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Human health risk assessment from combined exposure in the framework of plant protection products and biocidal products

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Abstract Cumulative risk assessment (CRA) is of major importance and one of the biggest challenges for the future as a legal requirement within the EU for active substances used in plant protection products (PPP) and biocidal products (BP). Therefore, it is important to develop a methodology to take into account cumulative and synergistic effects for both active substances and substances of concern (SoC). The implementation of cumulative aspects in regulatory decisions is highly demanded and promoted by EU parliament, EU commission, European Food Safety Authority (EFSA), European Chemicals Agency (ECHA) and national authorities. Based on EFSA's and ECHA's work on CRA, the Federal Institute for Risk Assessment (BfR) drafted a concept on how to take cumulative aspects into account in the regulatory context in risk assessments for operators, consumers and other uninvolved third parties. Application of this concept as part of the routine risk assessment for PPP and BP is envisaged as soon as suitable experience has been gained in a testing phase. The BfR draft concept uses dose-addition of individual active substances and SoC as the toxicological standard concept for CRA and proposes a tiered approach. It recommends to start with calculation of a hazard index (HI) for all relevant substances contained in the PPP or BP under consideration. Proceeding to higher tiers is currently foreseen if the HI is larger than 1, i.e., an unacceptable risk cannot be excluded. In higher tiers, the HI should be calculated with respect to common targets and might consider effect-specific NOAEL's (No Observed Adverse Effect Level) or relative potency factors, if available. Refinements should consider both the toxicity and the exposure part of the CRA and will depend on availability of relevant data. BfR acknowledges the complexity of the refinement work in mixture risk assessment to be done. The exposure assessment for operators, bystanders/residents and workers as well as the acute exposure assessment for consumers rely mainly on the active substances in a PPP or BP under consideration or on combinations of products for which simultaneous use is notified. Chronic consumer exposure assessment needs to take into account all relevant substances contained in the PPP or BP under consideration, but also the residue background of other pesticides in food, which have to be derived from representative food monitoring programmes. A representative food monitoring database is currently being developed. The assessment requires the application of complex probabilistic methods. It is planned that BfR will review the chronic CRA for each active substance and each CAG regularly as soon as all essential monitoring data are available. It is planned to carry out case studies on the impact on regulatory decisions. The paper is intended to promote further discussions of risk assessors, risk managers as well as stakeholders in this area on the applicability of CRA in routine authorisation procedures for PPP and BP and to encourage the flexible use of strategies in CRA.

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1 Introduction

According to article 14 of Regulation (EC) No. 396/2005 regarding decisions on applications concerning maximum residue levels (MRL), "known cumulative and synergistic effects shall be taken account of, when the methods to assess such effects are available."

According to Regulation (EC) 1107/2009 a plant protection product (PPP) shall meet the following requirements: "It shall have no immediate or delayed harmful effect on human health, including that of vulnerable groups, or animal health, directly or through drinking water (taking into account substances resulting from water treatment), food, feed or air, or consequences in the workplace or through other indirect effects, taking into account known cumulative and synergistic effects where the scientific methods accepted by the Authority to assess such effects are available."

For biocidal products (BP), article 8 to Regulation (EU) No. 528/2012 states: "Where the evaluating competent authority considers that there are concerns for human health, animal health or the environment as a result of the cumulative effects from the use of biocidal products containing the same or different active substances, it shall document its concerns (…) and include this as part of its conclusions."

As a consequence, cumulative and synergistic effects between different active substances as well as substances of concern (SoC; e.g. synergists, safeners, co-formulants of concern) have to be considered in all regulatory decisions concerning PPP and BP if scientifically robust methods are available to identify and assess them. Thus, there is the legal requirement to account for cumulative effects before active substances can be approved for use in PPP and BP, in MRL setting and during authorisation of PPP and BP on zonal and national level. Furthermore, human health assessment of cumulative effects is an important criterion in the assessment of samples in food monitoring.

In general, the same guidance and principles as laid down in the data requirements for PPP in accordance with Regulation (EC) No. 1107/2009 and for biocides in Regulation No. 528/2012 or any relevant guidance document for conventional exposure and risk assessment apply also to cumulative exposure and risk assessment.

