. Statement: benzimidazoles: an approach to defining a common aneugenic grouping. http://www.advisorybodies.doh.gov.uk/pdfs/benzi.pdf

Commission Directive 2002/63/EC of 11 July 2002 establishing Community methods of sampling for the official control of pesticide residues in and on products of plant and animal origin and repealing Directive 79/700/EEC (OJ L 187, 16.7.2002, p.30).

Conolly R, Wang J and Tan Y (2005). Physiologically based pharmacokinetic (PBPK) modeling as an alternative to relative potency factors (RPFs) in cumulative risk assessment: An example with acetylcholinesterase- (AChE) inhibiting pesticides. Toxicol. Sci. 84(S-1), 7. (Abstract 34).

COT (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment), 2002. Risk Assessment of Mixtures of Pesticides and Similar Substances. http://www.food.gov.uk/science/ouradvisors/toxicity/COTwg/wigramp/wigrampfinalreport

COT (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment), 2007. Statement on the COT Workshop on Evolving Approaches to Chemical Risk Assessment. http://www.food.gov.uk/multimedia/pdfs/cotstatementworkshop200703.pdf

Council Directive 86/362/EEC of 24 July 1986 on the fixing of maximum levels for pesticide residues in and on cereals (OJ L 221, 7.8.1986, P.37).

Council Directive 90/642/EEC of 27 November 1990 on the fixing of maximum levels for pesticide residues in and on products of plant origin, including fruit and vegetables (OJ L 350, 14.12.1990, p.71).

Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market (OJ L 230, 19.8.1991, p.1).

Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption (OJ L 330, 5.12.98, p.32)

Crofton, K.M., Craft, E.S., Hedge, J.M., Gennings,C., Simmons, J.E., Carchman, R.A., Carter, W.H. Jr, DeVito, M.J., 2005. Thyroid-hormone-disrupting chemicals: evidence for dose-dependent additivity or synergism. Environmental Health Perspectives. 113, 1549-1554.

CVUA (Chemisches und Veterinaeruntersuchungsamt Stuttgart) 2007. Toxikologische Bewertung von Mehrfachrueckstaenden in Obst und Gemuese. http://cvuas.untersuchungsämter-bw.de/pdf/druck/druck_pest_toxbewertungsmodel.pdf>

De Vriese, S., De Bakker, G., De Henauw, S., Huybrechts, I., Kornitzer, K., Leveque, A., Moreau, M., Van Oyen, H. The Belgian food consumption survey: aims, design and methods. Arch Public Health 2005, 63, 1-16.

EC (European commission), 1997. Guidelines for the generation of data concerning residues as provided in Annex II part A, section 6 and Annex III, part A, section 8 of Directive 91/414/EEC concerning the placing of plant protection products on the market and appendices A-I <http://ec.europa.eu/food/plant/protection/resources/publications_en.htm>

EFSA (European Food Safety Authority), 2004. Opinion of the Scientific Panel on Plant protection products and their residues (PPR) related to the evaluation of alachlor in the context of Council Directive 91/414/EEC The EFSA Journal (2004), 111, 1-34.<http://www.efsa.europa.eu/EFSA/Scientific_Opinion/ppr_opinion07_ej111_alachlor_en1,2.pdf>

EFSA (European Food Safety Authority), 2005. Summary of an Opinion of the Scientific Committee on a request from EFSA related to a Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic. The EFSA Journal 2005 282, 1-30 http://www.efsa.europa.eu/EFSA/Scientific_Opinion/sc_op_ej282_gentox_en3,0.pdf>

EFSA (European Food Safety Authority), 2006. Guidance of the Scientific Committee on a request from EFSA related to Uncertainties in Dietary Exposure Assessment. The EFSA Journal (2006) 438, 1-54. http://www.efsa.europa.eu/EFSA/Scientific_Opinion/sc_op_uncertainty%20exp_en,5.pdf>

EFSA (European Food Safety Authority), 2007b. Opinion of the Scientific Panel PPR related to the revision of Annexes II and III to Council Directive 91/414/EEC concerning the placing of plant protection products on the market - Toxicological and metabolism studies. The EFSA Journal. 449, 1-60. http://www.efsa.europa.eu/en/science/ppr/ppr_opinions/ej449_toxicology.html

EFSA (European Food Safety Authority), 2007c. Opinion of the Scientific Panel on Plant protection products and their Residues on a request from the Commission on acute dietary

intake assessment of pesticide residues in fruit and vegetables. The EFSA Journal (2007) 538, 1–88. http://www.efsa.europa.eu/EFSA/Scientific_Opinion/ppr_op_ej538_IESTI_summary_en,0.pdf

EFSA (European Food Safety Authority), 2007d. Reasoned opinion on the potential chronic and acute risk to consumers' health arising from proposed temporary MRLs. The EFSA Journal, http://www.efsa.europa.eu/EFSA/Scientific_Opinion/Reasoned_opinion,0.pdf

EPA (U.S. Environmental Protection Agency), 1999. Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity. January 29, 1999. Office of Pesticide Programmes, Office of Prevention, Pesticides, and Toxic Substances, Washington, D.C. Available on-line at: http://www.epa.gov/fedrgstr/EPA-PEST/1999/February/Day-05/.

