Industry perspective

Proposal for a manageable process to conduct cumulative risk assessments

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Overview

- EFSA documents on CAGs
- “Exclusion approach”
- WoE – full hazard characterization
- Target-organ NOAELs
- ECPA Evaluation
  - Including some examples
- Proposal for a manageable process
- Difficulties in handling large CAGs
- Summary
The (EFSA) Scientific Basis of Cumulative Risk Assessment – establishing CAGs

M-2009-0355
External scientific Report submitted to EFSA Identification of Cumulative Assessment Groups of Pesticides DTU Published April 2012

M-2012-1036
External Scientific Report 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 RIVM, ICPS, ANSES Published January 2013

M-2013-0171
External Scientific Report Toxicological data collection and analysis to support grouping of pesticide active substances for cumulative risk assessment of effects on the nervous system, liver, adrenal, eye, reproduction and development and thyroid system RIVM, ICPS, ANSES Published February 2016

EFSA Scientific Opinion
Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile Published July 2013 Updated November 2014

EFSA Technical Report Outcome of the public consultation Published July 2014

(Partial) CAGs for nervous and thyroid systems

Mandates
Data collection and initial interpretation

EFSA interpretation and public consultation

EFSA proposed CAGs (and associated reference doses)

No explicit grouping has been proposed based on these data collection. Compounds were indicated, which might have to be grouped for nervous system, liver, reproduction

DTU initially proposed 16 Level 1 CAGs (based on data collected for ASs approved up to 31/05/09)

EFSA decided that further consolidation of the data was required. New mandate and invitation to tender issued.

Consortium-proposed CAGs (based on EFSA agreed “framework”):
- Thyroid and nervous system CAGs “updated”
- Liver data set updated (CAGs proposed for the top-up ASs)
- Reproduction and developmental system data set updated (and CAGs proposed for the top-up ASs)
- First data set for effects on adrenal and eyes collected; CAGs proposed
The “exclusion” approach

- CAG level 1: Toxicological target organ
- CAG level 2: Common specific phenomenological effect
- CAG level 3: Common mode of action
- CAG level 4: Common mechanism of action

Rarely data available

Chemicals with common target organ toxicity (any study, dose level or species)

Exclusion

Only based on specific data
Weight of evidence needed

The methodology comprises four main steps as follows:

- Identification of the specific effects by:
  - i) exclusion of local effects
  - ii) exclusion of non-adverse effects
  - iii) exclusion of effects not relevant to humans
  - iv) evaluation of the unambiguous nature of the effect
  - v) identification of non-specific effects

- Characterisation of the specific effects
- Data collection
- Grouping of pesticides into CAGs

This proposed weight of evidence evaluation is not in all cases reflected by the assessment of specific compounds
Target-organ specific NOAELs → derivation of $\text{ADI}_{\text{adjusted}}$

EFSA tiered approach for hazard-based refinement

A NOAEL(target organ) can not be lower, than the overall NOAEL
In nervous system and thyroid groups a number of new NO(A)ELs have been introduced. For 12 compounds no NOAEL had been derived. For 8 compounds no NOAEL had been derived.

<table>
<thead>
<tr>
<th>Cumulative Assessment Group</th>
<th>No. of members for which common-effect NOAEL/100 &lt; critical ADI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid T-cell effects (96 ASs)</td>
<td>18/96</td>
</tr>
<tr>
<td>Thyroid C-cell effects (24 ASs)</td>
<td>2/24</td>
</tr>
<tr>
<td>Nervous system, motor division effects (53 ASs)</td>
<td>6/53</td>
</tr>
<tr>
<td>Nervous system, sensory division effects (21 ASs)</td>
<td>2/21</td>
</tr>
<tr>
<td>Nervous system, autonomic division effects (24 ASs)</td>
<td>2/24</td>
</tr>
<tr>
<td>Neurochemical effects (15 ASs)</td>
<td>8/15</td>
</tr>
<tr>
<td>Neuropathological effects (21 ASs)</td>
<td>1/21</td>
</tr>
</tbody>
</table>
Selected compounds had been evaluated by toxicologists within ECPA in detail

