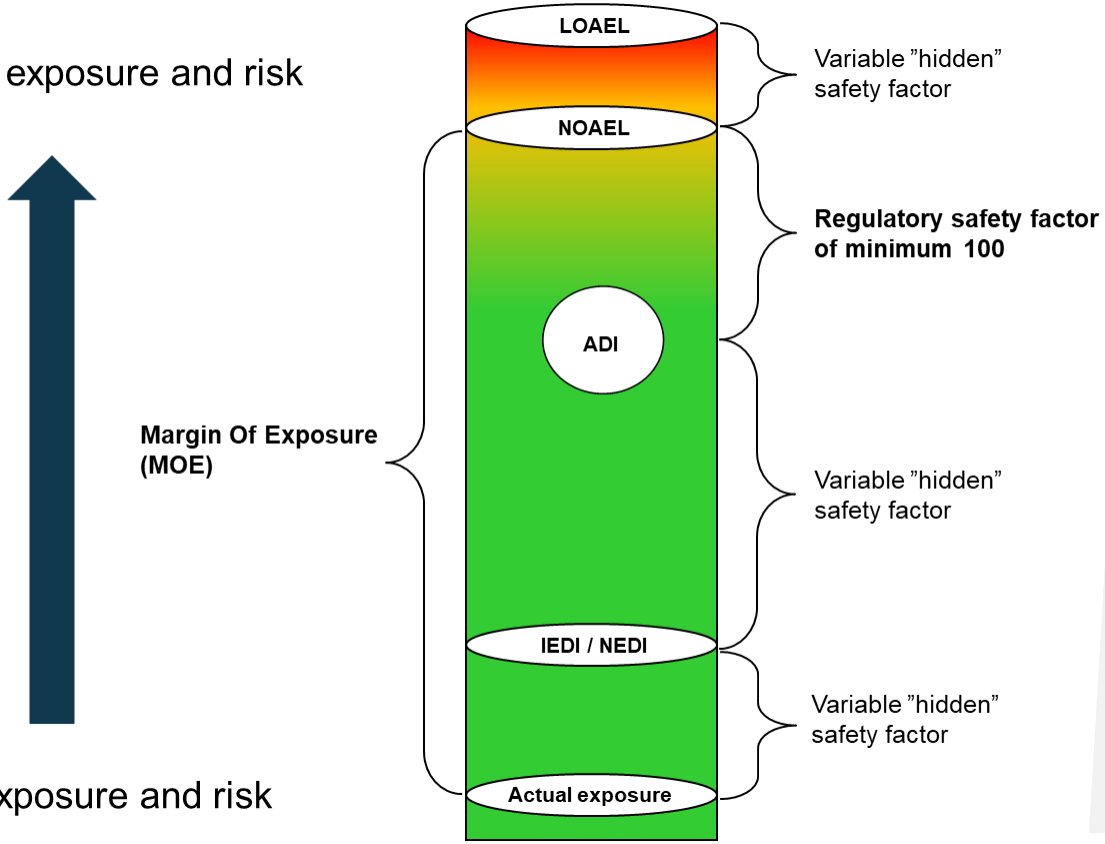
Agrochemical industry activities to address the EU regulatory requirements on cumulative risk assessment

Giovanna Semino
Bayer Crop Science Division
European Crop Protection Association (**ECPA**) Expert Group on Cumulative Risk Assessment

Toxicity endpoints and risk estimates for agrochemicals

Increasing exposure and risk



Very low exposure and risk

LOAEL: Lowest Observable Adverse Effect Level.

NOAEL: No Observable Adverse Effect Level.

ADI: Acceptable Daily Intake (Estimate of the amount of a substance in food, which can be ingested daily over a lifetime by humans without appreciable health risk)

IEDI / NEDI: International or National Estimated Daily Intake (Exposure estimate based on residue results from regulatory trials conducted according to the critical use).

