



# General introduction and on-going work of EFSA

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# LEGAL CONTEXT FOR PESTICIDES

## Legal basis

Regulation (EC) No 396/2005 (MRLs)

Regulation (EC) No 1107/2009 (Authorisation of PPPs)

Both regulations require cumulative risk assessment

- ❑ Achievement of a high level of protection
- ❑ Application of the precautionary principle when there is scientific uncertainty



## LEGAL CONTEXT FOR PESTICIDES

### When should a cumulative risk assessment be conducted?

Pre marketing situation

- ❑ Applications for MRLs (Art. 14 of Regulation (EC) No 396/2005)
- ❑ Authorisation of plant protection products (Art. 4 of Regulation (EC) No 1107/2009)

Post marketing situation

- ❑ Analysis of official monitoring results regarding acute and chronic risks to the health of consumers

### Various regulatory questions:

Safety of the use, safety of the MRL, actual level of safety



## DEVELOPMENT OF METHODOLOGIES

**2006 EFSA's 7th Scientific Colloquium – Cumulative Risk Assessment of pesticides to human health**

**2007 to 2013 Development of methodologies by the EFSA Panel on plant protection products and their residues**

- ❑ Hazard assessment: Cumulative Assessment Groups of pesticides
- ❑ Exposure assessment: Probabilistic modelling of the dietary exposure to pesticide residues
- ❑ Risk assessment: Tiered methodology for cumulative risk assessment



## DEVELOPMENT OF METHODOLOGIES

A **cumulative assessment group** is a set of pesticides that could plausibly act in combination and cause a specific toxicological effect.

All pesticides causing a common specific (adverse) effect are included within a same cumulative assessment group.

Why not similarity of chemical structure or mode of action?

- ❑ Often modes/mechanisms of action are unknown
- ❑ Different modes/mechanisms of action may contribute to a same adverse effect
- ❑ Consultation of the EU Commission

Pesticides included in a CAG are toxicologically characterised by appropriate indicators and relative potency factors.



## DEVELOPMENT OF METHODOLOGIES

Identification of the **specific effects** that adversely affect an organ or system.

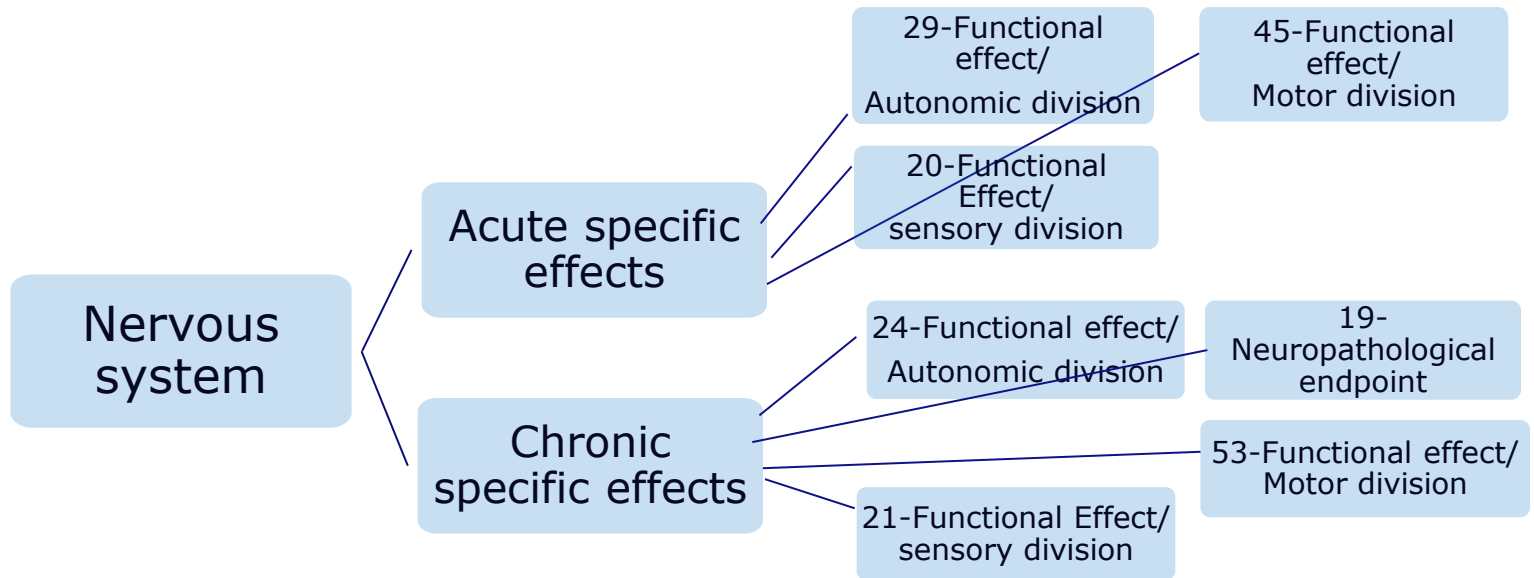
- ❑ Exclusion of local effects
- ❑ Exclusion of non-adverse effects
- ❑ Exclusion of effects not relevant to humans
- ❑ Unambiguous nature of the toxic effect
- ❑ Identification of non-specific effects

Expert judgement is needed as information supporting the precise nature of the adverse effect to specific organs or systems is often lacking.



