Industry perspective

Proposal for a manageable process to conduct cumulative risk assessments

Stephanie Melching-Kollmuss

18th May, 2016

Overview

European Crop Protection

- **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

European Crop Protection

Mandates

Data collection and initial interpretation

EFSA interpretation and public consultation

EFSA proposed CAGs (and associated reference doses)

M-2009-0355

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

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.

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

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

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

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

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

European Crop Protection

- 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

European Crop Protection

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

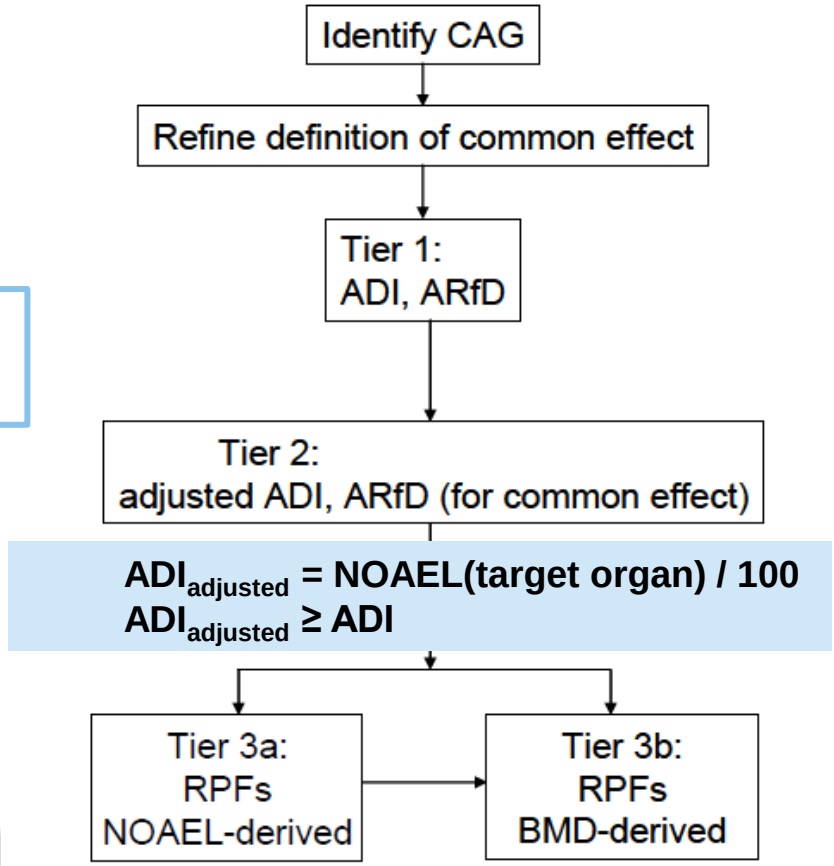
Page 4 of EFSA Scientific Opinion 2013

- **This proposed weight of evidence evaluation is not in all cases reflected by the assessment of specific compounds**

Target-organ specific NOAELs → derivation of $ADI_{adjusted}$

EFSA tiered approach for hazard-based refinement

A NOAEL(target organ) can not be lower, than the overall NOAEL



Target-organ specific NOAELs

European Crop Protection

- EFSA Scientific Opinion 2013
- In nervous system and thyroid groups a number of new NO(A)ELs have been introduced

Cumulative Assessment Group	No. of members for which common-effect NOAEL/100 < critical ADI
Thyroid T-cell effects (96 ASs)	18/96
Thyroid C-cell effects (24 ASs)	2/24
Nervous system, motor division effects (53 ASs)	6/53
Nervous system, sensory division effects (21 ASs)	2/21
Nervous system, autonomic division effects (24 ASs)	2/24
Neurochemical effects (15 ASs)	8/15
Neuropathological effects (21 ASs)	1/21

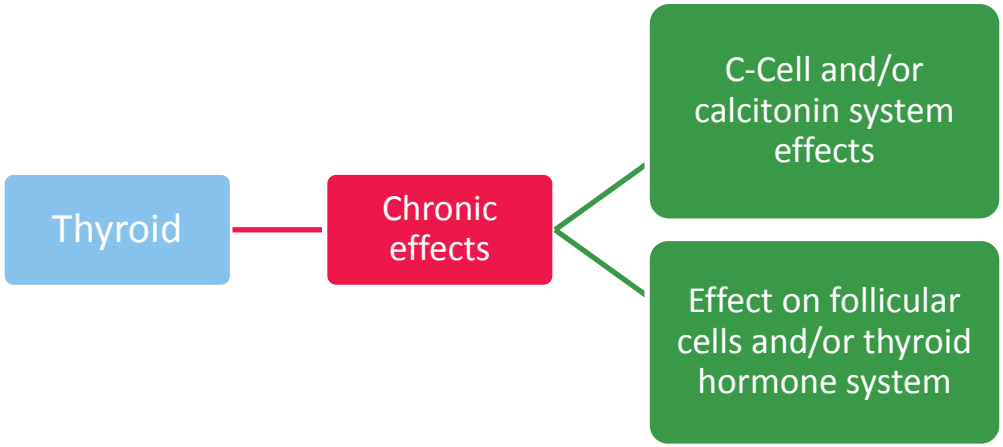
For 12 compounds no NOAEL had been derived