- Same data set
- Isolated occurrence → Effects were previously not considered treatment related
- Subtle changes → Effects were previously not considered adverse
- Shorter-term studies had been used to derive long-term endpoints
- Studies previously considered to be unreliable had been used for endpoint derivation

For a number of compounds in EFSA Scientific Opinion 2013 target-organ specific NOAELs are lower using different criteria than previously
Thyroid group (Level 2B)

Would make a huge thyroid follicular cell CAG at the level 2B
- Not manageable for cumulative risk assessment
## External Scientific Opinion 2016
### Proposal for liver groups

<table>
<thead>
<tr>
<th>Effect</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic hypertrophy</td>
<td>99/129</td>
</tr>
<tr>
<td>Effect on hepatocellular degeneration/death/</td>
<td>45/129</td>
</tr>
<tr>
<td>hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Effect on pigment</td>
<td>23/129</td>
</tr>
<tr>
<td>Effect on foci of cellular alteration</td>
<td>20/129</td>
</tr>
<tr>
<td>Effect on vascular lesion / angiectasis</td>
<td>5/129</td>
</tr>
<tr>
<td>Effect on karyomegalgy</td>
<td>5/129</td>
</tr>
<tr>
<td>Effect in bile duct hyperplasia</td>
<td>18/129</td>
</tr>
<tr>
<td>Effect on inflammatory cells infiltrates</td>
<td>11/129</td>
</tr>
<tr>
<td>Effect on cytoplasmic inclusion</td>
<td>4/129</td>
</tr>
<tr>
<td>Effect on cholecystitis</td>
<td>3/129</td>
</tr>
<tr>
<td>Effect on gallbladder hyperplasia</td>
<td>3/129</td>
</tr>
<tr>
<td>Effect on cholestasis</td>
<td>58/129</td>
</tr>
<tr>
<td>Effect on fatty changes</td>
<td>40/129</td>
</tr>
<tr>
<td>Effect on hepatocellular neoplasms</td>
<td>35/129</td>
</tr>
</tbody>
</table>
Proposal for grouping based on a full hazard characterization

- Effects should be treatment-related
- Effects should be specific to the organ / system
- Effects should be adverse
- Sensitivity of species shall be taken into account → human relevance
- Mode of action information shall be applied more stringently
  - Species-specific target-organ effects are not relevant for grouping
- Effects seen at high doses and/or effects secondary to general systemic toxicity only shall not be used for grouping, as they are not reflecting levels of potential human exposure
Examples for inappropriate grouping

**External Scientific Opinion 2016**

- Fluopyram: Motor Division (acute exposure)
- Ametoctradin: Thyroid follicular cell group (Level 2B) based on thyroid weights in f in one study (90-day rat)
- Metaflumizone: Considered for grouping in Repro group 2B, C, D, E, F, G, H,

**Previous EFSA decisions**

- „Fluopyram did not show any specific potential for neurotoxicity“ (EFSA 2013)
- Isolated effects on thyroid weights without histopathology was considered incidental (additional DAR 2012) (assessment of thyroid cell proliferation was negative)
- Inappropriate grouping in 2B, C, D, H, as effects were agreed to be secondary to severe general toxicity (EFSA, 2013)

We also consider some of the compounds in the EFSA Scientific Opinion 2013 as inappropriately grouped
Thyroid T-cell CAG 2B: CRA based on MRLs (to identify relative contribution to risk)

DE child (cumulative exposure = 3263.8 % of the adjusted ADI)
TMDI (excluding <LoQ MRLs) / mg/kg bw/d- including only CAG members for which monitoring data were available

We would not recommend to use MRL values for cumulative risk assessment (CRA), as this leads to unrealistic exposure scenarios

