European Food Safety Authority

Establishment of Cumulative Assessment Groups CAG's

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Vice-chair of the PPR Panel

Technical meeting with stakeholders on Cumlative Risk Assessment
Parma, 11th February 2014

Outline

- Status on developing and implementing risk assessment of combined exposure to multiple chemicals (2013) http://www.efsa.europa.eu/en/efsajournal/pub/3313.htm

- **Risk assessment methods for pesticides**
- Opinion evaluating existing methodologies. Tiered approach recommended (2008) http://www.efsa.europa.eu/en/efsajournal/doc/705.pdf

- Opinion testing proposed approach – triazoles (2009) http://www.efsa.europa.eu/en/efsajournal/doc/1167.pdf

- Guidance on the use probabilistic methodology for modeling dietary exposure (2012) http://www.efsa.europa.eu/en/efsajournal/pub/2839.htm

- **Grouping of pesticides (2013)** http://www.efsa.europa.eu/en/efsajournal/doc/3293.pdf

- Relevance of dissimilar MoA (2013) http://www.efsa.europa.eu/en/efsajournal/doc/3472.pdf

- Future steps and recommendation's

Concepts

Dose addition (concentration addition): All components in a mixture behave as if they were simple dilutions of one another.

There is good evidence (Kortenkamp et al., 2009) that combinations of chemicals which interact with the same well-defined molecular target indeed follow the dilution principles of dose addition

Independent action (response addition): A combination effect can be calculated from the responses of the individual mixture components by following the statistical concept of independent random events. Chemicals acting with strictly **independently dissimilar modes of action** when exposures occur simultaneously

Risk assesment of exposure to mixtures

Default methodology - the concept of dose addition

- The Non-Food Committees of the European Commission
- http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52012DC0252:EN:NOT

This requires detailed information on

- hazard and exposure of each chemical

Thus, the use of the dose addition concept is limited to known mixtures

Risk assesment methodology Pesticides

EFSA: development of methodology on addressing cumulative effects in relation to MRL-setting.

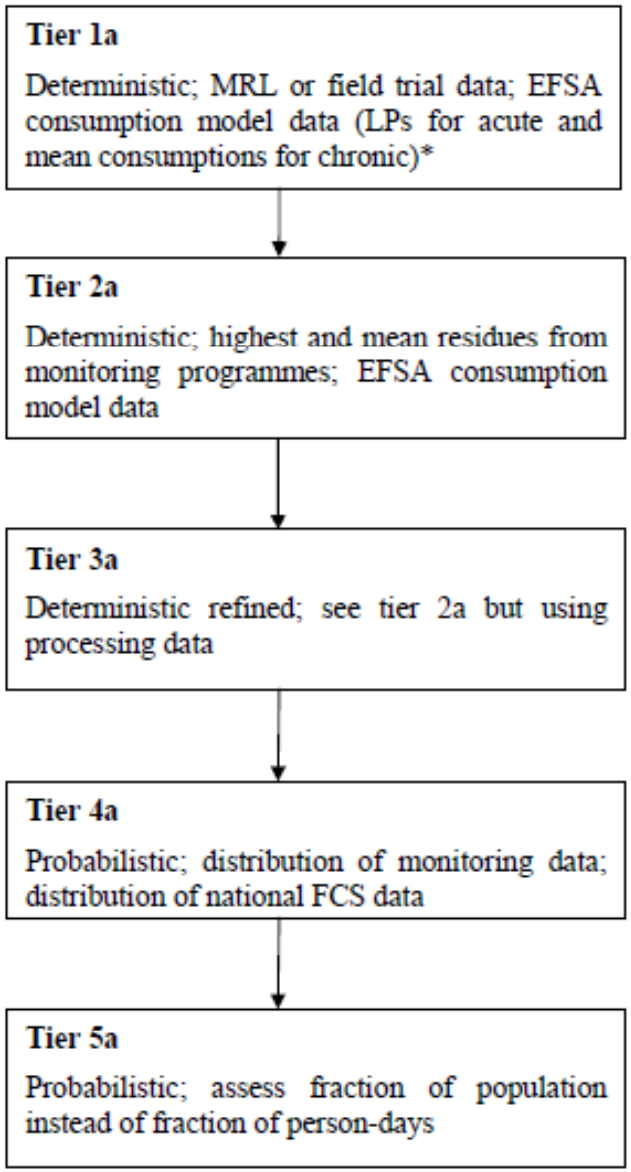
As exposure to pesticides from other sources than via food not generally available at time, opinion restricted to combined risk assessment to exposures from residues in food.