For 8 compounds no NOAEL had been derived

Target-organ specific NOAELs

- **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**

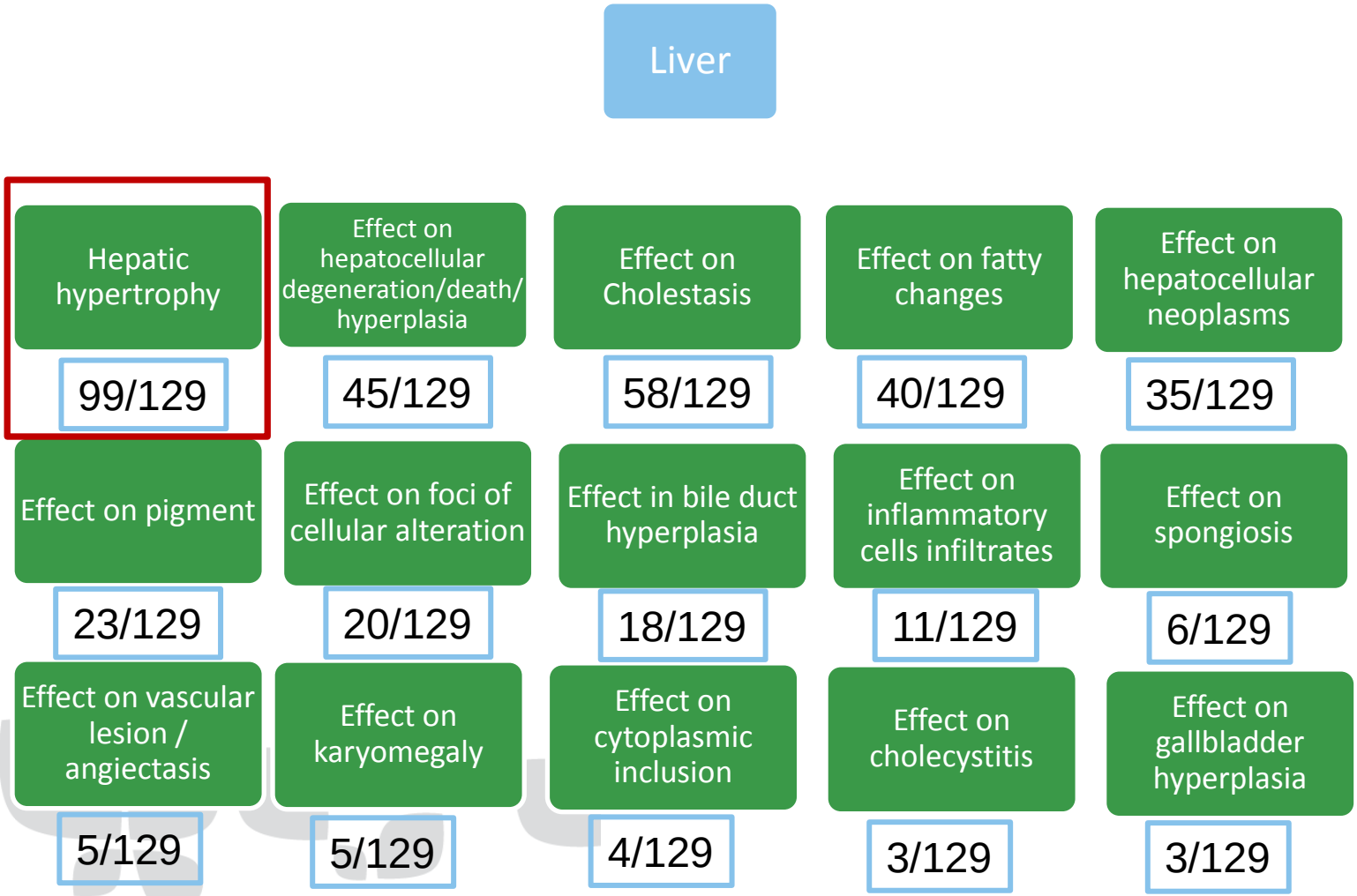
Thyroid group (Level 2B)