EPA (U.S. Environmental Protection Agency), 2000a. Guidance for Refining Anticipated Residue Estimates For Use in Acute Dietary Probabilistic Risk Assessment, U.S. Environmental Protection Agency, Office of Pesticide Programmes June 15, 2000. http://www.epa.gov/pesticides/trac/science/residues.pdf

EPA (U.S. Environmental Protection Agency), 2000b Choosing A Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern, Office of Pesticide Programmes, March 16, 2000. <http://www.epa.gov/pesticides/trac/science/trac2b054.pdf>

EPA (U.S. Environmental Protection Agency), 2002a. Background and Implementation of Proposed Methodology for Projecting Domestic Percent Crop Treated. http://www.epa.gov/scipoly/sap/meetings/2002/october/backgroundimplementation.pdf

EPA (U.S. Environmental Protection Agency), 2002b. Guidance on Cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity. Washington, DC. (available on-line at: http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf).

EPA (U.S. Environmental Protection Agency), 2002c. Preliminary cumulative organophosphorus risk assessment. Washington, DC. http://www.epa.gov/pesticides/cumulative, (accessed 18 April 2002).

EPA (U.S. Environmental Protection Agency), 2003. Integrated Risk Information System (IRIS). http://www.epa.gov/iris/gloss8_arch.htm

EPA (U.S. Environmental Protection Agency), 2005. Estimation of cumulative risk from N-methyl carbamate pesticides: preliminary assessment. Washington, DC. http://www.epa.gov/scipoly/sap/meetings/2005/august/preliminarynmc.pdf

EPA (U.S. Environmental Protection Agency), 2006a. Organophosphorus cumulative risk assessment. 2006 update. Washington, DC. http://www.epa.gov/pesticides/cumulative/2006-op/op_cra_complete.zip

EPA (U.S. Environmental Protection Agency), 2006b. Cumulative risk from chloroacetanilide pesticides. Washington, DC. http://www.epa.gov/pesticides/cumulative/chloro_cumulative_ risk.pdf

EPA (U.S. Environmental Protection Agency), 2006c. Cumulative risk from triazine pesticides.Washington, DC. http://www.epa.gov/oppsrrd1/REDs/triazine_cumulative_risk.pdf

EPA (U.S. Environmental Protection Agency). 2007a. Estimation of cumulative risk from N-methyl carbamate pesticides: preliminary assessment. Washington, DC. http://www.epa.gov/pesticides/cumulative/common_mech_groups.htm#carbamate

EPA (U.S. Environmental Protection Agency), 2007b. Revised N-methyl carbamate cumulative risk assessment, U.S. EPA September 24, 2007. http://www.epa.gov/oppsrrd1/REDs/nmc_revised_cra.pdf

FAO/WHO, (Food and Agriculture Organization/World Health Organisation), 2001. Pesticide Residues in Food – 2000. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residue in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues. Plant Production and Protection Paper 163 (Rome: FAO)

FAO, 2002. Submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed. http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/Download/FAOM2002.doc

Feron, V.J., Groten, J.P., 2002. Toxicological evaluation of chemical mixtures. *Food and Chemical Toxicology*, 40, 825-839.

Filipsson, A. F., Sand, S., Nilsson, J., and Victorin, K., 2003. The benchmark dose method—review of available models, and recommendations for application in health risk assessment. *Crit. Rev. Toxicol*., **33**, 505–542.

FQPA (Food Quality Protection Act), 1996. US PUBLIC LAW 104–170—AUG. 3, 1996, 110 STAT. 1489-1538

FSA (UK Food Standards Agency), 2005. Research and Survey Programmes Annual Report 2005. http://www.food.gov.uk/multimedia/pdfs/annualreport2005

FSA (UK Food Standards Agency), 2007. Research and Survey Programmes Annual Report for 2006. http://www.food.gov.uk/news/newsarchive/2007/apr/report

FSA (UK Food Standards Agency), 2007. Project details: Mixtures of pesticides research programme T10. http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/

Gray, L.E. Jr., Ostby, J., Wolf, C.J., Lambright, C., Parks, L., Veeramachenemi, D.N., et al., 2001. Effects of environmental antiandrogens on reproductive development in experimental animals. *Human Reproductive Update*, 7, 248-264.

Gordon, C.J., Herr, D.W., Gennings, C., Graff, J.E., McMurray, M., Stork, L., Coffey, T., Hamm, A., Mack, C.M., 2006. Thermoregulatory response to an organophosphate and carbamate insecticide mixture: testing the assumption of dose-additivity. *Toxicology*, 217, 1-13.

Groten, J.P., Schoen, E.D., van Bladeren, P.J., Kuper, C.F., van Zorge, J.A., and Feron, V.J., 1997. Subacute Toxicity of a Mixture of Nine Chemicals in Rats: Detecting Interactive Effects with a Fractionated Two-Level Factorial Design. *Fundamental and Applied Toxicology*, 36, 15-29.

Haws, L. C., Su, S. H., Harris, M., Devito, M. J., Walker, N. J., Farland, W. H., Finley,B., and Birnbaum, L. S., 2006. Development of a Refined Database of Mammalian Relative Potency Estimates for Dioxin-like Compounds. *Toxicol Sci*, 89, 4-30.

Heindel, J.J., Chapin, R.E., George, J., Gulati, D.K., Fail, P.A., Barnes, L.H., Yang, R.S., 1995. Assessment of the reproductive toxicity of a complex mixture of 25 groundwater contaminants in mice and rats. *Fundamental and Applied Toxicology*, 25, 9-19.

