European Food Safety Authority

Relevance of dissimilar mode of action for cumulative risk assessment

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Introduction: EFSA Opinion on relevance of dissimilar MoA

Mandate issued by EFSA:

- The EFSA Panel on Plant Protection Products and their Residues (PPR Panel) was asked to prepare a Scientific Opinion:

  Scientific Opinion on the relevance of dissimilar mode of action and its appropriate application for cumulative risk assessment of pesticides residues in food.

- The Opinion was published in December 2013:

  http://www.efsa.europa.eu/de/efsajournal/pub/3472.htm

Introduction: EFSA Opinion on relevance of dissimilar MoA

The Opinion on relevance of dissimilar mode of action…

- represents a further step in EFSA´s ongoing activities concerning cumulative risk assessment (CRA) of pesticide residues in food;

- was preceded by three Opinions (EFSA 2008, 2009, 2013) that dealt with the development of methodology for the purpose of performing CRA for pesticide residues in food;

- complements EFSA´s previous work in developing a methodology for identifying and grouping pesticides that exhibit similar toxicological properties in a specific organ or system:

Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups (CAGs) on the basis of their toxicological profile (EFSA 2013).

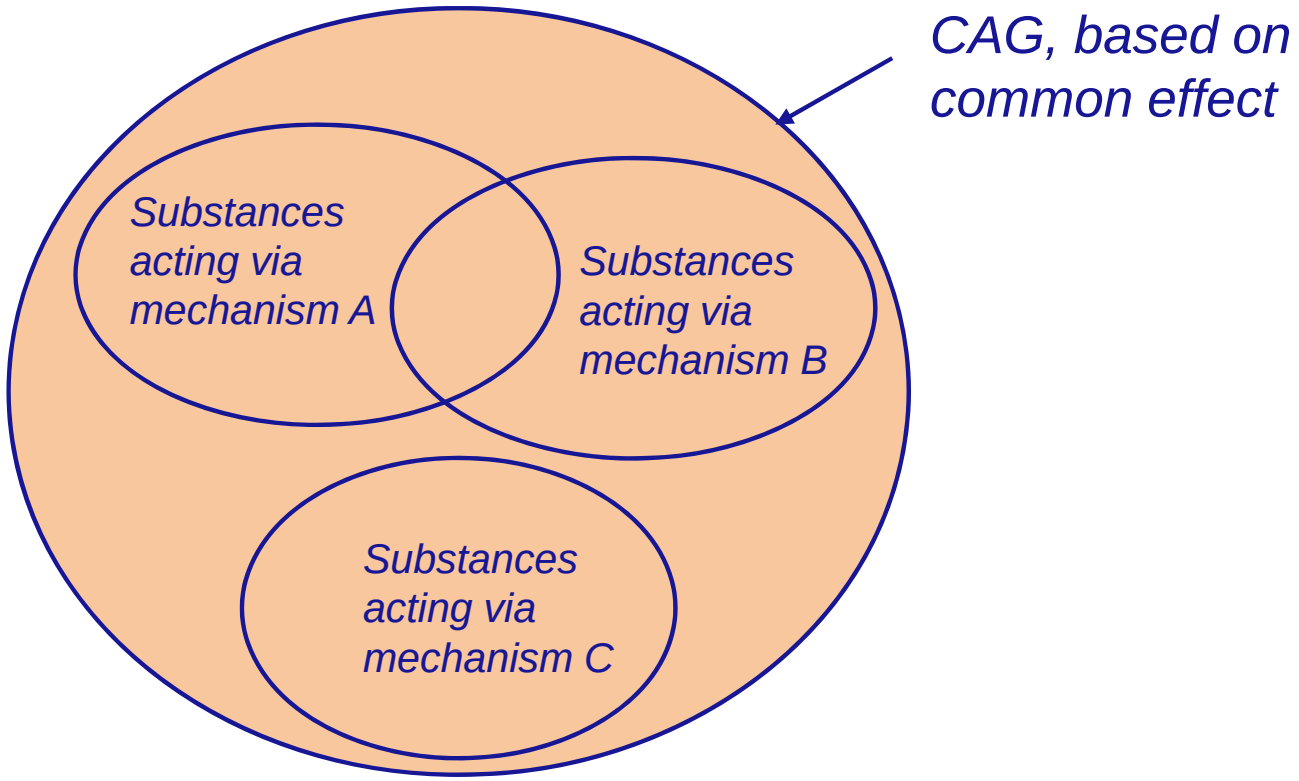
Previous Opinion on CAGs, EFSA 2013

Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile (EFSA 2013):