	Scientific Opinion 2013	External Scientific Report 2016
C-Cell and/or calcitonin system effects	22/287	10/129
Effect on follicular cells and/or thyroid hormone system	96/287	53/129

- **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



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)

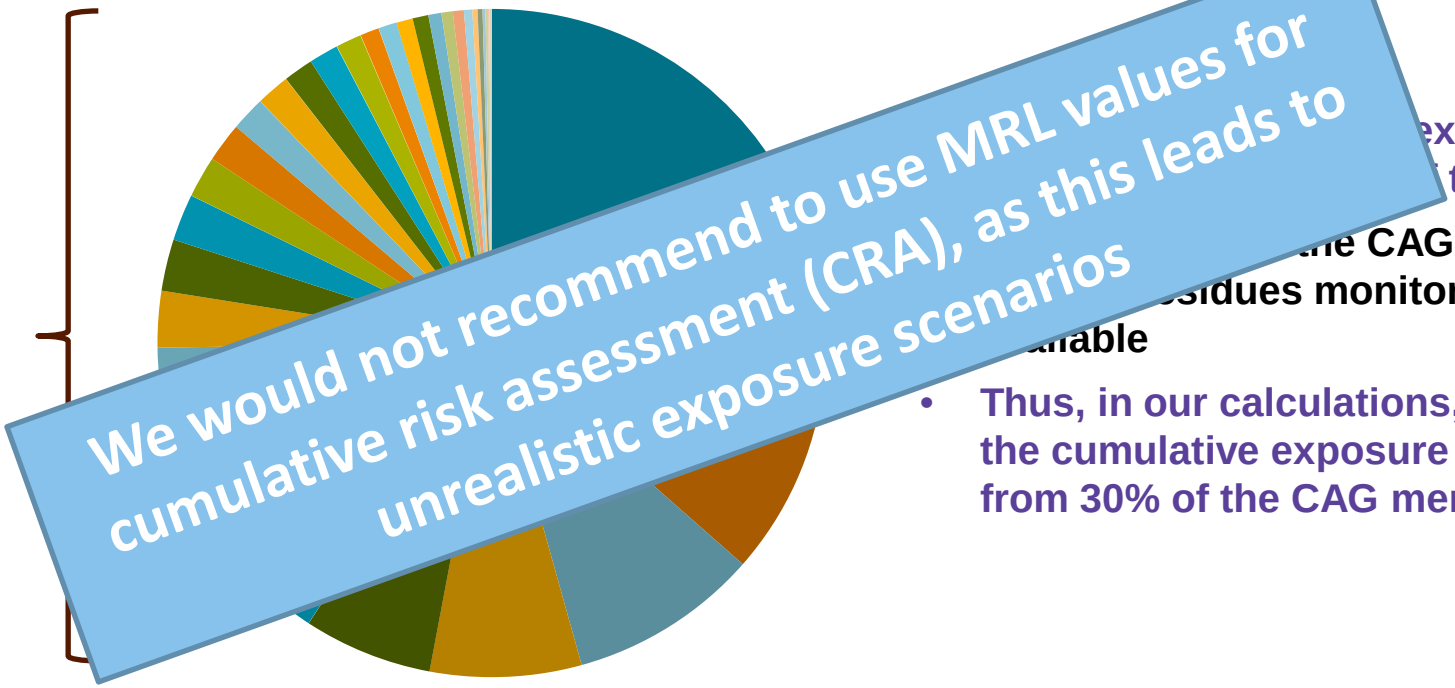
- We also consider some of the compounds in the EFSA Scientific Opinion 2013 as inappropriately grouped

Thyroid T-cell CAG 2B: CRA based on MRLs (to identify relative contribution to risk)