Synergistic effects not expected at the exposure levels of pesticide residues.

Risk assesment methodology Pesticides

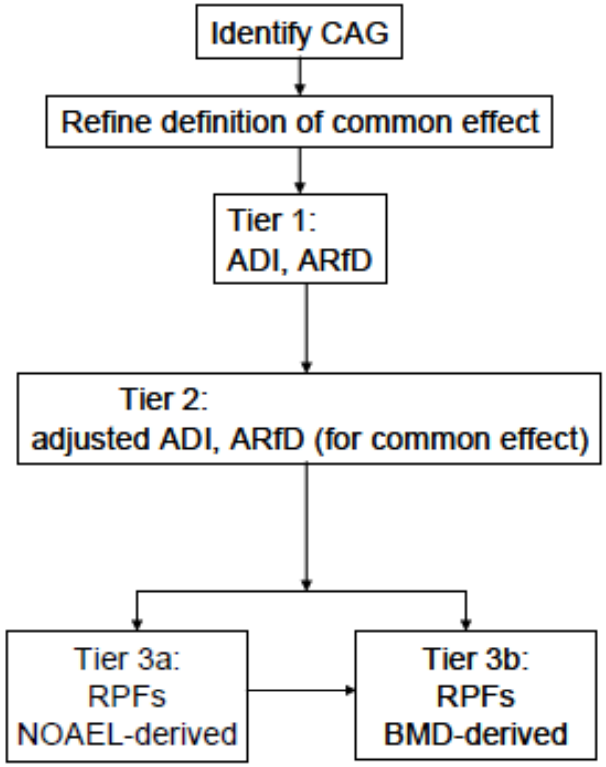
European Food Safety Authority

Tiered approach: Exposure



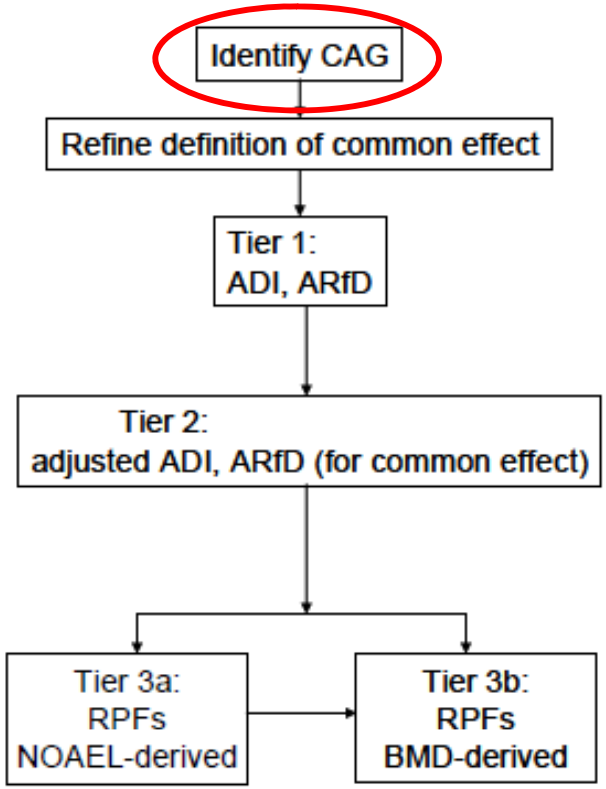
Risk assesment methodology Pesticides

Tiered approach: Hazard



Risk assesment methodology Pesticides

Tiered approach: Hazard



Risk assesment methodology
Triazoles

Triazoles for acute assessment	Triazoles for chronic assessment
bitertanol	bitertanol
cyproconazole	cyproconazole
diniconazole	difenoconazole
epoxiconazole	diniconazole
flusilazole	epoxiconazole
propiconazole	flusilazole
triadimefon	myclobutanil
-	propiconazole
-	tebuconazole
-	triadimefon
-	triadimenol

A comprehensive exercise to test methodology:

- Both exposure and hazard
- Well –defined group
  - Structure,
  - Pesticidal mode of action
  - Toxicological effects.