• Thus, in our calculations, 80% of the cumulative exposure was from 30% of the CAG members

CAG for thyroid T-cell system effects

- Buprofezin
- Metiram
- Cyprodinil
- Pyrethrins
- Chlorprofam
- Bupirimate
- Prochloraz
- Folpet
- Formetanate
- Dinocap
- Maneb
- Propineb
- Fipronil
- 2,4-D
- Thiophanate-methyl
- Imidacloprid
- Micyclotenil
- Haloxyfop-P (Haloxyfop-R)
- Cyproconazole
- Zoxamide
- Ethofenprox
- Spinosad
- Pyrimethanil
- Tetraconazole
- Ziram
- Fenbuconazole
- Mepanipyrim
- Lufenuron
- Thiabendazole
- Mancozeb
- Clofentezine
- Fluquinconazole
- Boscalid
- Fenoxycarb
- Thiacloprid
- Bromuconazole
- Propyzamide
- Tolrifluanid
Proposed flow chart for a manageable process

- Als initiating common adverse effect*

**Full Hazard Characterisation**
- Hazard-based “definitive” CAG (10s to 100s of members)
  - *Data collections can be used

**Exposure Characterisation**
- Residues data indicating potential co-occurrence
- Discrimination between “uses” and “non-uses” for non detects in monitoring data
- Food consumption data

**CAG for risk assessment** (low 10s of members?)
Difficulties in handling large CAGs

Monitoring data are not available for all scenarios/all compounds

- For example, of the two level 2 thyroid system CAGs partially defined by EFSA in 2014, monitoring data* were only available for 40/96 and 10/24 members of the T-cell-effects and C-cell-effects groups
- Additionally, not all crops are included in monitoring surveys
- For animal commodities there are relatively many fewer residue-level data than for plants (Boon et al., 2015**)

* For example, in relation to the data presented in the 2010 European Union Report on pesticide residues in food (EFSA Journal 2013;11(3):3130)
** Polly E. Boon et al., Cumulative dietary exposure to a selected group of pesticides of the triazole group in different European countries according to the EFSA guidance on probabilistic modelling, Food and Chemical Toxicology 79 (2015) 13-31
Some pesticide residue species are monitored using a „common moiety“ analysis method

- For example, measured residues of dithiocarbamate pesticides (including manebo, mancozeb, metiram, propineb, thiram and ziram) are all analysed and expressed as CS$_2$
- The 2013 EFSA proposed target-organ NOAELs, however, can vary significantly between the different species
- For example the largest divided by the smallest NOEAL is ca. 30 for the „thyroid T-cell CAG“ and ca. 190 for the nervous system chronic motor division effects CAG

Assumptions are required to interpret monitoring data (even for single AI)
Difficulties in handling large CAGs

Assumptions made in regard to „non-detect“ residue levels...

– If a residue is observed to be less than the validated LOQ of the analysis method does this mean that the „true“ residue level was zero or between zero and the LOQ?

– In their indicative cumulative risk assessment calculations (in the context of EU Reports on pesticide residues) the impact of incomplete information about „non-detects“ are clearly identified and discussed

  • In the example cumulative risk assessment calculations presented in the 2010 EU Report on Pesticide Residues in Food treating non-detects first as being at the level of the LOQ and then as being zero gave results that differed by a factor of more than 20

...can have a significant impact on the result of a CRA
Summary

- A more accurate hazard characterization would lead to hazard-based „definitive“ CAGs with lower numbers
  - Substances with lacking WoE for target organ toxicity shall not be included in target organ CAG

- Target-organ NOAELs cannot be lower than overall NOAELs

- External Scientific Opinion 2016 and data collection from 2013 needs to be revised

- Large CAGs necessitate multiple assumptions (e.g. monitoring data and methods, non-detects...)

- A better exposure characterization informs about potential co-occurrence

- Cumulative Risk Assessment can be done on relatively small groups after hazard- and exposure-based refinement
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Thanks for your attention

Questions?