Heindel, J.J., Chapin, R.E., Gulati, D.K., George, J.D., Price, C.J., Marr, M.C., Myers, C.B., Barnes, L.H., Fail, P.A., Grizzle, T.B., 1994. Assessment of the reproductive and developmental toxicity of pesticide/fertilizer mixtures based on confirmed pesticide contamination in California and Iowa groundwater. *Fundamental and Applied Toxicology*, 22, 605-621.

Hotchkiss, A.K., Parks-Saldutti, L.G., Ostby, J.S., Lambright, C., Furr, J., Vandenbergh, J.G., et al., 2004. A mixture of the "antiandrogens" linuron and butyl benzyl phthalate alters sexual differentiation of the male rat in a cumulative fashion. *Biol. Reprod.*, 71, 1852-1861.

ILSI, 1999. A framework for cumulative risk assessment. ILSI Press, Washington.

Institute of European Food Studies, 2003. Guidelines on the application of probabilistic modeling on the estimation of exposure to food chemicals (Prepared by the Monte Carlo Project). January 2003.

Jensen, A.F., Petersen, A., Granby, K., 2003. Cumulative risk assessment of the intake of organophosphorus and carbamate pesticides in the Danish diet. *Food Additives and Contaminants*, 20, 776-785.

Jonker, D., Freidig, A.P., Groten, J.P., de Hollander, A.E., Stierum, R.H., Woutersen, R.A., Feron, V.J., 2004. Safety evaluation of chemical mixtures and combinations of chemical and non-chemical stressors. *Reviews on Environmental Health*, 19, 83-139

Jonker, D., Jones, M.A., van Bladeren, P.J., Woutersen, R.A., Til, H.P., Feron, V.J., 1993a. Acute (24 hr) toxicity of a combination of four nephrotoxicants in rats compared with the toxicity of the individual compounds. *Food and Chemical Toxicology*, 31, 42-52.

Jonker, D., Woutersen, R.A., H.P., Feron, V.J., 1996. Toxicity of mixtures of nephrotoxicants with similar or dissimilar mode of action. *Food and Chemical Toxicology*, 34, 1075-1082.

Jonker, D., Woutersen, R.A., van Bladeren, P.J., Til, H.P., Feron, V.J., 1990. 4-Week oral toxicity study of a combination of eight chemicals in rats: comparison with the toxicity of the individual compounds. *Food and Chemical Toxicology*, 28, 623-631.

Jonker, D., Woutersen, R.A., van Bladeren, P.J., Til, H.P., Feron, V.J., 1993b. Subacute (4-wk) oral toxicity of a combination of four nephrotoxins in rats: comparison with the toxicity of the individual compounds. *Food and Chemical Toxicology*, 31, 125-136.

Kortenkamp, A., 2007. Ten years of mixing cocktails: a review of combination effects of endocrine-disrupting chemicals. *Environmental Health Perspectives*, 115, 98-105.

Looser, N., Kostelac, D., Scherbaum, E., Anastassiades, M., and Zipper, H., 2006. Pesticide Residues in Strawberries sampled from the Market of the Federal State of Baden-Wuerttemberg in the Period between 2002 and 2005. *J. Verbr. Lebensm*, 1, 135-141

Lowit, A., Dary, C., Powers F, Blancato, J., Setzer, RW., Conolly, R., and Seaton, M., 2004. Physiologically-based pharmacokinetic/pharmacodynamic modeling and cumulative risk

assessment: Case study for the N-methyl carbamate pesticides, EPA Science Forum http://www.epa.gov/nerl/news/forum2004/lowit_web.pdf

Madelin, R., 2004. The importance of scientific advice in the Community decision making process. Opening address to the Inaugural Joint Meeting of the members of the Non-Food Scientific Committees. Directorate General for Health and Consumer Protection, European Commission, Brussels.

Moser, V.C., 1995. Comparisons of the acute effects of cholinesterase inhibitors using a neurobehavioral screening battery in rats. *Neurotoxicology and Teratology*, 17, 617-625.

Moser, V.C., Casey, M., Hamm, A., Carter, W.H., Simmons, J.E., Gennings, C., 2005. Neurotoxicologial and statistical analysises of a mixture of five organophosphorus pesticides using a ray design. *Toxicological Sciences*, 86, 101-115.

OECD (Organisation for Economic Co-operation and Development), 1982. Organisation for Economic Co-operation and Development. Environment monographs No. 76. Guidance document for the development of OECD guidelines for testing of chemicals. OECD, Paris, 1993, 3-62.

Olgun, S., Gogal, R.M., Adeshima, F., Choudoury, H., Misra, H.P., 2004. Pesticides mixtures potentiate the toxicity in murine thymocytes. *Toxicology*, 196, 181-195.

Picard, D., 2003. Molecular mechanisms of cross-talk between growth factors and nuclear receptor signalling. *Pure Appl. Chem.*, 75, 1743-1756.

PSD (Pesticide Safety Directorate), 2005. PSD and ACP approach to assessing the mammalian toxicity (and consumer/operator risk assessment) of two or more compounds in a pesticide product (formulation), PSD Regulatory Update 05/2005, 12/04/2005 http://www.pesticides.gov.uk/uploadedfiles/Web_Assets/PSD/CombinedToxicity20050408.pdf

Rajapakse, N., Silava, E., Kortenkamp, A., 2002. Combining xenoestrogens at levels below individual No-Observed-Effect concnetrations dramaticlly enhances steroid hormone actions. *Environmental Health Perspectives*, 110, 917-921.