The implementation of cumulative aspects in the risk assessment for operators, consumers and other uninvolved third parties in the regulatory context is highly demanded and promoted by EU Parliament, EU Commission, EFSA and national authorities. Although insufficiently supported by the current legal data requirements, the complexity of these assessments has to be accounted for by the development of refined methods for exposure assessment, improved toxicological concepts and methodological support including IT tools and alternatives for conventional methods to avoid further animal testing.

Since 2008, EFSA published several opinions on issues of cumulative consumer risk assessment (EFSA 2008, 2009, 2012, 2013a, b). Guidance on risk assessment from combined exposure to multiple biocidal substances within a single biocidal product was recently published by ECHA (2013). It follows the tiering principles of refinement as described in Fig. 1 within the WHO/IPCS Framework on Combined Exposure (Meek et al. 2011). This ECHA guidance is based on different recent documents of the Scientific Committee on Health and Environmental Risks (SCHER), the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Emerging and Newly Identified Health Risks (SCHER, SCCS, SCENIHR 2011) and some publications found through a literature review.

Based on this preceding work, BfR drafted a concept on how to take cumulative aspects into account in the risk assessments for operators, consumers and other uninvolved third parties in the context of PPP and BP regulation.

Additionally, BfR is currently working on research projects in the field of CRA for operators, consumers and other uninvolved third parties. For environmental risk assessment, drafts for technical guidance documents and methods to assess cumulative effects and multiple residues were already developed by the Federal Environmental Agency (UBA).

Based on the EFSA and ECHA guidance, the risk assessment from combined exposure to one or multiple chemicals can be classified into the following three situations:

1. combined exposure to multiple substances by one source
   of release(s) and/or use(s).