European Crop Protection

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

CAG for thyroid T-cell system effects



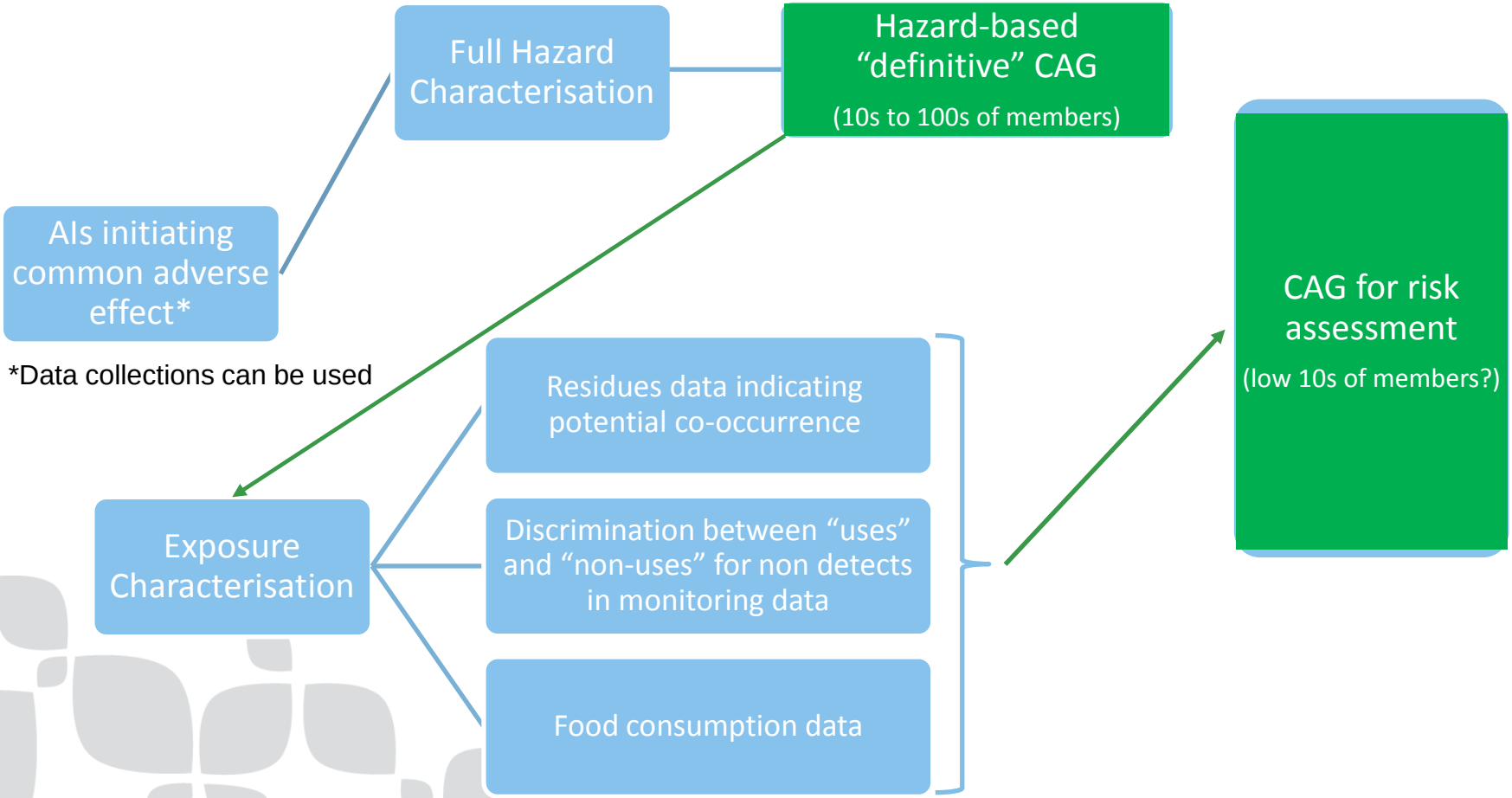
We would not recommend to use MRL values for cumulative risk assessment (CRA), as this leads to unrealistic exposure scenarios

exposure
the CAG
the CAG for only
sidues monitoring data
ilable

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

Buprofezin
Maneb
Ethofenprox
Mancozeb
Metiram
Propineb
Spinosad
Thiabendazole
Cyprodinil
Fipronil
Pyrimethanil
Clofentezine
Pyrethrins
2,4-D
Tetraconazole
Fluquinconazole
Chlorprofam
Thiophanate-methyl
Ziram
Boscalid
Bupirimate
Imidacloprid
Fenbuconazole
Fenoxycarb
Prochloraz
Myclobutanil
Mepanipyrim
Thiacloprid
Folpet
Haloxyfop-P (Haloxyfop-R)
Lufenuron
Bromuconazole
Formetanate
Cyproconazole
Thiamethoxam
Propyzamide
Dinocap
Zoxamide
Pendimethalin
Tolylfluanid

Proposed flow chart for a manageable process



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

Difficulties in handling large CAGs

- **Some pesticide residue species are monitored using a „common moiety“ analysis method**
  - For example, measured residues of dithiocarbamate pesticides (including maneb, 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

European Crop Protection

- **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**

Acknowledgements

- **ECPA J-TRAG**
  - Dave Johnson (Syngenta)
  - Giovanna Semino-Beninel (Bayer)
  - Frank Laporte (Bayer)
  - Monika Bross (BASF)
  - Neil Lister (Syngenta)
  - Tina Mehta (Dow)
  - Stephanie Melching-Kollmuss (BASF)
  - Stephanie Zedet (Nufarm)

European
Crop Protection

Thanks for your attention

Questions?