Regulation (EC) N° 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC (OJ L 70, 16.3.2005, p.1).

Slob, W., 2006. Probabilistic dietary exposure assessment taking into account variability in both amount and frequency of consumption. *Food and Chemical Toxicology*, 44, 933–951.

Stork, L.G., Gennings, C., Carchman, R.A., Carter, W.H. Jr., Pounds, J., Mumtaz, M., 2006. Testing for additivity at selected mixture groups of interest based on statistical equivalence testing methods. *Risk Analysis*, 26, 1601-1612.

Tajima, O., Schoen, E.D., Feron, V.J., and Groten, J.P., 2002. Statistically designed experiments in a tiered approach to screen mixtures of Fusarium mycotoxins for possible interactions. *Food and Chemical Toxicology*, 40, 685-695.

Teuschler LK, Rice GE, Wilkes CR, Lipscomb JC and Power FW., 2004. A feasibility study of cumulative risk assessment methods for drinking water disinfection by-product mixtures. *J Toxicol Environ Health A*, 67, 755-777.

TNO Nutrition and Food Research, EFCOSUM Group, 2001. European Food Consumption Survey Method. Final report. Proj. No. 220267/01.01.

Travis, K.Z., Hamilton, D., Davies, L., O'Mullane, M., Mueller, U., 2004 Acute Intake. In : Pesticide Residues in Food and Drinking Water. Human Exposure and Risks. Edited by D. Hamilton and S. Crossley. John Wiley & Sons, Ltd ISBN: 0-471-48991-3.

USDA (United States Department of Agriculture), 2007. Pesticide Data Program Annual Summary, Calendar Year 2006. http://www.ams.usda.gov/science/pdp/Summary2006.pdf

Van den Berg, M., Birnbaum, L.S., Denison, M., De Vito, M., Farland, W., Feeley, M., Fiedler, H., Hakansson, H., Hanberg, A., Haws, L., Rose, M., Safe, S., Schrenk, D., Tohyama, C., Tritscher, A., Tuomisto, J., Tysklind, M., Walker, N., Peterson, R.E., 2006. The 2005 World Health Organization reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. *Toxicological Sciences*, 93, 223-241.

Van Raaij, M.T.M., Ossendorp, B.C., Slob, W., Pieters, M.N., 2005. Cumulative exposure to cholinesterase inhibiting compounds: a review of the current issues and implications for policy. RIVM Report 320108001/2005, Bilthoven.

Walker, N.J., Crockett,P.W., Nyska, A., Brix, A.E., Jokinen,M.P., Sells,D.M., Hailey, J.R., Easterling, M., Haseman, J.K., Yin, M., Wyde, M.E., Bucher, J.R., Portier, C.J., 2005. Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds". *Environmental Health Perspectives*, 113, 43-48.

WHO (World Health Organization), 1997a. Food consumption and exposure assessment of chemicals. Report of a FAO/WHO Consultation. Geneva, Switzerland 10-14 February 1997.

WHO (World Health Organization), 1997b. Guidelines for predicting dietary intake of pesticide residues (revised).Geneva, Switzerland. WHO/FSF/FOS/97.7.

WHO (World Health Organization), 2006a, Global Environment Monitoring System - Food Contamination Monitoring and Assessment Programme (GEMS/Food), http://www.who.int/foodsafety/chem/gems/en/index1.html

WHO (World Health Organization), 2006b, Global Environment Monitoring System - Food Contamination Monitoring and Assessment Programme GEMS/Food Consumption Cluster Diets, Table 2 - GEMS/Food Consumption Cluster Diets, August 2006 http://www.who.int/foodsafety/chem/ClusterDietsAug06.xls

WHO (World Health Organization), 2007, Exposure Assessment for Chemicals in Food, Report of the FAO/WHO Workshop, Annapolis, Maryland, USA, 2-6 May 2005. http://www.who.int/entity/ipcs/food/exposure_assessment.pdf

WHO (World Health Organization), 2008a. International Programme on Chemical Safety (IPCS) Draft IPCS Framework and Sample Case Study. Combined exposure to Multiple Chemicals. February 25th/08.

WHO (World Health Organization), 2008b. GEMS/FOOD data sets used by the Joint FAO/WHO Meeting on pesticide residues (JMPR to assess short-term dietary intake of certain pesticide residues. http://www.who.int/foodsafety/chem/acute_data/en/

Wilkinson, C.F., Christoph, G.R., Julien, E., Kelley, J.M., Kronenberg, J., McCarty, J., Reiss, R., 2000. Assessing the risk of exposures to multiple chemicals with a common mechanism of toxicity: how to cumulate?. *Regulatory Toxicology and Pharmacology*, 31, 31-43.

Yang, R.S.H., and Dennison, J.E., 2007. Initial analyses of the relationship between "Thresholds" of toxicity for individual chemicals and "Interaction Thresholds" for chemical mixtures. *Toxicology and Applied Pharmacology*, 223, 133-138.