Actual exposure: Can be estimated form pesticide residue monitoring data. Usually far below the IEDI / NEDI since market share < 100% and substance not always used at the highest authorised rate and shortest PHI.

EU legal requirements for Cumulative Risk Assessment (CRA) of agrochemicals

- Currently single substances are toxicologically evaluated but exposure is to multiple substances

+

+

Pesticide A → Risk assessment → No Risk → approval

Pesticide B → Risk assessment → No Risk → approval

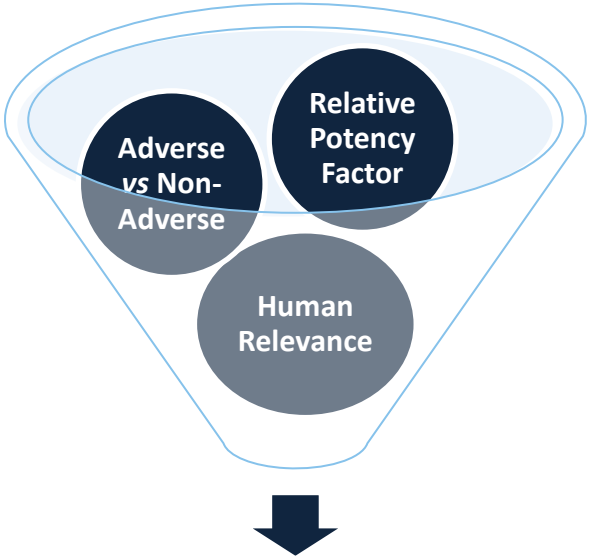
Pesticide A + B → **CRA**

Implementation of CRA required by the EU Regulations (EC) No. 1107/2009 and (EC) No. 396/2005 on MRLs as soon as methodologies available

EFSA approach for CRA

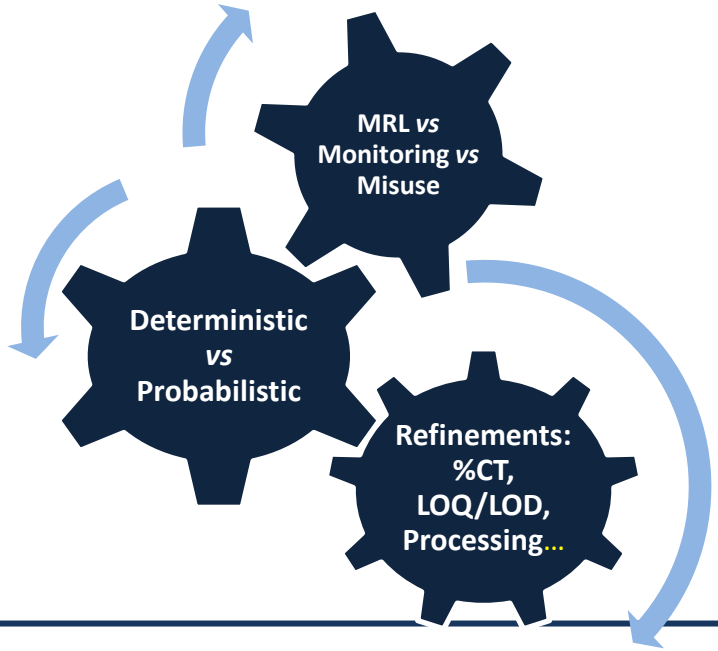
HAZARD

Grouping substances on the basis **of a common** effect on the same organ Cumulative Assessment Group (CAG)



EXPOSURE

Each component of the CAG contributes to the effect in proportion of its dose and individual potency, i.e. **dose additivity**



Grouping substances based on effect on same organs (CAGs): EFSA approach

Regulation 1107/2009
"ensure that the chances of failing adverse effects or of underestimating their importance are reduced to a minimum"

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

Data rarely available

Any effect in any study, dose level or species

EFSA finalized CAGs (2019)

Nervous system

5 common specific effects
(5 CAGs level 2)

