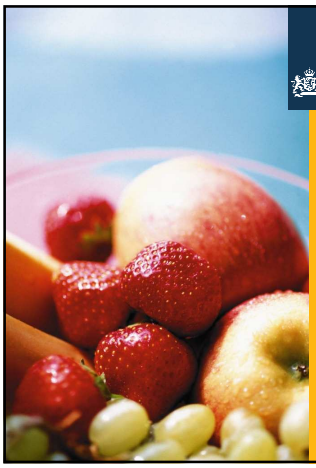

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Cumulative risk assessment of pesticide residues in food

Legal framework and state of affairs

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18 June 2012

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Content

- Introduction
- Hazard assessment
- Exposure assessment
- Risk assessment; tiered approach
- Next steps

Regulation EC 396/2005

Art 14 (Decision on applications concerning MRLs)
" …Regulation on the setting, modification… of an MRL… shall be prepared by the Commission … 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…"

Milestones

- **November 2006**: EFSA Colloquium on Cumulative Risk Assessment of Pesticide in Humans : The way forward

efsa
European Food Safety Authority

- **April 2008**: First opinion EFSA PPR Panel on the suitability of existing methodologies:
  Three possible forms of combined toxicity, but only dose-addition is relevant.
  Integration of methodologies into a **tiered approach** concept
- **June 2009**: Second opinion EFSA PPR Panel on a CRA for triazole fungicides: exercise aiming at **testing the tool**
  Refinement of the tiered approach
  Identification of needs for future developments

EFSA PPR Panel 2008 Opinion & drinking water

- 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, exposure to multiple pesticide residues in drinking water could be toxicologically relevant if several highly toxic pesticides sharing the same mode of action were simultaneously present, each at its 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 the vast majority of cases.

Hazard assessment

- Response-addition
- **Dose-addition**
- Interaction (e.g. synergistic, antagonistic)

Common Mode/Mechanism Group (CMG) versus **Cumulative Assessment Group (CAG)**

How to group compounds in a **CAG:**

- Chemical structure
- Mechanism of pesticidal action
- Common toxic effect (target organ)
- Toxic mode of action

⇒ Find relevant toxic end-point for all compounds in the CAG

Low dose effects

"*All substances are poisons. It's the dose that makes the poison.*" (Paracelsus, a 16th century) Challenged!

"low dose hypothesis": some chemicals cause reactions at doses in ranges of micrograms or even nanograms per kilogram of body weight, e.g. hormones

……. Endocrine disruptors? (e.g. some pesticides, industrial chemicals like dioxins and PCBs, food contact material bisphenol A)

No threshold dose below which there is no adverse effect?

14 and 15 June 2012: **EFSA's 17th Scientific Colloquium on low dose response in toxicology and risk assessment**

Establishment of a CAG (triazole example)

Final approach adopted by the panel:

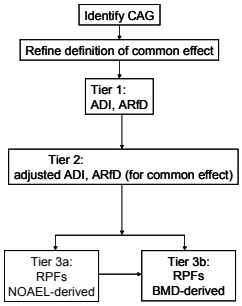
- ***Acute effects***: all triazoles showing cranio-facial effects in developmental studies were selected in the CAG for acute assessment: bitertanol, cyproconazole, diniconazole, epoxiconazole, flusilazole, propiconazole and triadimefon
- ***Chronic effects***: liver toxicity. 7 triazoles from the acute group plus adding 4 other hepatotoxic triazoles for which there were extensive residue monitoring data difenoconazole, myclobutanil, tebuconazole, triadimenol

High workload and expert judgement

Hazard characterisation

- Regulatory Reference Values (RVs)
- Common Effect RVs
- Derivation of Relative Potency Factors
- Use of BMDs instead of NOAELS for determining relative potency: to be considered as a scientific refinement

Revised proposal for tiered hazard assessment



Exposure assessment (1)

Four exposure scenarios:

- 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

Exposure assessment (2)

- First tier : Deterministic
- Second tier : Probabilistic

Both require specific inputs for each of the 4 scenarios

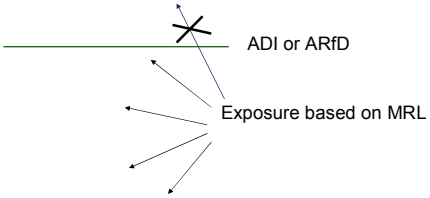
Possible use of processing data

Provide 2 different types of information

High work load in both cases and special expertise required in probabilistic modelling

Residues: MRLs

MRL = Maximum Residue Limit
= based on Good Agricultural Practice
= NOT a toxicological limit value!