ABBREVIATIONS

BMD/BMDL	Benchmark Dose/Benchmark Dose Lower Limit
BB-DR	Biologically Based Dose-Response modeling
CAG	Cumulative Assessment Group
CMG	Common Mechanism Group
CRI	Cumulative Risk Index
CSAF	Chemical-Specific Adjustment Factors
FQPA	Food Quality Protection Act
GAP	Good Agricultural Practice
HI	Hazard Index
HQ	Hazard Quotient
IESTI	International Estimate of Short Term Intake
LP	Large Portion
MOA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limit
NMC	N-methyl carbamates
NOAEL	No Observed Adverse Effect Level
OP	Organophosphorus Pesticide
PEF	Potency Equivalency Factor
RAC	Raw Agricultural Commodity
RfP	Reference Point
RPF	Relative Potency Factor
RV	Reference Value
STMR	Supervised Trials Median Residue
TEF	Toxic Equivalency Factor
UF	Uncertainty Factor

GLOSSARY

acetylcholinesterase inhibitor
Compound that inhibits acetylcholinesterase, thereby interfering with the transmission of impulses between certain nerve cells and at the neuromuscular junction causing overstimulation.

Note: Examples include carbamates (e.g., carbaryl and aldicarb) and organophosphates (e.g., malathion and chlorpyrifos)

acute exposure
A contact between an agent and a target occurring over a short time, generally less than a day. (Other terms, such as "short-term exposure" and "single dose," are also used.) [ISEA]

acute reference dose (ARfD)

Estimate of the amount of a substance in food and/or drinking water, normally expressed on a body weight basis, that can be ingested in a period of 24 h or less without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation [JMPR].

acute toxicity
Adverse effects of finite duration occurring within a short time (up to 14 d) after administration of a single dose (or exposure to a given concentration) of a test substance or after multiple doses (exposures), usually within 24 h of a starting point (which may be exposure to the toxicant, or loss of reserve capacity, or developmental change, etc.) [IUPAC].

additive effect
Consequence that follows exposure to two or more chemical agents which act jointly but do not interact. The total effect is the simple sum of the effects of separate exposure to the agents under the same conditions [IUPAC].

aggregate risk
the risk associated with all pathways and routes of exposure to a single chemical. (EPA, 1999)

assessment factor
(see uncertainty factor)

BMD
A dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background [EPA]The BMR is normally specified as 5% for continuous data and 10% for incidence data.

chronic effect
Consequence that develops slowly and/or has a long lasting course: may be applied to an effect that develops rapidly and is long-lasting [IUPAC].

chronic exposure
A continuous or intermittent long-term contact between an agent and a target. (Other terms, such as "long-term exposure," are also used.) [ISEA]

chronic toxicity
Adverse effects following chronic exposure. 2. Effects that persist over a long period of time whether or not they occur immediately upon exposure or are delayed [IUPAC].

Common Mechanism Group (CMG)
In the USA, a group of chemicals determined to cause a common toxic effect by a common mechanism of toxicity. The CMG is defined using US EPA's previously released Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity. Not all members of a CMG should necessarily be included in a more refined quantitative estimate of cumulative risk. [US EPA]

common mechanism of toxicity
pertains to two or more pesticide chemicals or other substances that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (i.e. interpreted as mode of action). [US EPA]

composite sample
Combined increment samples, or combined replicate samples, or combined samples from replicate trials. Preferred term to "bulk sample", which is ambiguous [IUPAC].

concurrent exposure
Interpreted as potential human exposure by all relevant pathways, durations, and routes that allows one chemical to add to the exposure of another chemical such that the total risk is an estimate of the sum of the exposures to the individual chemicals. This includes simultaneous exposures as well as any sequential exposures that could contribute to the same joint risk, either by overlapping internal doses or by overlapping toxic effects. [US EPA]

cumulative risk
Probability of any defined harmful effect occurring through a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism/mode of toxicity[32] [IUPAC].

Note: in the context of this opinion, it is intended more specifically to be the risk deriving from the exposure to compounds that share the same mode of action (dose addition) or that have similar effects but do not act at the same molecular target (response addition) and is contrasted to synergistic risk. Although the term "cumulative risk" has sometimes been used when referring generally to the risk from exposure to more than one pesticide (see EFSA colloquium), in the context of this opinion, it refers more specifically to the risk deriving from combined exposure to compounds that share the same mode of action or that have similar effects but by different modes of action.

Cumulative Assessment Group (CAG)
A group of chemicals that could plausibly act by a common mode of action, not all of which will necessarily do so. Membership of a CAG can usually be refined (reduced) by application of successively higher tiers of the approach described in this Opinion.

[32] It should be noted that the US EPA has, in other contexts, defined cumulative risk assessment in a broader manner– "The examination of the accumulation (over time, across sources, across routes, etc.) of stressors or exposures that can cause adverse effects, and then the integration of the effects these stressors or exposures cause into an estimate and characterization of the risk caused to the individual or population by the stressors acting together" (USEPA, 2001i).

dose addition
(see simple similar action)

dose additivity
(see simple similar action)

eaters only analysis
Also known as "consumers only" analysis. A risk assessment which uses as and limits its population base to eaters of the commodity (or commodities) of interest. Contrast to "per capita analysis" which considers both eaters and non-eaters of the commodity.

exposure
Concentration or amount of a pesticide (or agent) that reaches a target organism, system, or (sub-) population in a specific frequency for a defined duration [IUPAC].

exposure assessment
The process of estimating or measuring the magnitude, frequency and duration of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, it describes the sources, pathways, routes, and the uncertainties in the assessment. [ISEA]

exposure pathway
The course an agent takes from the source to the target. [ISEA]

exposure period
The time of continuous contact between an agent and a target. [ISEA]

exposure route
The way an agent enters a target after contact (e.g., by ingestion, inhalation, or dermal absorption). [ISEA]

exposure scenario
A combination of facts, assumptions, and inferences that define a discrete situation where potential exposures may occur. These may include the source, the exposed population, the time frame of exposure, microenvironment(s), and activities. Scenarios are often created to aid exposure assessors in estimating exposure. [ISEA]

feedstuffs.
Various products of vegetal and animal origin, in their natural state, fresh or preserved, and products derived from the industrial processing thereof, and organic and inorganic substances, whether or not containing additives, which are intended for use in oral animal feeding