2 CAGs Retained for CRA

Brain and/or erythrocyte AChE inhibition
(47 substances)

Alteration of the motor division
(119 substances)

Thyroid

2 common specific effects
(2 CAGs level 2)

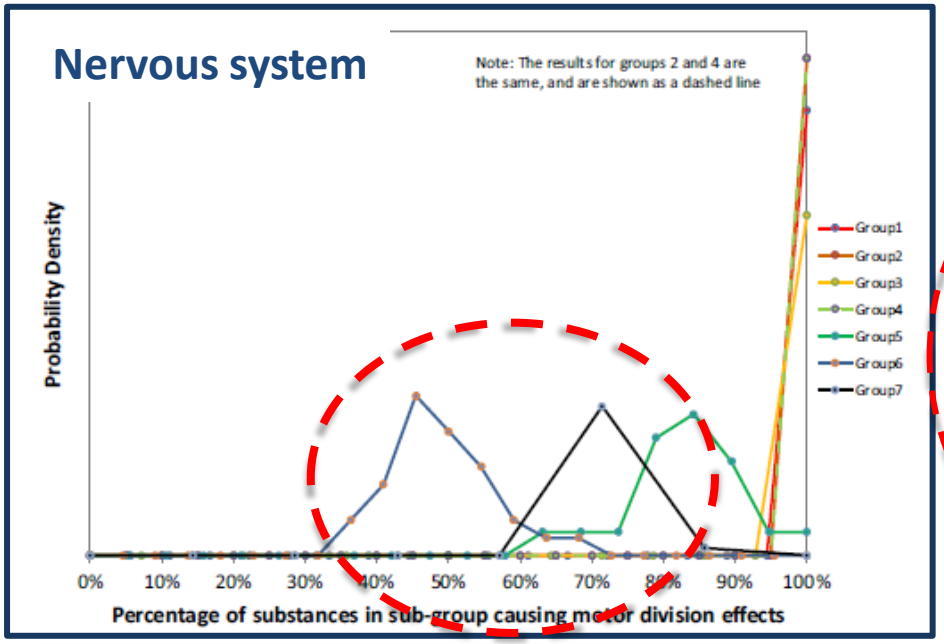
2 CAGs Retained for CRA

Hypertrophy, hyperplasia and neoplasia of C-cells
(17 substances)

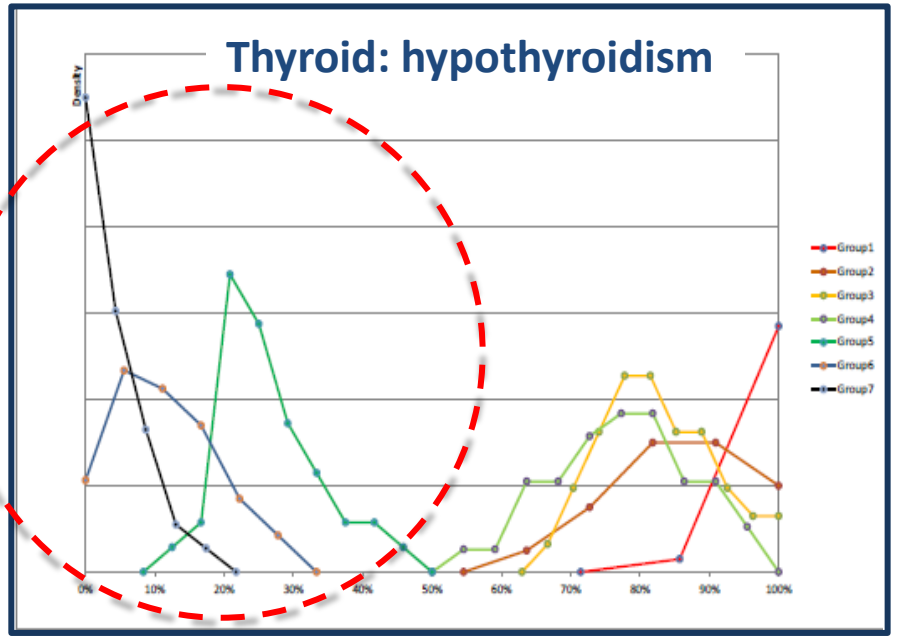
Hypothyroidism
(128 substances)