Methodology on grouping of pesticides

EFSA Journal 2013;11(7):3293

SCIENTIFIC OPINION

Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile[1]

EFSA Panel on Plant Protection Products and their Residues (PPR)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

- **Mandate on cumulative assessment grouping: Terms of reference was only on Hazard Assessment and the identification of cumulative Assessment Groups (CAGs) based on their toxicological profile**

Methodology on grouping of pesticides

- Every pesticide may theoretically occur in a food item, the grouping of active substances in CAGs for the purpose of MRL setting cannot be driven by exposure assessments.
- Grouping has to be based on criteria solely derived from the intrinsic properties of the chemicals under consideration. These may include chemical structure, mode of action or the induction of common adverse effects.
- Such grouping criteria and CAGs may also be of use in exposure assessment-driven CRA, especially at higher tiers of the analysis.

Methodology on grouping of pesticides

Grouping criteria based on overly narrow definitions of modes of action or chemical structural criteria might miss substances that also contribute to a combined effect.

- Studies showed that combinations of chemicals with shared toxicity but diverse modes of action also exhibited joint effects.
- **THUS:** Approach takes as its starting point the common or shared adverse effects of components in a mixture.

Grouping of pesticides

Grouping approaches for chemicals:

- US-EPA, pesticides (Food Quality Protection Act) *common mechanism of toxicity*: OP's, carbamates, triazines, chloroacetanilides, pyrethrins/pyrethroids.
- US – dealing with contaminated sites (non-pesticides): exposure driven followed by considerations on *common mode of action*:
- National Research Councel (US 2008) on anti-androgens and CRA: *Common adverse outcome*

Grouping approaches

Similar Mode of Action ? What concept for performing Cumulative Risk Assessment(CRA)?

- Lack of reliable criteria for similarity of mechanisms and modes of action.
- Opinions about what should qualify for “similarity” differ considerably
- Grouping effort requires information about mechanisms or modes of action in relation to multiple toxic endpoints. Unfortunately, such information is often not available for many pesticides. The data requirements for the approval of pesticides, as laid down in Commission Regulation (EU) No 283/20136, are not geared towards meeting the requirements of CRA.

Methodology on grouping of pesticides

Prepatory work: Identifying adverse effects relevant for CRA, and of forming a basis for CAGs of pesticide active substances authorised in the EU.

- DTU 2012. Identification of Cumulative Assessment Groups of pesticides.
  http://www.efsa.europa.eu/en/supporting/pub/269e.htm

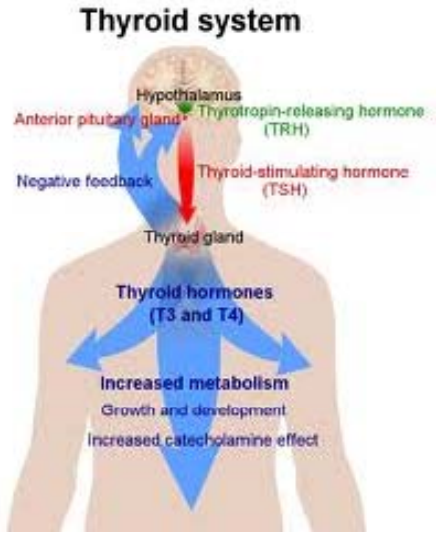
- Data collection for specific organs/organ systems, and which was published in 2013 (ANSES/ICPS/RIVM, 2013).
  http://www.efsa.europa.eu/en/supporting/pub/392e.htm

- However, according to EU residue monitoring programmes, some consumer exposure may occur from residues of non-approved pesticides. Pesticides not authorised in EU but where import tolerances exist should in the future also be included in CAG.
  - GP/EFSA/PRAS/2013/02: 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

Grouping of pesticides: Method

- **Identification of specific effect**
  - exclusion of local effects
  - exclusion of non-adverse effect
  - Exclusion of effects not relevant to humans
  - Evaluation of unambiguous nature of the effect
  - Identification of non-specific effects
- **Characterisation of the specific effects**
- **Data collection**
- **Grouping of pesticides into cumulative assessment groups (CAG's)**