Food Quality Protection Act (FQPA)
A 1996 update/amendment to the U.S. Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Federal Food Drug and Cosmetic Act (FFDCA). FQPA fundamentally changes the way EPA regulates pesticides to "establish a more consistent, protective regulatory scheme, grounded in sound science". FQPA mandates a single, health-based standard for all pesticides in all foods; provides special protections for infants and children; expedites approval of safer

pesticides; creates incentives for the development and maintenance of effective pesticides; and requires periodic re-evaluation of pesticide registrations and tolerances to ensure that the scientific data supporting pesticide registrations will remain up to date in the future [IUPAC].

Good Agricultural Practices (GAP)
Good Agricultural Practice (GAP) in the use of pesticides includes the officially recommended or nationally authorized uses of pesticides under actual conditions necessary for effective and reliable pest control. It encompasses a range of levels of pesticide applications up to the highest authorized use, applied in a manner which leaves a residue which is the smallest amount practicable

hazard
Inherent property of an agent (e.g., pesticide) or situation having the potential to cause adverse effects when an organism, system, or (sub-) population is exposed to that agent or situation [IUPAC].

hazard assessment
Process that includes hazard identification and characterization and focuses on the hazard in contrast to risk assessment where exposure assessment is a distinct additional step [IUPAC].

Index Chemical
The chemical used as the point of reference for standardizing the common toxicity of the chemical members of the CAG. The index chemical should have a clearly defined dose-response, be well defined for the common mechanism of toxicity, and have a toxicological/biological profile for the common toxicity that is representative of the CAG. [US EPA]

interaction
Considered to be any form of joint action deviating from dose additivity or response additivity, resulting in a stronger (synergistic; also potentiating, supra-additive) or a weaker (antagonistic; also inhibitive, sub-additive, infra-additive) effect than expected.

intake
The process by which an agent crosses an outer exposure surface of a target without passing an absorption barrier, i.e. through ingestion or inhalation (see dose). [ISEA]

limit of detection (LOD)
Lowest concentration of a pesticide residue in a defined matrix where positive identification can be achieved using a specified method. [IUPAC]

limit of quantitation[1] (LOQ)
Lowest concentration of a pesticide residue in a defined matrix where positive identification and quantitative measurement can be achieved using a specified analytical method. [IUPAC]

limit of reporting[1]
Practical limit of residue quantitation at or above the LOQ. The conservative limit of quantitation for a defined matrix and method, which may vary between laboratories or within the one laboratory from time to time because of different equipment, techniques, and reagents. Commonly

either the lower limit of the calibrated range of the method or the lowest level at which quantitative recovery of the analyte has been demonstrated. [IUPAC]

market basket survey
Pesticide residue monitoring on a wide range of food items collected from consumer points of sale and in proportions approximating consumption patterns in the local population. [IUPAC]

Note: Samples are prepared for analysis according to Codex guidelines, i.e., minimal preparation. See also total diet study.

maximum residue limit (MRL)
Maximum concentration of a residue that is legally permitted or recognized as acceptable in, or on, a food, agricultural commodity, or animal feedstuff as set by Codex or a national regulatory authority [IUPAC].

Note 1: The term tolerance used in some countries is, in most instances, synonymous with maximum residue limit.

Note 2: Normally expressed as a mass ratio = mass/(fresh mass) (usually units mg kg–1) for food commodities and as mass ratio = mass/(dry mass) (usually units mg kg–1) for animal

mechanism of action
Detailed explanation of the individual biochemical and physiological events leading to a toxic effect

Note: contrast this with mode of action (see)

mode of action
Description of the major steps leading to an adverse health effect following interaction of the compound with biological targets

Note: For the purpose of this document the term "mode of action" (MOA) rather than "mechanism of action" will be used. "Mode of action" refers to the major steps ("key events") leading to an adverse health effect following interaction of the compound with biological targets whereas "mechanism of action" is a detailed explanation of the individual biochemical and physiological events leading to a toxic effect (Boobis et al., 2006). It should be noted that in U.S. EPA, documents relating to cumulative risk assessment, when the term "mechanism of action" is used it implies "mode of action" as defined above. Thus, a common mechanism of toxicity is defined as when "two or more pesticide chemicals …. cause a common toxic effect by the same, or essentially the same, sequence of major (or key) biochemical events" (EPA, 1999).

no-observed-adverse-effect level (NOAEL)
Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure [IUPAC].

organophosphorus pesticide (OP)
Generic term for pesticides containing phosphorus but commonly used to refer to insecticides consisting of acetylcholinesterase inhibiting esters of phosphate or thiophosphate including parathion, chlorpyrifos, diazinon, and malathion. [IUPAC]

pathway of exposure
The physical course a pesticide takes from the source to the organism exposed (e.g., through food or drinking water consumption or residential pesticide uses). [US EPA]

Point of Departure (POD)
In the USA, a dose that can be considered to be in the range of observed responses without significant extrapolation. A POD can be a data point or an estimated point that is derived from observed dose response data. A POD is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposure. The dose-response point that marks the beginning of a low-dose extrapolation. This point is most often the upper bound on an observed incidence or on an estimated incidence from a dose-response model. (EPA, 2003)