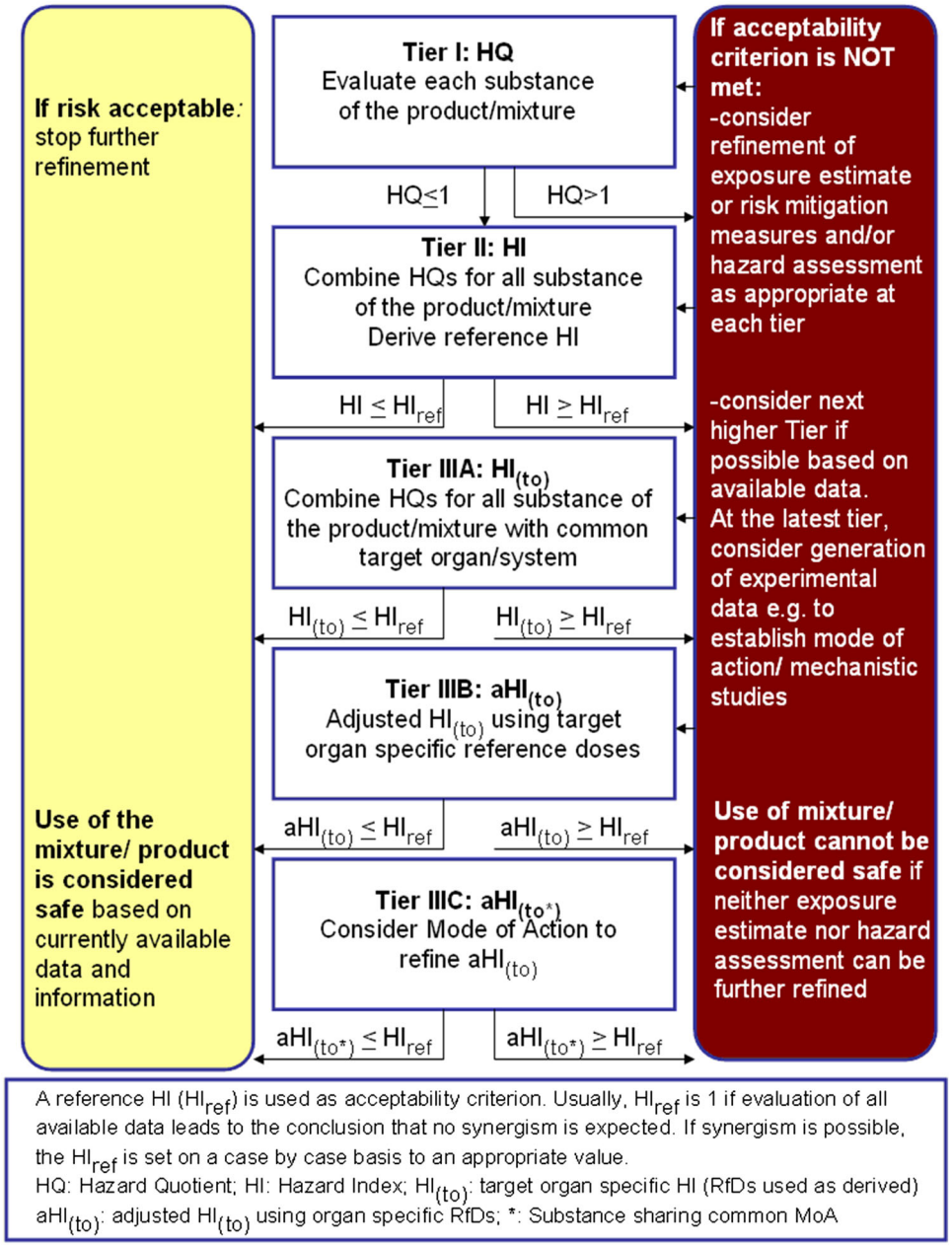

Fig. 1 Simplified overview of the assessment method: The *diagram* shows the risk assessed for each population type: primary and secondary exposure (ECHA 2013)

2. combined exposure to multiple substances by different sources
   of release(s) and/or use(s).
3. aggregated exposure to single substances from different sources
   of release(s) and/or use(s).

Irrespective of the situation, the assessment should be based on:

- the scientific state-of-the-art;
- simple concepts to allow routine application;
- tiered approaches starting with simple, conservative and deterministic exposure assumptions and, if required, continuing with refinements, e.g. by probabilistic methods if available;
- harmonised concepts which are used throughout all involved agencies/parties.

As a starting point, this paper deals with human health risk assessment from combined exposure only, while questions of aggregate exposure assessment are not covered herein. Furthermore, possible combination effects between PPP and BP on the one hand and substances falling under the scope of further regulations (pharmaceuticals, veterinary pharmaceuticals, food additives, contaminants) on the other

hand have been largely disregarded in previous concepts and will also not be covered by this BfR concept.

Employing CRA in regulatory procedures, especially when higher tier probabilistic calculations get involved, requires not only efforts by risk assessors, but also by risk managers in terms of transparent communication of the results of such assessments. To be able to base regulatory decisions on CRA, risk managers have to clearly define which protection goal is aimed for operators, consumers and other uninvolved third parties. It has to be clarified and communicated to the public which results indicate acceptability of the risk and which do not.

It is essential to develop concepts that do not lead to further data requirements concerning animal studies and that support the necessary paradigm shift in risk assessment strategies while taking on board all stakeholders including the applicants.

2 Toxicological assessment of mixtures

Humans are exposed to different chemical substances which may act independently or interact. For assessing combined effects of chemical mixtures, several approaches have been developed in recent years by different bodies, which are also applicable to human health risk assessment of PPP and BP. In the case that chemicals act independently but have a similar mode of action, dose-addition may be assumed, while for dissimilar mode of action effect-addition is considered. If interaction has to be expected, antagonism (lower effect than expected for dose addition) or synergism (higher effect than expected for dose addition) might occur.

In accordance with conclusions from the discussions on EU level (Kortenkamp et al. 2009) BfR proposes to use dose-addition as the standard concept for CRA in the first tier of a tiered approach. This concept is predictive and sufficiently conservative for chemicals with similar and dissimilar mode of action. Since information on the mode of action of active substances or SoC used in PPP or BP is often limited, cumulative assessments can not be refined by grouping for similar modes of action in these cases.