## DEVELOPMENT OF METHODOLOGIES

### Example of CAGs: Nervous system



## DEVELOPMENT OF METHODOLOGIES

### Example of CAGs: Thyroid system







## DEVELOPMENT OF METHODOLOGIES

### **Consequence** of the methodology to establish CAGs:

- ❑ Substantial CAGs, but:
  - Cumulative risks are likely to be driven by a few pesticides or pesticides/commodity combinations
  
- ❑ Potential to overestimate the actual cumulative risks, but:
  - Further refinement might potentially be achieved when detailed information of the precise toxicological modes of action and on actual combined toxicity is available  
*e.g. AChE inhibition*



## DEVELOPMENT OF METHODOLOGIES

### **Recommendation** of the PPR Panel:

- ❑ Research on characterising adverse outcome pathways to refine CAGs.





## DEVELOPMENT OF METHODOLOGIES

### Guidance for probabilistic modelling of dietary intake

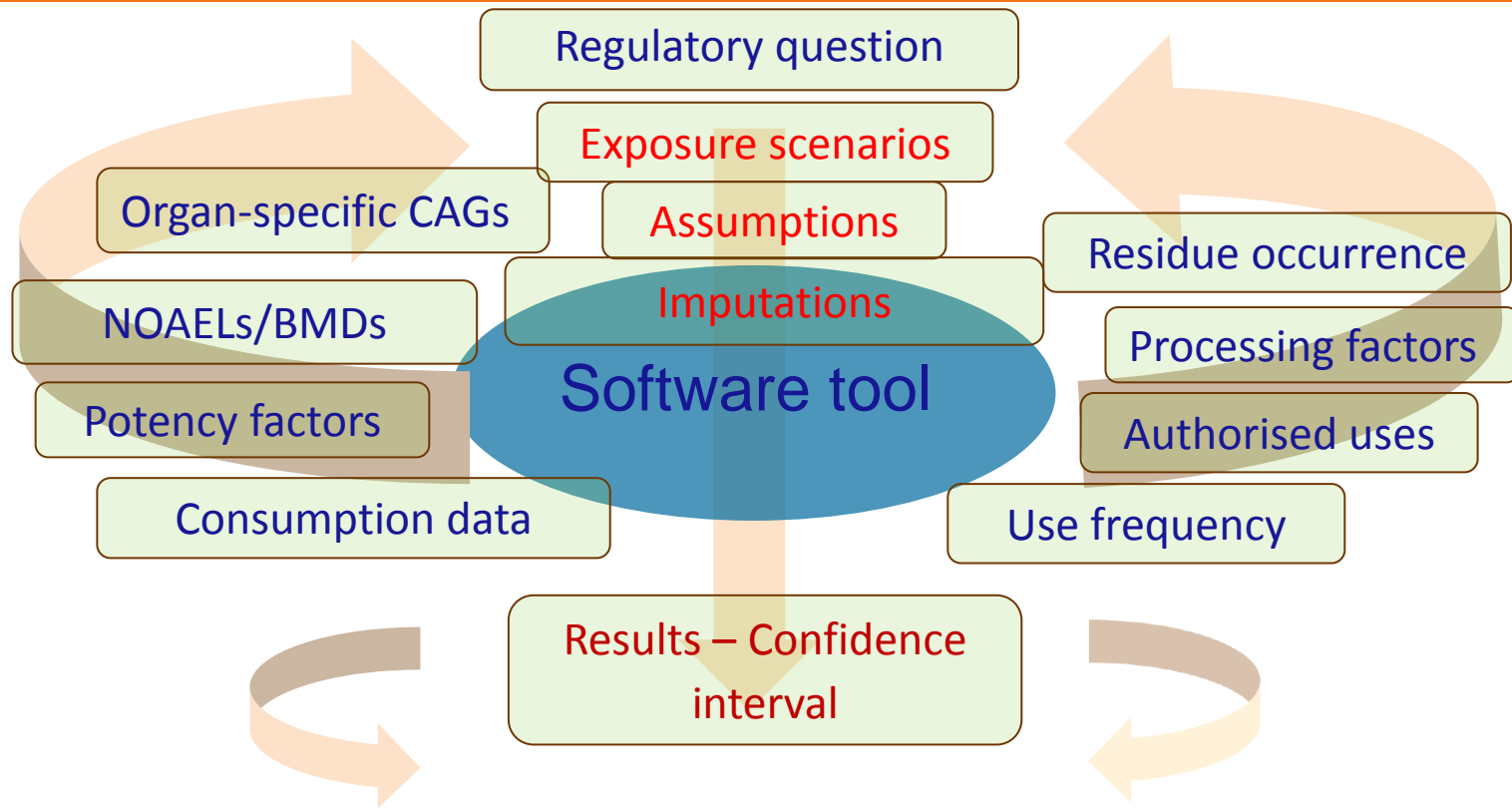
Probabilistic modelling is essential for cumulative risk assessment, especially for acute effects