EFSA finalized CAGs (2019)

- Likelihood of including substances not causing the effects
- Outcome of the uncertainty analysis of the expert knowledge elicitation (EKE) techniques

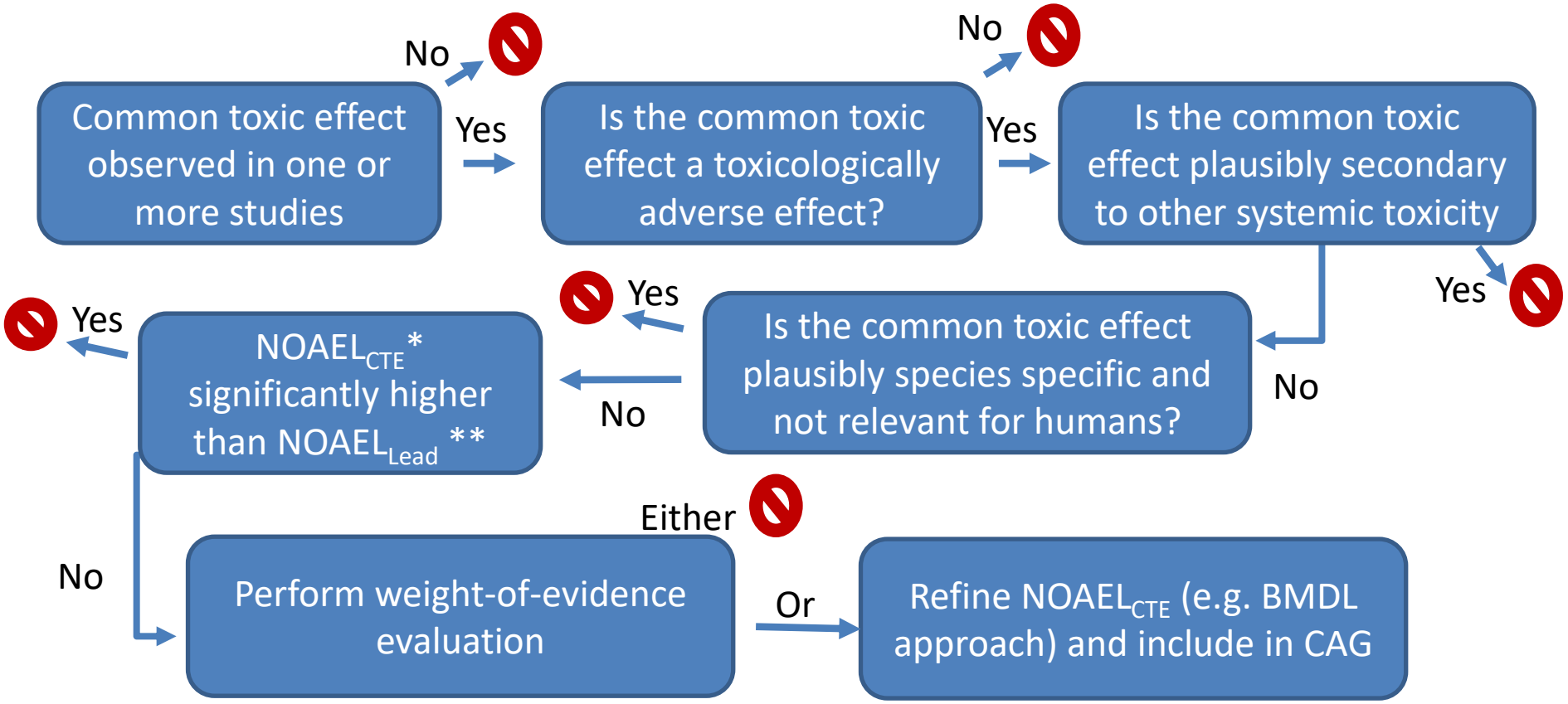


Groups 6 & 7: ~ 14 substances /119 unlikely to cause effects



Groups 5, 6 & 7: ~ 44 substances/128 unlikely to cause effects

ECPA tiered approach: relevant NOAEL



NOAEL$_{CTE}$ – lowest NOAEL for the Common Toxic Effect
****NOAEL$_{Lead}$ – NOAEL used for ADI, ARfD**

= not include in the CAG

Colnot_Reg_Tox_Pharm_2017

ECPA : streamline number of CAG level 2

EFSA (2016) External Report : Liver CAG

Hepatic hypertrophy	Effect on Cholestasis	Hepatocellular degeneration/death/hyperplasia (necrosis)	Effect on fatty changes	Effect on hepatocellular neoplasms
99/129	58/129	45/129	40/129	35/129
Effect on pigment	Effect on foci of cellular alteration	Effect in bile duct hyperplasia	Effect on inflammatory cells infiltrates	Effect on spongiosis
23/129	20/129	18/129	11/129	6/129
Effect on vascular lesion / angiectasis	Effect on karyomegaly	Effect on cytoplasmic inclusion	Effect on cholecystitis	Effect on gallbladder hyperplasia
5/129	5/129	4/129	3/129	3/129

- Disparate substances grouped together (no common mode of action)
- Same chemicals belong to more than one subgroup

ECPA proposal on liver group refinement: Grouping based on common pathogenesis

- Consider known and common pathophysiology of toxic lesions

Primary Lesions

direct consequence of chemical interaction with a biological target

Secondary Lesions

which are **a consequence** of, (or that arise out of) a **previous** pathological change.