The assessment of possible cumulative effects of active substances in PPP and BP normally relies on the available toxicological studies with a single substance. Data requirements for active substances comprise an extensive set of toxicological studies (in vitro and in vivo), which normally meet the criteria of good laboratory praxis (GLP) and are conducted in accordance with internationally accepted test protocols (e.g. OECD test guidelines). Usually several dose levels are tested which are always clearly above the expected human exposure level. The principal aim of these studies is—besides recognition of critical effects—the identification of the respective NOAEL. From the most appropriate studies for the most sensitive animal species the respective toxicological reference values are derived, e.g. the Acceptable Daily Intake (ADI) covering oral long-term exposure, the A[O]EL (Acceptable [Operator] Exposure Level) for the operator, worker, bystander and resident safety and, where necessary, the Acute Reference Dose (ARfD) covering oral short-term exposure.

For assessing SoC in PPP and BP, normally only safety data sheets are available but no toxicological studies as for active substances. To fill this gap, first drafts of alternative concepts have been developed and are currently under discussion. Existing reference values from other areas of regulation, such as the occupational exposure limit value (MAK, MAC) or the Derived No Effect Level (DNEL) are applicable only to a limited extent because the information on which these reference values are based is not always assessable, the assessment was not performed by independent bodies or peer reviewed or is based on human data.

Cumulative assessments assuming dose-addition are normally based on the toxicological data for the single substances and appropriate calculation models. The BfR concept is making use of the following, internationally acknowledged standards:

- Hazard quotient, HQ (ratio of exposure and toxicological reference value derived for each single substance in the product/mixture).
- Hazard index, HI [without and with consideration of "Cumulative Assessment Groups" (CAG)]
- Reference point index, RI (consideration of target or effect specific NOAEL's).
- Relative potency factors (RPF).

The calculations use internationally agreed toxicological reference values or benchmark dose/NOAEL values mainly from animal studies and compare them to exposure estimates (see Sects. 3 and 4 for further details on exposure). The resulting exposure/toxicity ratios (HQs) for all active substances in the mixture and those SoC for which a reference value can be derived are then added. If the sum (i.e. HI) is below or equal to 1, the cumulative risk is deemed being acceptable. However, it should be noted that this approach is only justified if dose-addition or

effect-addition applies. Especially, possible synergistic effects cannot be appropriately covered.

If the sum of the ratios is higher than 1 indicating the possibility of an unacceptable risk with respect to human health, a refined assessment is necessary. This may be achieved by restricting it to those compounds included in one CAG, because these compounds are much more likely to exhibit similar effects. CAGs may be based on common chemical structures, common target organs, common toxicological effects or common mechanisms of action. The definition of CAGs is currently ongoing on European level and is urgently needed for adequate and harmonized CRA for PPP and BP. In 2013, EFSA published a Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups and proposed CAGs for the thyroid and nervous system, i.e. CAGs based on common target organs (EFSA 2013a). Agreement on further CAGs (e.g. liver, reproductive system) is expected in 2015.

US EPA already defined CAGs for organophosphates, *N*-methyl carbamates, pyrethroids, 1,3,5-triazines and chloroacetanilides based on same mechanism of action and common chemical structures (available at http://www.epa.gov/oppsrrd1/cumulative).

Having in mind that refinements should not be restricted to either the toxicity or the exposure part of the CRA, but should in the first place be applied to that part which is easier to refine (depending on availability of data and the complexity of the refinement work to be done), BfR proposes the following tiered approach of assessments starting with cumulative assessment in Tier II in accordance with the scheme proposed by ECHA (2013) which is displayed in Fig. 1:

- *Tier I* HQ for each substance under consideration (no combined risk assessment).
- *Tier II* HI for all substances under consideration (without taking into account CAGs or mode/mechanism of action).
- *Tier IIIA* $HI_{(to)}$ for all substances under consideration with a common target organ/system (i.e. attributed to the same CAG or the same sub-group of a CAG, if appropriate).
- *Tier IIIB* $aHI_{(to)}$ ("adjusted Hazard Index") for all substances under consideration with a common target organ/system, calculated by utilisation of target-specific reference doses (NOAEL's and safety factor(s)).
- *Tier IIIC* $aHI_{(to^*)}$ for all substances under consideration with a common target organ/system and a common mode of action, calculated by taking into account the relative potency of substances.