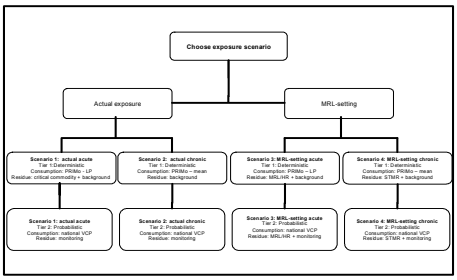


Background – deterministic exposure assessments

Defined as:
the summed chronic (average) potency-adjusted (using RPFs) exposure from all pesticides included in the respective CAG, based on national monitoring residue levels.
→ 7 triazoles in acute CAG; 11 triazoles in chronic CAG

Assuming:
<LOR = ½LOR for commodities where in at least one sample detectable residues were found;
< LOR = zero for commodities where in none of the samples detectable residues were found.

Revised proposal for tiered exposure assessmen



Cumulative risk assessment

Resulting proposed tiering of Risk characterisation

- HI (deterministic)
- adHI and/or NOAEL-based RPF methodology (deterministic)
- BMD-based RPF Methodology (probabilistic)

Main recommendations for simplification

- Starting with a CAG as refined as the data allow
- Restricting exposure assessment to 2 tiers, one deterministic and one probabilistic

Proposed tiered approach (2nd EFSA PPR opinion on

Hazard	Exposure deterministic	Exposure probabilistic
ADI, ARfD	HI – A1	HI-A2
Adjusted* ADI, ARfD	adjusted HI - B1	adjusted HI - B2
NOAEL*/BMD*	RPF-C1/D1	RPF –C2/D2

* for common effect

Issues

- CAGs: Criteria for establishment
- UF
- BMD determination
- Metabolites
- Handling of non-detects
- Technical issues in probabilistic modelling
- Uncertainties
- Generation and quality of data
- Desired level of protection

CRA not yet possible on a routine basis

Next steps at EFSA/EU level (1)

➢Identification and consensus on CAGs
New PPR Panel mandate
Terms of reference adopted by the PPR Panel Oct 2009
Art 36 grant was completed April 2012; now second grant
CRA will be addressed from a toxicological endpoint perspective rather than from a chemical class perspective.
Opinion in 2013

➢Guidance for probabilistic modelling in CRA
Adoption by the EFSA PPR Panel scheduled on 21 June 2012

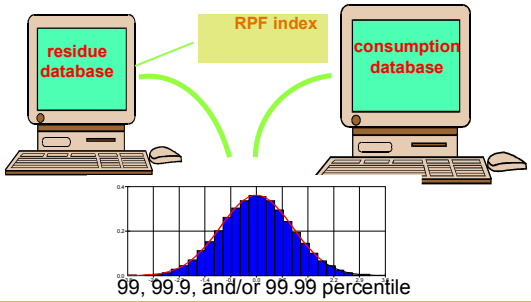
Next steps at EFSA/EU level (2)

➢Definition of the desired level of protection; EFSA asked COM for advise 15Sept2011

Response (**letter COM 26Sept2011**)
- Maintain current level of protection
- Residues in drinking water and residues of substances used as veterinary drugs:
'It is important to address this because otherwise it would be too easy to criticise us for only presenting part of the picture.'

⇨ Taken into account in 'Guidance for probabilistic modelling in CRA'
- Case study using MCRA platform (RIVM) see https://mcra.rivm.nl/

FP7 project ACROPOLIS cumulative exposure



Case study CRA substances in drinking water, NL

- Concentration data NL 2002 – 2009
- Hazard Index all compounds, no CAG defined
- Assumption: water consumption = 2 L/day; all contaminants measured in 1 year present at the same time
- Σ HI < 1, means the combined risk is considered acceptable

Results:
- Maximum Σ HI was 0,09

preliminary results

Acknowledgements

- **Scientific Opinion of the Panel on Plant Protection Products and their Residues (PPR), published 10 Sept 2009**
http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902879573.htm

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Thank you for your attention!

Questions?