- For substances leading to a common specific effect, often modes/mechanisms of action are not known.
- Different modes/mechanisms of action may contribute to a common outcome.
- Thus, methodology of the CAG Opinion follows a pheno-menological approach, based on organ or system toxicity.
- **All pesticides causing a common specific (adverse) effect are included within a cumulative assessment group (CAG).**

Previous Opinion on CAGs, EFSA 2013

➢ CAGs based on phenomenological effects may thus include substances acting via different modes/mechanisms of action, but contributing to a common adverse outcome.



Previous Opinion on CAGs, EFSA 2013

- Proposal on default application of the concept of dose/concentration addition (DA) for the assessment of cumulative risks for a CAG.

- Questions concerning default use of DA:
  - Are there conditions where application of DA to pesticides that exhibit toxicity through dissimilar modes of action would lead to an underestimation of cumulative effects?

  - Which alternative methodology would be appropriate in such cases?

Scope of Opinion on relevance of dissimilar MoA

- Assessment of the relevance of dissimilar mode of action for combination effects and CRA

- Evaluation of the **applicability of the existing methods** for predicting mixture toxicity for substances acting by different modes of action:
  - Methods based on the concept of dose addition (DA)
  - Methods based on the concept of independent action (IA)

- Identification which methods need to be considered for CRA

Scope of Opinion on relevance of dissimilar MoA

- Focusing on **hazard assessment** aspect of CRA
- Restriction to pesticide combinations with dissimilar modes of action that produce **a common specific adverse effect** on the same target organ/system
- Not dealing with substances eliciting toxic effects in different organs/systems
- Not focusing on the topic of synergisms

Preparatory project

- Report on supporting project commissioned by EFSA was published in January 2012:

Investigation of the state of the science on combined actions of chemicals in food through dissimilar modes of action and proposal for science-based approach for performing related cumulative risk assessment

http://www.efsa.europa.eu/de/supporting/pub/232e.htm

Relevance of dissimilar MoA for combination effects

- There is good experimental evidence that combination effects can arise from co-exposure to chemicals that produce common adverse outcomes through different mechanisms and modes of action.
  - Examples: Faust et al., 2003; Crofton et al., 2005; Rider et al., 2008; Rider et al., 2010; Christiansen et al., 2009; Hass et al., 2012; Ermler et al., 2013b

- There are cases in which combinations of substances acting by different mechanisms, and present at individual dose/concentration levels around or below their NOAELs, produced joint effects.
  - Examples: Christiansen et al., 2009; Hass et al., 2012

- **The PPR Panel concludes that dissimilar modes of action are relevant to the assessment of cumulative risks from pesticide residues in food.**

Dose/concentration addition (DA)

- Concept based on the assumption that all components of a mixture behave as if they were simple dilutions of one another.

- Concept implies that every toxicant in the mixture contributes to the combination effect in proportion to its dose and individual potency.

$$\sum_{i=1}^{n} \frac{c_i}{ECx_i} = 1$$

- Empirical evidence for validity in mammalian systems:
  - Mammalian *in vivo* studies for which mixture effects may be approximated by DA, e. g. Crofton et al., 2005; Rider et al., 2008; Rider et al., 2010; Hass et al., 2012

- Several CRA methods in practical use that are derived from the concept of dose addition (e. g. Hazard Index-, Point of Departure Index -, Toxic Equivalency Factor approach)

Independent action (IA) and response addition

Independent action concept:

➢ Assumes that a combination effect can be calculated from the responses of the individual mixture components (response addition) by following the statistical concept of independent random events.

$$E(c_{mixture}) = 1 - \prod_{i=1}^{n} (1 - E(c_i))$$

➢ Applicable for simultaneous exposure to several chemicals if they act via **strictly dissimilar independent modes of action**

Independent action (IA): Mode of action considerations

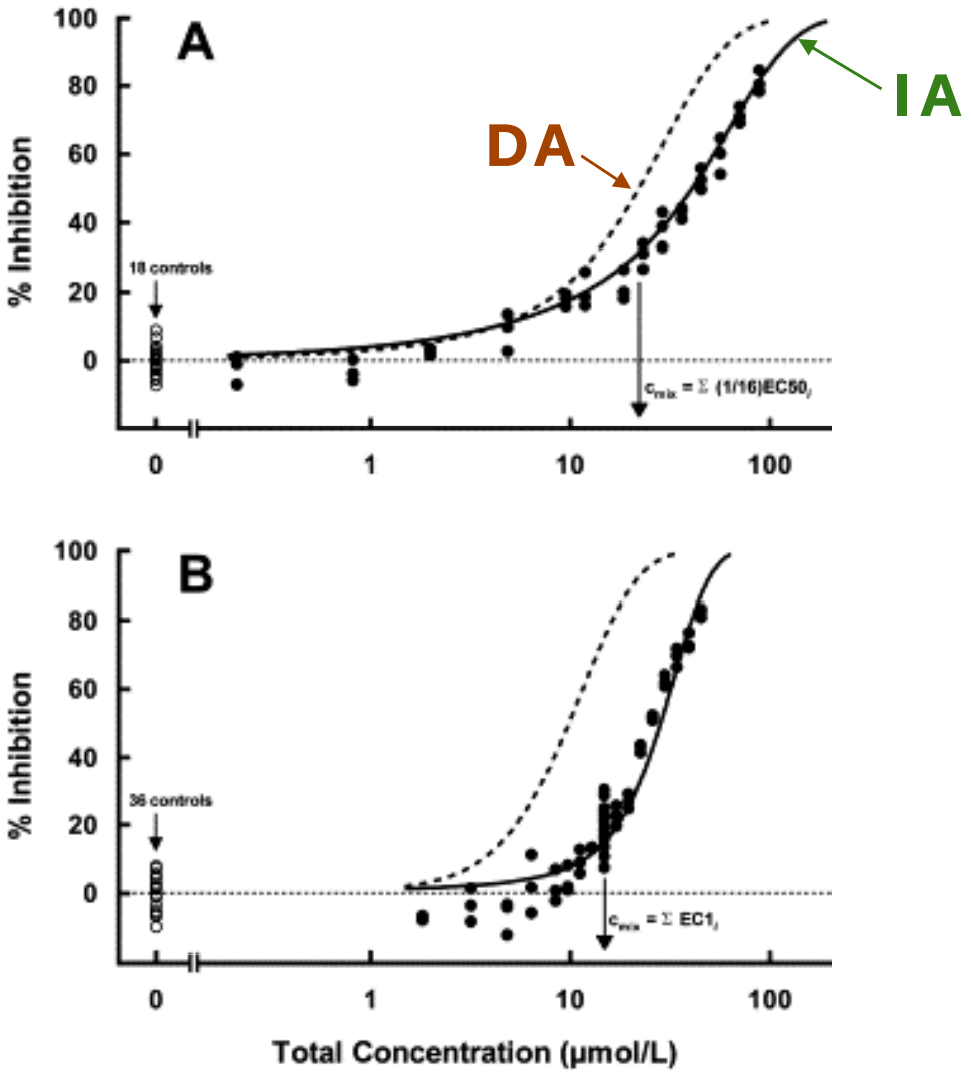
- Use of IA as an assessment concept for combination effects requires knowledge or demonstration that modes of action of individual substances in a mixture are acting in a **strictly independent manner**, a condition rarely met in practice.