For the time being, BfR decided not to develop specific models based on effect-addition and to base its concept for CRA on dose-addition only. At this stage, only Tier II evaluations can be used in regulatory procedures while refinements in Tier III can only be applied to a limited extent because only few CAGs are currently available. Regarding Tier IIIC, a standardized methodology to derive relative potency factors for a CAG has to be developed.

3 Cumulative risk assessment with respect to application safety

3.1 General considerations

CRA considers different substances during the same exposure period. All active substances and SoC operators and other unintentionally involved people may be simultaneously exposed to, have to be taken into consideration for PPP and BP. SoC means any substance which has an inherent capacity to cause an adverse effect on humans and is present or is produced in a product in sufficient concentration that the occurrence of such an effect is likely. SoC are identified according to the corresponding regulations and guidance documents for BP and PPP. For the time being, CRA is restricted to individual products or intended mixtures of products. Established exposure models will be used for the exposure assessment.

3.2 Consideration of cumulative risk assessment in the context of PPP and BP authorisation

The CRA based on the HI and further consideration of CAGs follows a tiered approach. Appropriate reference values must be available for each tier. In Tier II deterministic point estimates and worst-case assumptions might be included. However, if this results in exposure estimates exceeding the reference value, further refinement using more realistic toxicological data or exposure patterns is required. Further risk mitigation measures can be considered as well. If the cumulative exposure results in a non-acceptable risk, a corresponding exposure study with the product may overrule this assessment. In general, a HI below or equal to 1 (default reference HI) is acceptable. However, if synergistic effects are

expected, this value should be adapted on a case-by-case basis.

- *Tier I* HQ for each relevant substance contained in the PPP or BP under consideration (single substance basis, no CRA).
  Tier I comprises the evaluation of each substance alone. The HQ of each relevant substance has to be ≤1. If a non-acceptable risk (i.e. HQ >1) is identified for at least one substance even under consideration of all possible risk mitigation measures or exposure refinements, the assessment is terminated.
- *Tier II* HI for all relevant substances contained in the PPP or BP under consideration (without taking into account CAGs).
  The HI is calculated by summing up the HQs of all relevant components. If the HI is ≤1, the risk is acceptable; if the HI is >1, proceeding to Tier III is required. Alternatively, further risk mitigation measures or a refinement of the exposure assessment might be possible.
- *Tier IIIA* $HI_{(to)}$ for all those relevant substances contained in the PPP or BP under consideration with a common target organ/system (i.e. attributed to the same CAG).
  The $HI_{(to)}$ is calculated by combining HQs for all substances with a common target organ or system without the use of target-specific reference values. If the $HI_{(to)}$ is ≤1, the risk is acceptable. If the $HI_{(to)}$ is >1, refinement according to Tier IIIB or IIIC might be possible. Alternatively, further risk mitigation measures or a refinement of the exposure assessment might be possible.
- *Tier IIIB* $aHI_{(to)}$, i.e. adjusted HI for all those relevant substances contained in the PPP or BP under consideration with a common target organ/system (attributed to the same CAG), calculated by utilisation of target-specific reference values.
  The $aHI_{(to)}$ is calculated by combining target-specific reference values if a non-acceptable risk has been identified in Tier IIIA. If the $aHI_{(to)}$ is ≤1, the risk is acceptable. If not, further risk mitigation measures or a refinement of the exposure assessment might be possible.
- *Tier IIIC* $aHI_{(to^{+})}$, i.e. adjusted HI for all those relevant substances contained in the PPP or BP under consideration with a common target organ/system and a common mode of action, calculated by taking into account the relative potency of substances (relative potency factors).

4 Cumulative risk assessment with respect to residues in food

4.1 General considerations

Consumers are normally exposed to a complex pattern of multiple residues with low individual levels which are consumed in a broad range of food items.

Several methods are available for cumulative exposure assessment in food. They differ by their degree of complexity. Methods used range from simple deterministic calculation models (e.g. EFSA 2013b) to laborious probabilistic models (e.g. EFSA 2009, 2012).

Concerning the toxicological assessment of cumulative residues, a tiered approach is proposed which is detailed in Sect. 4.2.