Special consideration is needed for substances provoking neoplasia

➡ ***this category is included in the group of primary endpoints***

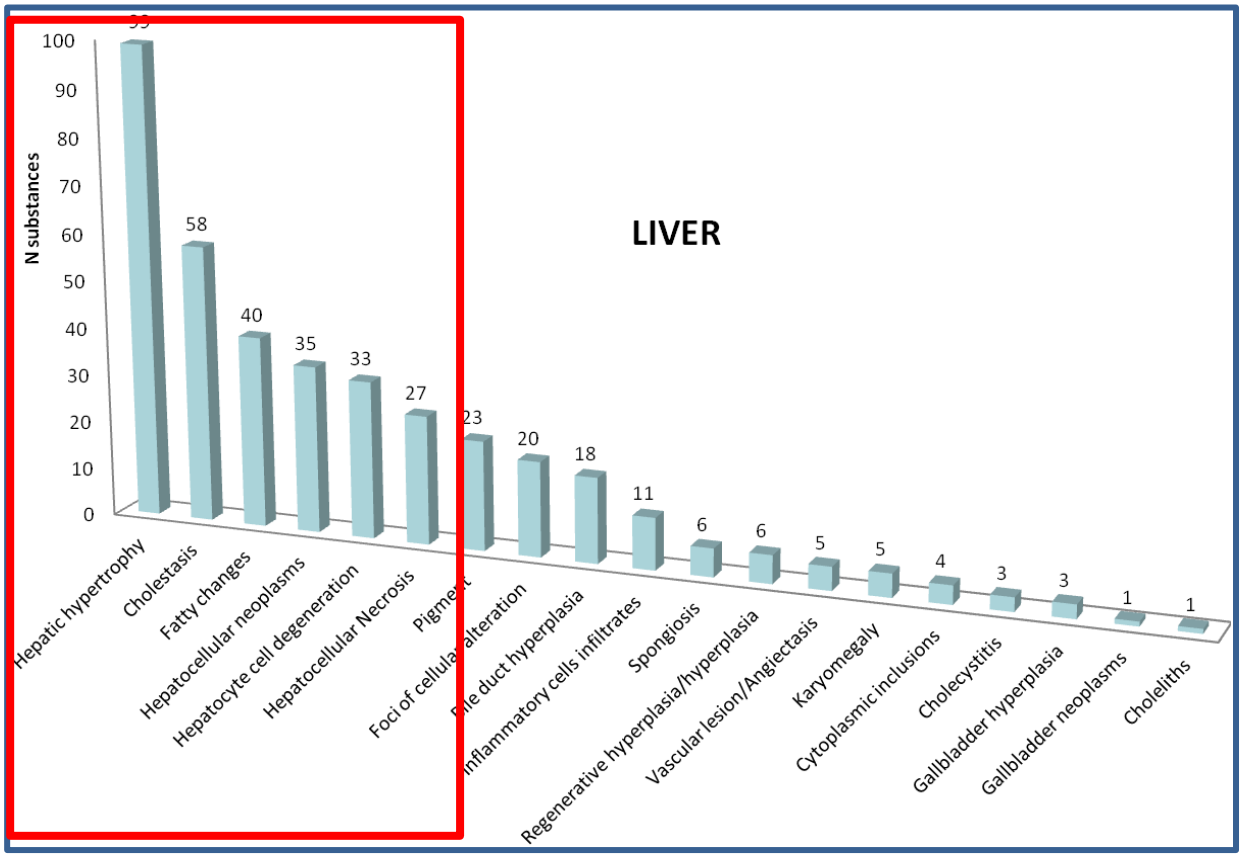
Liver CAGs to be retained

- Hepatic hypertrophy
- Effect on hepatocellular neoplasms
- Effect on Cholestasis
- Effect on hepatocellular degeneration/death/ hyperplasia
- Effect on fatty changes
- Effect on pigment
- Effect on foci of cellular alteration
- Effect in bile duct hyperplasia
- Effect on inflammatory cells infiltrates
- Effect on spongiosis
- Effect on vascular lesion / angiectasis
- Effect on karyomegaly
- Effect on cytoplasmic inclusion
- Effect on cholecystitis
- Effect on gallbladder hyperplasia

The number of Liver CAGs are decreased from 15 to 6

Any risk of excluding a hepatotoxic chemical ?

Number of active substances for each specific effect on Liver (EFSA Report, 2016)



The 6 CAGs for primary effects represent CAGs with most of the substances included those presenting secondary effects

EFSA 2019 Pilot Assessment

- **Target organs**
  - Thyroid (Chronic)
  - Nervous system (Acute)
- **Retrospective Risk assessment**
  - Official pesticide monitoring data (Art 32 Reg 396/2005)
  - Reference period 2014 – 2016
- **Population groups**
  - Adults (BE, CZ, DE, IT)
  - Children (BG, FR, NL)
  - Toddler (DK, NL, UK)
- **Food commodities**