Reference point (RfP)
The term "Reference Point" is used in this opinion as used by the EFSA Scientific Committee to replace the term Point of Departure (see) that is used by US EPA. In addition, contrary to EPA, the NOAEL or the LOAEL are also included in the definition of RfP (EFSA, 2005). Although Reference Point is normally abbreviated to RP (e.g. see COT, 2007, http://www.food.gov.uk/multimedia/pdfs/cotstatementworkshop200703.pdf), here it is abbreviated to RfP, to distinguish it from Relative Potency

Reference Value (RV)
The estimated maximum dose (on a body mass basis) or exposure concentration of an agent to which an individual may be exposed over a specified period without appreciable risk. The acceptable daily intake (ADI), the acute reference dose (ARfD) and the acceptable operator exposure level (AOEL) are health-based reference values commonly used in risk assessment of plant protection products. They are usually set by dividing the no observed adverse effect level (NOAEL) from the most appropriate toxicological study by an assessment factor (also known as a safety or uncertainty factor) to allow for inter-individual variability and scientific uncertainty (EFSA, 2007b).

Relative Potency Factor (RPF)
The ratio of the toxic potency (usually expressed as the RfP) of a given chemical to that of an index chemical in the Common Assessment Group (CAG). Relative potency factors are used to convert exposures of all chemicals in the CAG into their exposure equivalents of the index chemical. [US EPA]

risk assessment
Process intended to calculate or estimate the risk to a given target organism, system, or (sub-) population, including the identification of attendant uncertainties, following exposure to a particular pesticide or agent of concern as well as the characteristics of the specific target system. It is the first component in a risk analysis process [IUPAC].

Note: The risk assessment process includes four steps: hazard identification, hazard characterization (related term: dose–response assessment), exposure assessment, and risk characterization.

risk characterization
The qualitative and, wherever possible, quantitative determination, including attendant uncertainties of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub-) population, under defined exposure conditions [IUPAC].

risk management
Decision-making process involving considerations of political, social, economic, and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyze, and compare regulatory and nonregulatory options and to select and implement appropriate regulatory response to that hazard [IUPAC].

Note: Risk management comprises three elements: risk evaluation; emission and exposure control; and risk monitoring.

route of exposure
Means by which a chemical enters an organism after contact (e.g., ingestion, inhalation, or dermal absorption [IUPAC].

simple dissimilar action
Describes the modes of action and possibly, but not necessarily, the nature and site of the toxic effect, when they differ among the chemicals in the mixture.

Note: Also referred to as simple independent action or independent joint action or response additivity:

simple similar action
Describes the mode of action when all chemicals in the mixture act in the same way, by the same mechanism/mode of action, and differ only in their potencies. The effects of exposure to a mixture of these compounds are assumed to be the sum of the potency-corrected effects of each component.

Note: also referred to as similar joint action or dose additivity or relative dose additivity

supervised trials
Scientific studies for estimating maximum residue limits in which pesticides are applied to crops or animals according to specified conditions intended to reflect commercial practice after which harvested crops or tissues of slaughtered animals are analyzed for pesticide residues. Usually, specified conditions are those which approximate existing or proposed good agricultural practice [IUPAC].

surveillance
Systematic sampling and residue analysis of commodities, and collation and interpretation of data, in order to ensure compliance with established maximum residue limits. Surveillance may be directed at domestic, imported, or exported commodities.

synergy
The result of an interaction between two or more pesticides resulting in an effect that is more than dose additive or response additive.

synergism
Pharmacological or toxicological interaction in which the combined biological effect of two or more substances is greater than expected on the basis of the simple summation of the toxicity of each of the individual substances [IUPAC].

response addition
see simple dissimilar action

total diet study
Pesticide residue monitoring to establish the pattern of residue intake by a person consuming a defined diet. [IUPAC]

Note: Primary sampling is as for a market basket survey, but the samples are further processed as for domestic consumption, i.e. further trimming and cooking as appropriate to local practice.

toxic equivalency factor (TEF)
Ratio of the toxicity of a chemical to that of another structurally related chemical (or index compound) chosen as a reference. [IUPAC]

toxicodynamics
Process of interactions of toxicologically active substances with target sites in living systems, and the biochemical and physiological consequences leading to adverse effects [modified from IUPAC].

toxicokinetics
Process of the uptake of substances (e.g., pesticides), by the body, the biotransformations they undergo, the distribution of the parent compounds and/or metabolites in the tissues, and their elimination from the body over a period of time. 2. Study of such processes. [modified from IUPAC]

uncertainty factor
Reductive factor by which an observed or estimated no-observed-adverse-effect level of a pesticide is divided to arrive at a criterion or standard (reference value, see above) that is considered safe or without appreciable risk [IUPAC].

Also known as an assessment or safety factor.

Sources for Definitions:

[IUPAC]: Stephenson, Gerald R., Ferris I.G., Holland P.T., Nordgerg M., 2006. Glossary of terms relating to pesticides, (IUPAC Recommendations 2006), Pure Appl. Chem., Vol. 78, No. 11, pp. 2075–2154.

[US EPA]: (U.S. Environmental Protection Agency)

[ISEA]: Zartarian V., Bahadorf T., and McKone T., 2005. Adoption of an Official ISEA Glossary. J. Expos. Anal. & Environ. Epid. 15 (1-5).