4.2 Consideration of cumulative risk assessment in the context of PPP and BP authorisation

4.2.1 Acute cumulative risk assessment related to the GAP(s) under consideration

As far as acute (short-term) exposure is concerned, it is justified to focus the cumulative exposure assessment on those substances which are contained in the PPP or BP under consideration, since consumers are likely to get exposed to residues of these substances simultaneously via treated food. Exposure to further active substances resulting from other applications or from differently treated other food items, which are all consumed within a short time period (i.e. within 24 h) are not taken into account.

- *Tier I* HQ for each relevant substance contained in the PPP or BP under consideration and for which an ARfD has been allocated (single substance basis; no CRA).
  For all active substances and/or safeners in a PPP, which are acutely toxic, the HQ is calculated. This is done for each substance by performing a deterministic IESTI calculation [international estimated short-term intake (IESTI); point estimate] with the calculation models EFSA PRIMo [Pesticide Residue Intake Model (PRIMo), EFSA 2008] and NVS II (German consumption model, BfR 2011) and based on the respective ARfD of the substance. If a non-acceptable risk is identified for at least one substance, the assessment is terminated.
- *Tier II* HI for all relevant substances contained in the PPP or BP under consideration and for which

an ARfD has been allocated (without taking into account CAGs).
Summing up the HQs obtained in Tier I results in the HI as already described in Sect. 3.2 for operators, workers, bystanders and residents.
If Tier II results in a HI >1, the assessment needs to be refined. This is done in Tier IIIA by restricting the cumulative assessment to those active substances which belong to the same CAG because they act on a common target organ/system.

- *Tier IIIA* $HI_{(to)}$ for all those relevant substances contained in the PPP or BP under consideration, for which an ARfD has been allocated and which act on a common target organ/system (i.e. attributed to the same CAG).
  If Tier IIIA still results in a $HI_{(to)}$ >1, Tier IIIB provides the possibility to derive ARfDs for specific target organs and select the appropriate ARfD which is then used to calculate the so called $aHI_{(to)}$.
- *Tier IIIB* $aHI_{(to)}$, i.e. adjusted HI for all those relevant substances contained in the PPP or BP under consideration, for which an ARfD has been allocated and which act on a common target organ/system (attributed to the same CAG), calculated by utilisation of target-specific reference values.
- *Tier IIIC* $aHI_{(to^*)}$, i.e. adjusted HI for all those relevant substances contained in the PPP or BP under consideration, for which an ARfD has been allocated and which act on a common target organ/system with a common mode of action, calculated by taking into account the relative potency of substances (relative potency factors).
  If Tier IIIC finally results in a $aHI_{(to^*)}$ >1, a health risk for consumers cannot be excluded and authorization of the use(s) under evaluation is rejected.

Only the specific contribution of the PPP or BP under evaluation to the overall short-term intake is considered, though consumers might get exposed to further residues of the same active substances or to residues of other active substances from the same CAG with their food during the time period relevant for short-term assessment (normally 24 h). However, from typical detection frequencies and residue levels in monitoring programmes it is obvious that a worst case exposure as high as that one considered in the assessment (based on large portion, highest residue from supervised trials reflecting the most critical GAP, variability factor etc.) is extremely unlikely to occur for more than one substance at a time. Restricting the acute cumulative assessment to residues from the use(s) under consideration therefore seems to be sufficiently conservative. The efforts needed to achieve more realistic exposure calculations by applying laborious, non-routine probabilistic models are not counterbalanced by the additional gain of information.

4.2.2 Chronic cumulative risk assessment

The use of the PPP or BP under consideration normally provides only a minor contribution to the overall chronic exposure of consumers to residues of the respective active substances and of substances belonging to the concerned CAGs. Summing up hazard quotients (on basis of the individual ADI values) for the active substances contained in the PPP or BP as for the acute cumulative assessment is therefore not recommended.

The calculation parameters currently used in chronic risk assessment for a single substance reflect a very conservative scenario: it is assumed that all food items contain residues of the active substance, though this is nearly never observed in practice. For those food commodities which are derived from the uses under consideration, median residue levels (STMR/STMR-P) obtained in supervised field trials are used, while for all other food commodities residues at MRL level are assumed. The exposure is then compared to the ADI value. If required, further refinement is possible by replacing MRLs by further STMR/STMR-P values, which are obtained from the residue trials underlying the MRLs.