- ❑ Various regulatory questions
- ❑ Basic and refined modelling
- ❑ Acute and chronic exposure
- ❑ Sensitivity analysis
- ❑ Presentation of results and of uncertainties
- ❑ Check list for transparent reporting





## DEVELOPMENT OF METHODOLOGIES





## DATA HANDLING AND MANAGEMENT

Future repository of information: **EFSA Data Warehouse**

<http://www.efsa.europa.eu/en/press/news/150302>

- ❑ Use of the EFSA Data Warehouse to store the information needed for cumulative risk assessment
- ❑ Access rules
- ❑ Different aggregation levels or data providers, stakeholders and general public.





## DEVELOPMENT OF METHODOLOGIES

### Tiered methodology for cumulative risk assessment

- ❑ Assessment using the concept of **dose addition** which assumes that each component of the CAG contributes to the effect in proportion of its dose and individual potency.
- ❑ Different modes of expression of the combined toxicity are possible: (Hazard Index, adjusted Hazard Index, Combined margin of exposure, Index compound approach)
- ❑ Tiered process with different level of refinement of the hazard characterisation (NOAELs – BMDs) and/or of the exposure assessment (Deterministic – Probabilistic)
- ❑ PBTK and PBDT modelling as possible approach for further development



## DEVELOPMENT OF METHODOLOGIES

### **Some recommendations** of the PPR Panel:

- ❑ Research in mammalian systems to investigate the applicability of independent action and identify cases where independent action might provide more conservative predictions of mixture effects.
- ❑ To address residual uncertainties as to whether default application of dose addition is generally sufficiently conservative, it is important to better define determinants of synergisms, by researching the possibility of toxicokinetic and toxicodynamic interactions





## DEVELOPMENT OF METHODOLOGIES

**New challenges** created by cumulative risk assessment

- ❑ New way to express and communicate risk
- ❑ Definition of new Protection Goals
- ❑ Scientific complexity
- ❑ Uncertainties







## DEVELOPMENT OF A SOFTWARE TOOL

### **2010-2013 ACROPOLIS Project**

Funded by the EU Commission

RIVM and 17 partners and associated partners

Development of MCRA, a web-based tool accessible for stakeholders performing probabilistic cumulative and aggregated exposure to pesticides

Alignment on the PPR Panel guidance on probabilistic modelling

Wide support from Member States



# IMPLEMENTATION OF CUMULATIVE RISK ASSESSMENT

## 2014 First EFSA implementation plan of cumulative risk assessment

- ❑ EFSA/RIVM Framework Partnership Agreement (FPA)
- ❑ Internal activities to produce CAGs and the first cumulative risk assessments (CRAs).





# IMPLEMENTATION OF CUMULATIVE RISK ASSESSMENT

## EFSA/RIVM FPA (2015-2016)

### Improvement of the capacity of the MCRA tool:

- ❑ Scalability of the MCRA tool for large cumulative assessment groups (Action completed, MCRA Version 8.1)
- ❑ Development of a data model compatible with the EFSA data Warehouse and organising information used by the MCRA software (contract to be signed in May-June 2016)

### Pilot project (*Post marketing situation*):

- ❑ Cumulative exposure assessment of pesticides with acute effects on the nervous system (External Scientific report end 2016)
- ❑ Cumulative exposure assessment of pesticides with chronic effects on the thyroid (External Scientific Report end 2016)



# IMPLEMENTATION OF CUMULATIVE RISK ASSESSMENT

## Internal activities

2016-2018: EFSA Scientific Reports on CAGs

- ❑ Nervous system, liver, adrenals, eyes, reproduction and development and thyroid system.
- ❑ Public consultations

2017: EFSA Scientific reports on Cumulative Risk Assessments (*Post marketing situation*)

- ❑ Acute effects on the nervous system
- ❑ Chronic effect on the thyroid



## COOPERATION

### 2016 and beyond: Second EFSA implementation plan of cumulative risk assessment

#### Possible new areas of cooperation:

- ❑ Linking of industrial and household processes investigated in processing studies for pesticides and the EFSA Food coding system and collection of processing factors.
- ❑ Establishment of additional CAGs (kidneys, testes and heart) and update of those established.
- ❑ 2<sup>nd</sup> EFSA/RIVM partnership agreement aiming at using, maintaining and improving the MCRA tool for the cumulative risk assessment of pesticide residues in food and feed commodities