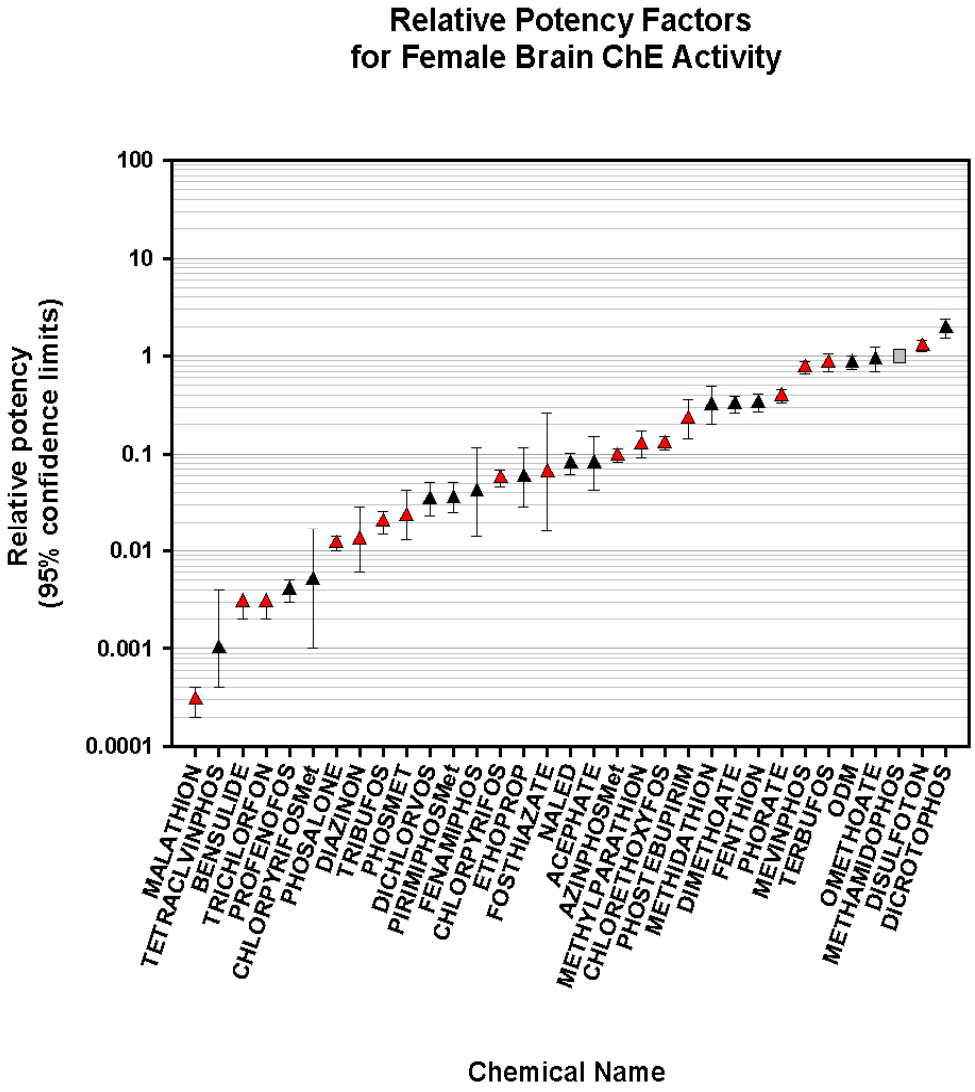
Table 6 Average cumulative intake of the Danish population, expressed as % of the ADI, of OP pesticides, as based on RIKILT or EPA RPFs. Calculation have been made assuming non detects as either =0 or = ½ of LOQ.

food items	RIKILT RPFs				EPA RPFs			
	Non detects=0		Non detects=0.5x LOQ		Non detects=0		Non detects=0.5x LOQ	
	Adult	Child	Adult	Child	Adult	Child	Adult	Child
Fruit and vegetables	0.7	1.8	1.5	4	0.03	0.07	7	17
Cereals	0.08	0.2	0.5	1	0.001	0.003	4	10

Table 7 Comparison of RPF for OPs determined by PSD (UK) and EPA (USA), based on repeated dose studies.

OP	EPA (IC: methamidophos)	PSD # (IC Chlorpyrifos)	Ratio PSD/EPA
Chlorpyrifos	0.1	1	10
Dichlorvos	0.037	0.3	8
Dimethoate	0.33	1	3
Malathion	0.0003	0.003	10
Pirimiphos methyl	0.029	0.05	1.7

Figure 5.


Relative Potency Factors
for Female Brain ChE Activity
Relative potency
(95% confidence limits)
100
10
1
0.1
0.01
0.001
0.0001
MALATHION
TETRACLVINPHOS
BENSULIDE
TRICHLORFON
PROFENOFOS
CHLORPYRIFOSMet
PHOSALONE
DIAZINON
TRIBUFOS
PHOSMET
DICHLORVOS
PIRIMIPHOSMet
FENAMIPHOS
CHLORPYRIFOS
ETHOPROP
FOSTHIAZATE
NALED
ACEPHATE
AZINPHOSMet
METHYLPARATHION
CHLORETHOXYFOS
PHOSTEBUPIRIM
METHIDATHION
DIMETHOATE
FENTHION
PHORATE
MEVINPHOS
TERBUFOS
ODM
OMETHOATE
METHAMIDOPHOS
DISULFOTON
DICROTOPHOS
Chemical Name