- Independence of action is not necessarily equivalent to dissimilar action.

- Widely used definitions of mode of action do not define when a mode is sufficiently separate or distinct to support an assessment in favour of using IA.

Independent action (IA) and response addition

➢ To date, applicability of IA for predicting effects of mixtures composed of dissimilarly acting chemicals has only been demonstrated for bacteria and unicellular algae.



Example:
Inhibition of reproduction (population growth) of *Scenedemus vacuolatus* by mixture of 16 dissimilarly acting substances
(*From: Faust et al., Aquatic Toxicology 63, 2003*)

Independent action (IA) and response addition

- Even in such cases (with relevance to ecotoxicity) for which IA provided accurate predictions, DA yielded the more conservative prediction.

- **No example of the validity of IA with mammals, mammalian cells or with multi-cellular organisms has been identified to date.**

- **These considerations support default use of DA for the approximation of mixture effects.**

Difficulties concerning application of IA concept in CRA

- No established method for CRA based on independent action

- Pragmatic assumption that mixture effects will not arise if all components are below their individual effect levels is difficult to verify, due to difficulties in defining doses/concentrations without effect.

- Use of IA puts demands on data quality of required input values that cannot be met in practice. Application of response addition method for predictions of toxicity requires detailed descriptions of effects, also in the low dose range, that are rarely available.

Conservatism of DA as compared to IA

- No case documented in the scientific literature where IA provided more conservative predictions of combination effects than DA, and where at the same time IA was also more accurate

- In tests and systems with relevance to ecotoxicity: More conservative mixture toxicity estimate usually provided by DA

- Studies involving mammalian data: More conservative predictions by DA have often been observed.

- Empirical evidence and results of mathematical simulation studies indicate that quantitative differences under realistic exposure conditions between predicted mixture effects derived from DA or IA are likely to be small.

- **The PPR Panel concludes that DA is a sufficiently conservative default approach to protect consumers´ health.**

Uncertainties

- Uncertainty as to whether examples for applicability of IA exist for mammalian systems or multicellular organisms
  - Applicability of IA to mammalian systems has not been demonstrated to date.

- Uncertainty as to whether IA tends to underestimate combination effects for endpoints relevant to mammalian toxicity

Uncertainties

- Lack of data on mode of action of pesticide active substances concerning health effects; resulting difficulties in deciding whether substances are acting in a strictly independent manner

- Uncertainty regarding the occurrence of interactions (antagonisms or synergisms)
  - Current evidence indicates that synergisms are less likely to occur at low doses/concentrations corresponding to dietary exposure to mixtures of pesticide residues in food.

Conclusions

- Distinctions between similar and dissimilar mode of action are fraught with conceptual and practical difficulties and are of limited relevance in cumulative risk assessment practice.

- **Pesticides that produce common adverse outcomes on the same target organ/system should be grouped together in cumulative assessment groups (CAGs).**

- **Their combined effects should be assessed by using the concept of dose addition as a pragmatic and conservative default approach for the purpose of assessing cumulative risk in relation to MRL setting or risk assessment of chemical mixtures in practice.**

Impact of grouping approach...

- Some of the cumulative assessment groups obtained by using a phenomenological approach may contain a large number of pesticides.

- Even with a mixture of many pesticides affecting the same target organ/system, the majority of them might not contribute significantly to a given combination effect because….
  - exposure is very low and/or
  - potency in relation to the considered effect is weak.

- Cumulative risks from actual exposure are likely to be driven mainly by a few pesticides in a mixture.

Recommendations

- More research required in mammalian systems to investigate the applicability of independent action

- More knowledge required on distribution of slopes of dose response curves in mammalian systems to distinguish cases for which IA might provide the more conservative prediction

- Key knowledge on mode/mechanism of action with relevance to CRA should be enriched.
  - More research required on characterising adverse outcome pathways

- More research required on the possibility of toxicokinetic and toxicodynamic interactions, in order to better define determinants of interactions, e. g. of synergisms.