Aktivitäten der EFSA zu toxikologischen Grundlagen für die kumulative Risikobewertung

Hans Steinkellner, Pesticides Unit

Mehrfachrückstände von Pestiziden in Lebensmitteln -
Von der wissenschaftlichen Grundlagenbewertung zur regulatorischen Umsetzung, Bundesinstitut für Risikobewertung, 19. März 2013, Berlin

Legislative background for CRA

Regulation EC 396/2005 on maximum residue levels (MRLs)

Art 14 (Decision on applications concerning MRLs)

" …account shall be taken of… 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…"

Whereas (6)

"It is also important to carry out further work to develop a methodology to take into account cumulative and synergistic effects. In view of human exposure to combinations of active substances and their possible aggregate and synergistic effects on human health, MRLs should be set after consultation of the European Food Safety Authority…"

EFSA Colloquium on CRA

2006 The EFSA's 7th Scientific Colloquium Report - Cumulative Risk Assessment of Pesticides to Human Health: The Way Forward

http://www.efsa.europa.eu/en/supporting/pub/117e.htm

- **develop methodology for CRA on basis of existing approaches**
- **develop criteria for grouping substances**
- **consider also dissimilar MoA**
- **develop guidance for probabilistic exposure modeling**
- **PPR Panel to prepare opinion taking into account recommendations**

PPR Opinion on CRA 2008

2008 PPR Scientific Opinion 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
http://www.efsa.europa.eu/en/efsajournal/pub/705.htm

Recommendations/conclusions

- **Dose addition of relevance for CRA for dietary residues** (interaction and response addition not considered)
- **Establishment of CAGs:**

  1. Preliminary inclusion in CAG (based on chemical structure, pesticidal MEA, MOA/MEA of mammalian toxicity or common toxic effect)

  2. Definitely identify substances with common specific effect

  3. Refine groupings by using different MoA/MeA

  - **Tiered approach for hazard assessment:**

    Hazard index (HI), adjusted hazard index (aHI), Reference Point Index (RfPI) Relative Potency Factor (RPF), PBTK models

- **Tiered approach for exposure assessment:**
  - Deterministic (MRLs or values from intake assessments)
  - Probabilistic (calculated values)

PPR Opinion on CRA 2009

European Food Safety Authority

2009 PPR Scientific Opinion for a selected group of pesticides from the triazole group to test possible methodologies to assess cumulative effects from exposure through food from these pesticides on human health
http://www.efsa.europa.eu/en/efsajournal/pub/1167.htm

- **Scenarios:** Acute (cranial malformations)/Chronic (liver toxicity)
- **Deterministic and probabilistic exposure assessment**
- **Recommendations:** - Start with a CAG as refined as data allow
  - Establish CAGs for pesticides on a EU level
  - Restrict exposure assessment to one deterministic and one probabilistic tier
  - Develop guidance for exposure assessment

PPR Guidance probabilistic exposure

2012 **PPR guidance on the use of probabilistic methodology for modelling dietary exposure to pesticide residues**

http://www.efsa.europa.eu/en/efsajournal/pub/2839.htm

- Covers basic assessments
- Methods for quantification of major sources of variability
- Definition of appropriate scenarios (MRL setting/authorisation and actual exposure)
- Evaluation of uncertainties
- Case studies illustrating approaches

PPR opinion CAGs

<u>2013</u> Scientific opinion on the identification of pesticides to be included in cumulative assessment groups (CAGs) on the basis of their toxicological profile

(mandate received October 2009, (extended) deadline for adoption: 30 April 2013)

Preparatory project I

2012 Art. 36 Grant Identification of Cumulative Assessment Groups of Pesticides (launched already 2009)
http://www.efsa.europa.eu/en/supporting/pub/269e.htm

- Data collection and evaluation for a.s. included in Annex 1 to Dir 91/414 until 31 May 2009
- Identification of effects (not) relevant for CRA
- Collection of mechanistic information
- Preparation of a data base

Preparatory project I – DTU report

efsa
European Food Safety Authority

Summary :

- **224 a.s. (of 344) considered as relevant for CAGs**
- **Grouping approach with different levels of refinement:**

  CAG Level 1 Organ system affected

  CAG Level 2 Specific effect

  CAG Level 3 Mode of action

  CAG Level 4 Mechanism of action

- **CAGs proposed for:**

  adrenal gland, bone marrow, bones / skeleton, cardiovascular system, eye, gallbladder, haematological system, kidney, liver, muscles, nervous system, parathyroid gland, reproductive and developmental toxicity spleen, thyroid gland, urinary bladder

- **No CAGs proposed for:**

  gastrointestinal tract, immune system, lung, lymph node, pancreas, pituitary gland, salivary gland, skin, thymus

Supporting project II

<u>2013</u> Toxicological data analysis to support grouping of pesticide active substances for cumulative risk assessment of effects on liver, on the nervous system and on reproduction and development

- Data collection to consolidate parts of DTU Report
- Active substances identified as having relevant effects by DTU + 63 additional active substances not considered

Risk management issues

In 2011 DG SANCO has given formal advice to EFSA on a series of risk management issues related to implementation of cumulative risk assessment for pesticides

PPR WG on Cumulative Assessment Groups

- **Development of a methodology building on:**
  - Previous PPR opinions
  - DTU report
  - Recommendations on risk management elements from DG SANCO
- **Consolidation of data collection/evaluation and grouping from DTU + evaluation of additional substances 63 substances approved until 31 12 2011** (e.g. adrenals, eye, thyroid, urinary bladder, cardiovascular effects, muscle, parathyroid, bones, haematological system, kidney)
- **Establishment of cumulative assessment groups**

Next steps

- **Establishment of CAGs for all organs/effects taking into account work already carried out** (consolidated data collections and hazard identification/characterisation for eye, adrenals, liver effects, effects on reproduction and development)

- **Inclusion of substances detected as residues in monitoring programmes for grouping**

- **Inclusion of substances approved since 1 January 2012**

- **Development of an overall robust and comprehensive framework for CRA of pesticide residues**

efsa
European Food Safety Authority

Members of the PPR WG on Cumulative Assesment Groups

Susanne Hougaard Bennekou (Danish EPA) - Chair

Karen Hirsch-Ernst (BfR)

Alberto Mantovani (ISS, Rome)

Antonio Hernandez Jerez (Univ of Granada)

Andreas Kortenkamp (Brunel Univ London)

Roland Solecki (BfR)

PPR opinion Relevance of dissimilar MoA

PPR Scientific opinion on the relevance of dissimilar mode of action (response addition) and its appropriate application for cumulative risk assessment of pesticides in food

(current deadline Dec 2013)

- Procurement contract **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 (published January 2012)**

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

➢ Final report suggests that the use of approaches for dose addition would cover response addition

Dankeschön

und… Alles Gute!