Having the conservative calculation scenario for each single active substance in mind, the chronic consumer risk assessment in the framework of PPP or BP authorization is considered as being sufficiently conservative and covering also possible cumulative effects.

In principle, a more realistic assessment of the overall chronic exposure of consumers to residues of a specific pesticide or pesticides of a specific CAG requires the use of statistical programmes which are able to handle distributions of monitoring and consumption data (e.g. Monte Carlo simulation). Representative monitoring data are needed to calculate realistic background concentrations. On European level, the monitoring database is currently under development. The EU multi-annual control programme according to Art. 29 of Reg. (EC) No. 396/2005 (monitoring) is running already for a couple of years now and the largest part of the envisaged

food basket has already been covered. However, preparation of data for the use in distribution-based calculation programmes is still ongoing.

One important issue in deriving realistic background concentrations is the handling of "non-detects" (ND), i.e. of the (usually large) number of monitoring samples, in which residues of the respective pesticide were below the limit of quantification (LOQ). Among others, the following options (or combinations thereof) are currently discussed:

- Use the number of the LOQ for a ND sample.
- Use the number of ½ LOQ for a ND sample.
- Treat ND samples as being zero.

The last option (i.e., to treat ND samples as being zero) could only be used for those commodities which are known to have never been treated with the pesticide in question. However, the worldwide application pattern of pesticides is normally not known.

As the European programme, the German food monitoring relies on a representative food basket. The German representative food basket has been composed on the basis of national consumption surveys. The national multi-annual monitoring programme is intended to cover the food basket once within 6 years. Sampling frequencies differ between foods. The first monitoring cycle (after having restructured the German monitoring to cover needs of consumer risk assessment) will be complete in 2014. As soon as all these data are available, BfR intends to calculate the background concentration for German consumers. As already mentioned above, the question of how to consider non-detects is of key importance for the results.

In principle, chronic CRA in the framework of an authorisation procedure of a PPP could be conducted as follows: for all uses under consideration (i.e., for all pesticide/commodity combinations under consideration) the respective STMR value is used, while for all other commodities and all other pesticides belonging to the CAG under consideration the background level is used. The calculation would be done with a distribution-based programme (e.g. Monte Carlo simulation). However, having in mind that Monte Carlo simulations require huge amounts of data and time, efforts and gain in knowledge should be balanced. Especially the evaluation of minor uses not considerably contributing to the overall food intake might not need a full cumulative assessment, at least not if a large number of more important uses are already authorised for the same active substance or other substances belonging to the respective CAG.

As already mentioned above, chronic CRA is not expected to reveal risks which have been overlooked in the past and is expected to be dispensable in the context of a PPP or BP evaluation. Based on current knowledge BfR thinks it is justified to review the chronic CRA for each active substance and each CAG regularly after a 6 years monitoring cycle has been completed, but not in the context of each PPP or BP evaluation. To check the validity of this assumption, BfR will conduct some case studies as soon as all required monitoring data from the German (and later on also from the EU) monitoring programmes are available.

4.3 Consideration of cumulative risk assessment in the context of evaluating monitoring data

4.3.1 Deriving background levels for consumer exposure

One of the intentions of the German food monitoring programme is to derive realistic levels of pesticide residues to which German consumers are exposed. As described above, the German food monitoring is based on a representative food basket, which is covered once every 6 years, with the first monitoring cycle being complete in 2014 and providing for the first time all data needed to calculate realistic background concentrations for consumers. Biocidal active substances are not yet part of this monitoring. Such background levels are fed into distribution-based calculation programmes to assess the chronic cumulative exposure of consumers. The results are strongly influenced by the still pending decision on how to include non-detects in the calculation (see above). The largest influence is expected for pesticides with only few authorized uses on the one hand and a low ADI on the other hand.

BfR intends to derive background concentrations for each active substance and each CAG which is available at that time, when data from the first monitoring cycle are complete.

4.3.2 Assessment of individual samples

Since residues found in individual food samples are not assumed to be generally present at these levels in consumed foods, only an acute risk assessment is conducted.