  - 30 raw primary commodities (plant origin only, most frequently consumed)
  - Food for infants and young children
  - Water
- **Exposure (probabilistic approach) calculated with two different software**
  - EFSA used SAS ® Software
  - RIVM used MCRA Software

EFSA Pilot Assessment: Tiered approach (SCoPAFF instructions)

	TIER I	TIER II
Unspecific definitions	Most potent active substance is allocated to each sample	Random allocation of authorized active substances to each sample
Left-censored data	½ LOQ for food-substance combinations with quantifiable findings	½ LOQ based on estimated use frequencies assuming 100% crop treatment
Missing measurement	Highest values assigned to the most contaminated samples	Random assignment of missing measurements to available samples
Drinking water	Imputed at 0.1 µg/L for the 5 most potent substances	Imputed at 0.05 µg/L for the 5 most potent substances
Processed Food	Use processing factors. Otherwise assume all pesticides in the raw primary commodity will reach the end consumer without any loss of residue due to processing	

Tier III: Expert judgement by assessing uncertainties

Outcome EFSA Pilot Assessment

- The 2019 probabilistic cumulative risk assessment conducted by EFSA concluded that the threshold for regulatory consideration **is not exceeded** for substances with chronic effects on the thyroid nor for substances with acute effects on the nervous system.