Grouping of pesticides



CAG's for effects on thyroid system:
103 of 287 active substances:

C-cells (calcitonin systems): 25 substances
thyroid follicular cells and the T3/T4 system: 98 substances

Grouping of pesticides

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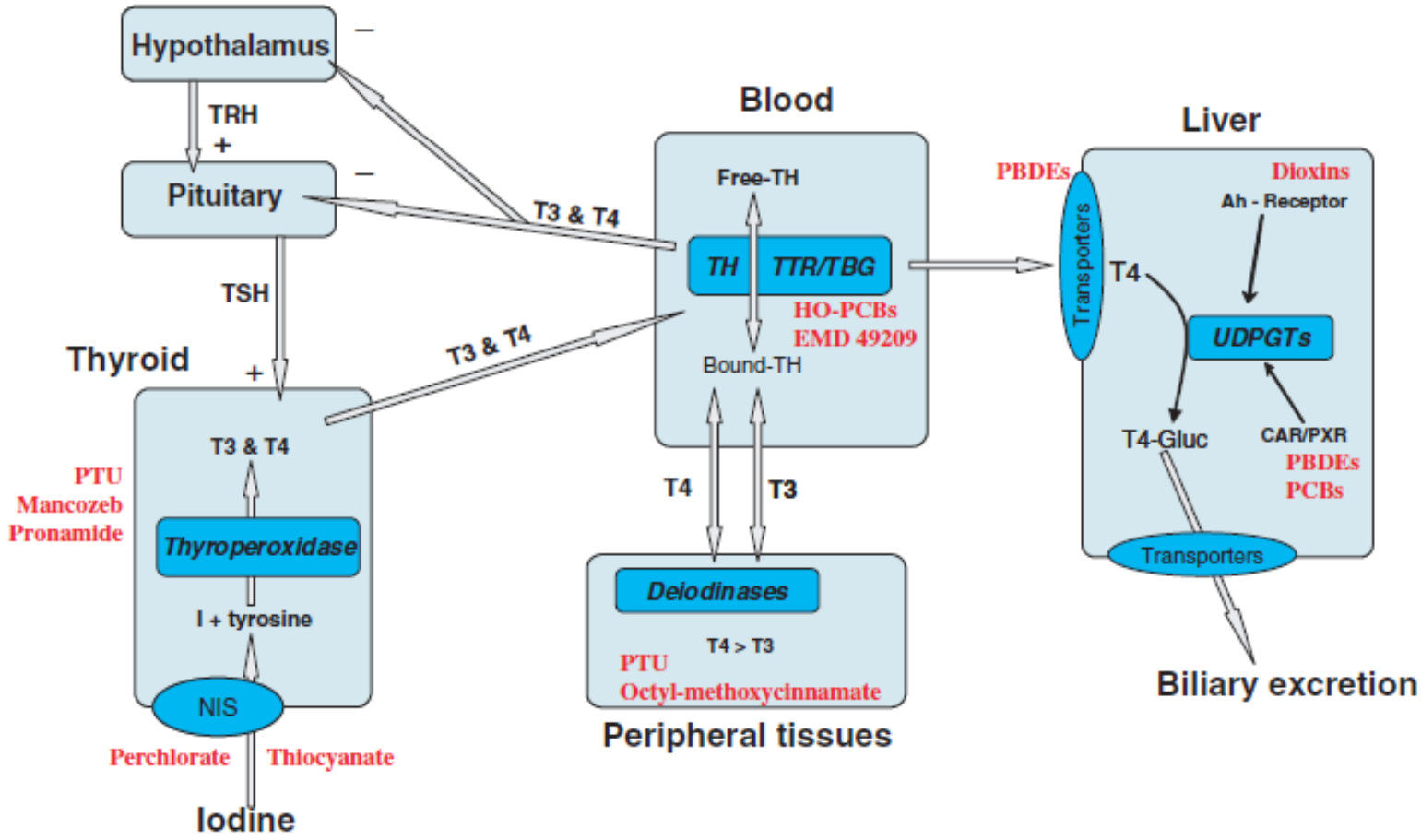