- *Tier I* HQ for each substance which is detected in the sample at levels ≥LOQ and for which an ARfD has been allocated (single substance basis; no CRA).

For all acutely toxic substances found in the sample the HQ is calculated. This is done for each substance by performing a deterministic IESTI calculation with the calculation models EFSA PRIMo and NVS II and based on the respective ARfD of the substance. If a non-acceptable risk is identified for at least one substance in the sample, the assessment is terminated.

- *Tier II* HI for all substances which are detected in the sample at levels ≥LOQ and for which an ARfD has been allocated (without taking into account CAGs).
  Summing up the HQs results in the HI as already described in Sects. 3.2 and 4.1.
  If Tier II results in a HI >1, the assessment needs to be refined. This is done in Tier IIIA by restricting the cumulative assessment to only those active substances in the sample, which can be attributed to the same CAG because they act on a common target organ/system.
- *Tier IIIA* $HI_{(to)}$ for all those substances which are detected in the sample at levels ≥LOQ, for which an ARfD has been allocated and which act on a common target organ/system (i.e., attributed to the same CAG).
  If Tier IIIA still results in a $HI_{(to)}$ >1, Tier IIIB provides the possibility to derive specific ARfDs for specific target organs and select the appropriate ARfD which is then used to calculate the $aHI_{(to)}$.
- *Tier IIIB* $aHI_{(to)}$, i.e. adjusted HI for all those substances which are detected in the sample at levels ≥LOQ, for which an ARfD has been allocated and which act on a common target organ/system (i.e. attributed to the same CAG), calculated by utilisation of target-specific reference values.
- *Tier IIIC* $aHI_{(to^*)}$, i.e. adjusted HI for all those substances which are detected in the sample at levels ≥LOQ, for which an ARfD has been allocated and which act on a common target organ/system with a common mode of action, calculated by taking into account the relative potency of substances (relative potency factors).
  If Tier IIIC finally results in a $aHI_{(to^*)}$ >1, a health risk for consumers cannot be excluded.

4.4 Consideration of cumulative risk assessment in the context of MRL setting

It is proposed that the Evaluating Member State (EMS) for an MRL according to articles 10–12 of Regulation (EC) No. 396/2005 continues to deliver MRL proposals only for the commodity/pesticide combination(s) in question without consideration of CAGs and background levels. EFSA should then in a second step additionally consider background levels for European consumer groups for the respective CAGs and on this basis re-evaluate the safety of all MRLs proposed. The proposed role of EFSA in this process results from the fact that EFSA would collect and evaluate European monitoring data submitted in the framework of the EU multi-annual control programmes. Moreover, EFSA has an overview of the consumption data reported by EU MS and—in the context of Art. 12 evaluations—collects data on all GAPs authorized in EU MS and on further aspects of the assessment (such as processing factors or conversion factors).

If MS and EFSA would agree to the proposed two-step procedure, no changes would result for the EMS assessments.

5 Concluding remarks

New approaches to safety testing, including CRA, require new strategies to stringent but flexible evaluation of the suitability and performance of methods (Leist et al. 2014). The paper is intended to promote further discussions of risk assessors, risk managers as well as stakeholders in this area on the applicability of CRA in routine authorisation procedures for PPP and BP and to encourage the flexible use of strategies in CRA.

Against this background, the authorities responsible for the risk assessment for humans and the environment and for the risk management of PPP in Germany, namely the Federal Office of Consumer Protection and Food Safety (BVL), the BfR and the UBA, developed a German Guidance on CRA in order to provide (1) the current scientific understanding of the regulatory requirements, (2) the available options for implementation as well as (3) guidance on the current practice in CRA in Germany. An overview of the German Guidance is given in "Assessment of the risks resulting from exposure to pesticide mixtures and multiple pesticide residues to humans and wildlife" (Solecki et al. 2014). It is intended to inform interested experts from industry, academia, regulatory bodies and NGOs about the current status of the implementation of mixture risk assessment from the perspectives of human health risk assessment, environmental risk assessment and risk management, which are interrelated elements for the implementation of cumulative

aspects in regulatory decisions in Germany. The present publication is the human health part of the German Guidance. The part related to environmental risk assessment is published elsewhere (Frische et al. 2014).

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