- The outcome was reached using a Tiered approach that highlighted many sources of uncertainties with respect to both exposure and toxicity.

- Uncertainties on the outcome of the assessment was estimated quantitatively using expert knowledge eliciting (EKE) methods

Sources of uncertainties of the pilot assessment for thyroid and nervous system

Sources of uncertainty related to exposure assessment	Sources of uncertainty related to toxicity assessment
• Missing processing factors (+/++) • Biases due to selective sampling (•/+) • Incomplete coverage of diets (-/•) • Metabolites not considered (-/•) • Unspecific analytical methods (-/+) • Assumptions on use frequencies (-/+) • Imputation of unmeasured residues (•) • Fixed variability factor (•) • Representativeness of consumption surveys ? • Analytical uncertainty …	• Adequacy of CAG : substances wrongly allocated to the CAG or missing substances (-/•) • Accuracy of NOAEL values (-/•) • Dose addition (•) • Dose-response relationship (-/+) • Suitability of exposure calculation method with regard to relevant toxicokinetic and toxicodynamic processes (•/+) …

ECPA exposure-related initiatives for CRA

- Industry can contribute to minimise sources of uncertainties highlighted in the EFSA pilot assessment for chronic effects on the thyroid and acute effects on the nervous system.
- Industry could support in
  - Generation or gathering of supplementary processing data,
  - Development of specific analytical methods,
  - Compilation of use frequency data
- Need to clarify who shall generate supplementary data to refine the assessment for those risk drivers that are not supported by companies present in the EU.

Overall Conclusion on ECPA activities

- **Establish robust criteria for Grouping**
  - Treatment-related
  - Adverse
  - Specific
  - Not occurring at overly high systemic toxicity
  - Flow scheme – transparent application of criteria

- **Dose additivity**
  - Deviation from dose additivity at low doses?
  - Extrapolation of existing pharmacokinetic data on single substances to multiple exposure situation

- **Reduce uncertainties in CRA**
  - Generate data to overcome sources of uncertainties highlighted in the EFSA pilot assessment

Members of the ECPA subgroup on Cumulative Risk Assessment

Angela Klemens	FMC	Residue & Exposure Expert
Bruce Young	Bayer	Residue & Exposure Expert
Cheryl Cleveland	BASF	Residue & Exposure Expert
Claire Stephenson	Adama	Residue & Exposure Expert
David Parker	Syngenta	Residue & Exposure Expert
Frank Laporte	Bayer	Residue & Exposure Expert
Giovanna Semino	Bayer	Toxicologist
Simon Hill	Syngenta	Toxicologist
Luciano Merolla	Corteva	Residue & Exposure Expert
Monika Bross	BASF	Residue & Exposure Expert
Stephanie Melching-Kollmuss	BASF	Toxicologist
Stephanie Nadzialek	ECPA	-
Tina Mehta	Adama	Toxicologist

Abbreviations and Acronyms

EFSA	European Food Safety Authority
SCoPAFF	Standing Committee on Plant, Animal, Food and Feed
WHO	World Health Organisation
IPCS	International Programme on Chemical Safety
ECPA	European Crop Protection Association
LOQ	Limit of Quantification
NOAEL	No Observed Adverse Effect Level
ADI	Acceptable Daily Intake
ARfD	Acute Reference Dose
CAG	Cumulative Assessment Group
MCR	Maximum Cumulative Ratio
MOE	Margin of Exposure
PRIMo	Pesticide Residue Intake Model
MCRA	Monte Carlo Risk Assessment
SAS	Statistical Analysis System

Thank you for your kind attention