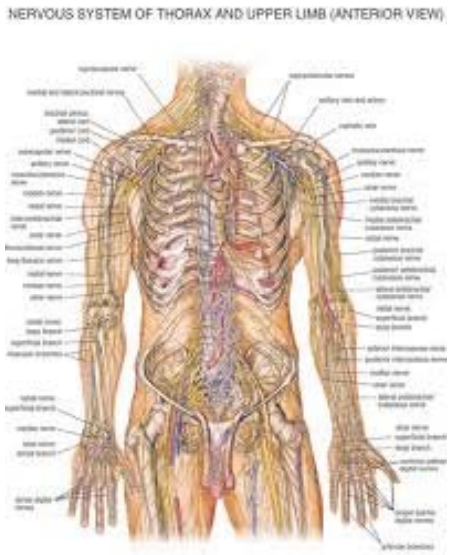
Crofton, K. 2008

Grouping of pesticides

CAG's for the nervous system:
68 of 287 active substances

Acute exposure (49)
- Motor division (45)
- Sensory division (21)
- Autonomic division (29)

Chronic exposure (65)
- Motor division (53)
- Sensory division (22)
- Autonomic division (24)
- Neuropathological changes (21)



Grouping of pesticides

CAG's for the nervous system:
Based on phenomological effects

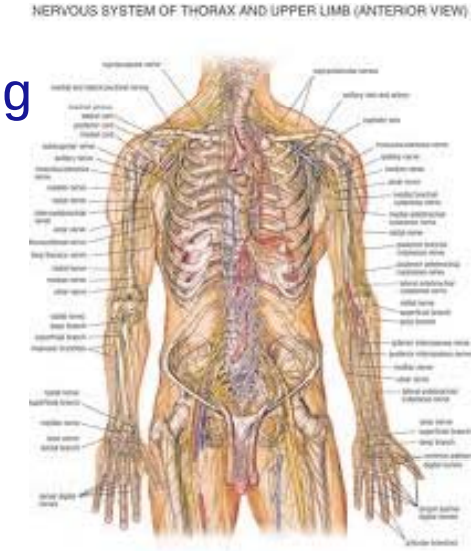
Acute exposure (49)

- Motor division (45)

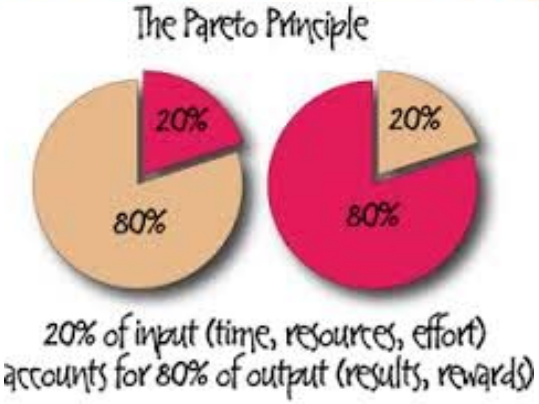
indicator of specific effect: ataxia
convulsions, hunched posture, landing
reduced motor
activity etc.

Modes of action:

Inhibition of AChE (8)
Type I pyrethroid (2)
Type II pyrethroid (6)
Nicotinic AChR agonist (5)
Others….
Unknown



Grouping of pesticides: Impact?



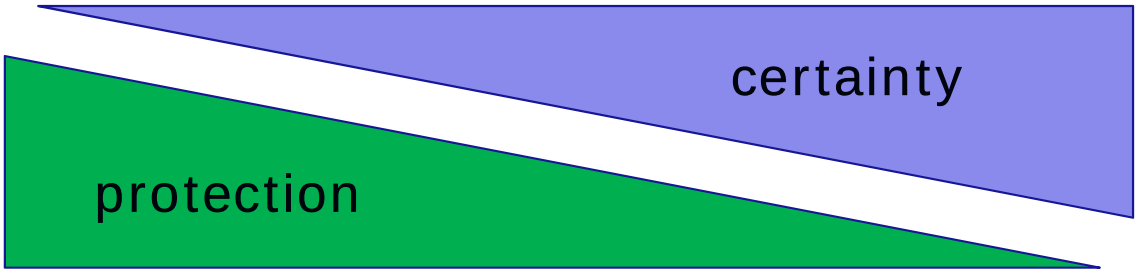
The CAGs derived from this methodology could in principle be used to support CRA resulting from non-dietary exposures (i.e. operator, worker, bystander and resident exposure).

The application of grouping methodology has yielded CAGs with sometimes large numbers of pesticides.

- little indication of cumulative risk may be inferred from the size of CAGs *per se*

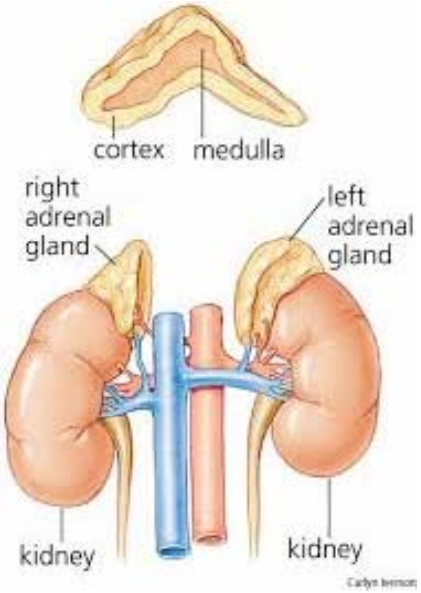
Within large CAGs, the majority of pesticides might not contribute significantly to a given combination effect, either because exposure is very low, and/or because potency in relation to the effect considered is weak. Instead, cumulative effects are likely to be driven mainly by a few active substances within the group.

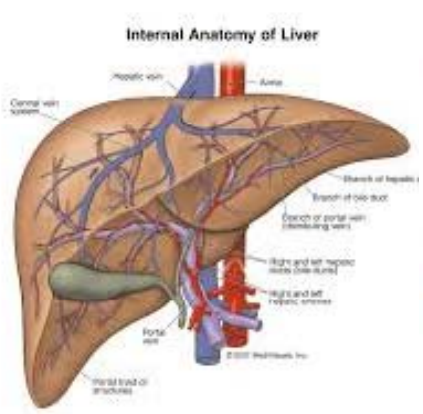
Uncertainties

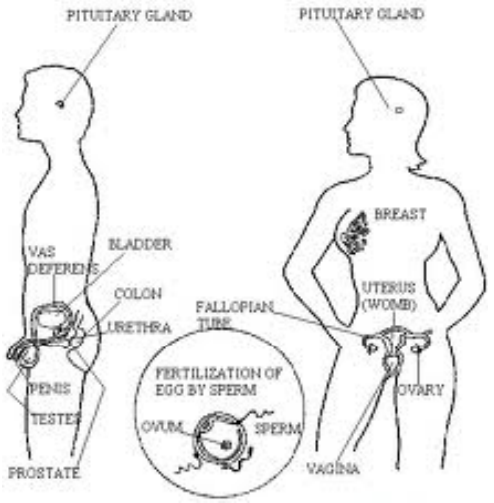


- No experimental information
- Different MoA's causing common adverse outcome – dose addition?
- Not based on assessment of original data- DAR's
- Considerable change over time in reporting and assessment
- Change over time in data requirements, study protocols – i.e. end points investigated

Grouping of pesticides







Comprehensive preliminary work has been done on effects on the liver, adrenals, eye and developmental and reproductive system and provides a starting point for developing CAGs also for these systems in the future. Further refinement of grouping maybe achieved when data on the precise toxicological mode of action are available.

However, information that justifies any deviation from dose-addition might also be necessary to consider for such a refinement.

Recommendations

International Frameworks Dealing with Human Risk Assessment of Combined Exposure to Multiple Chemical (EFSA 2013).

Recommendations:

- Harmonise terminology and methodology. Develop methodology on ecological RA and animal health
- Longer term activity methodology for RA of exposure to multiple chemicals with other stressors
- Exposure: collection of occurrence data for priority chemicals in individual food samples, methodologies to perform aggregate exposure assessment
- Hazard: more information on Mode of Action/Mechanism of Action
- Development of guidance for uncertainty analysis.

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