18 September 2019

Risk assessment of combined exposure to multiple chemicals in EFSA

Experience gained and lessons learned

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DATA Unit

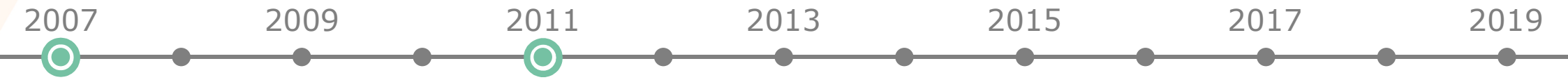
Trusted science for safe food

European Food Safety Authority

Overview

- Development activities
- Cumulative risk assessment of pesticides
- Future perspectives
- Engagement of Member States

Development activities



Legal background

- *Regulation 396/2005 on the setting of MRLs*
- *Regulation 1107/2009 on the authorisation of PPPs*
- *"take into account known cumulative and synergistic effects* of pesticides *when the methods are available"*

Development activities for pesticides

- *Tiered methodology for cumulative risk assessment (PPR, 2009)*
- *Methodology for probabilistic exposure assessment (PPR, 2012)*
- *Methodology for cumulative assessment groups (PPR, 2013)*
- *Monte Carlo Risk Assessment software (ACROPOLIS Project, 2013)*

Pilot for pesticides

- *Effects on the thyroid and the nervous system*
- *Framework partnership agreement with RIVM (MCRA software)*
- *Issued for public consultation in 2019*

Cross-cutting activities

- *Scientific colloquium (2015)*
- *Guidance on the risk assessment of combined exposure to multiple chemicals (SC, 2019)*

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CRA Pesticides – Scope of the project

- **Retrospective risk assessment:**
  - Official pesticide monitoring data (Art.32 Reg. 396/2005)
  - Reference period 2014-2016
- **Target organs:**
  - Thyroid (chronic)
  - Nervous system (acute)
- **Population groups:**
  - Adults (BE, CZ, DE, IT)
  - Children (BG, FR, NL)
  - Toddlers (DK, NL, UK)
- **Food commodities:**
  - 30 Raw primary commodities (plant origin only, most frequently consumed)
  - Food for infants and young children
  - Water

CRA Pesticides – Cumulative assessment group

420 active substances have been reviewed

Thyroid

2 effects of relevance

2 CAGs retained for assessment

Hypertrophy, hyperplasia and neoplasia of C-cells *(CAG-TCP, 18 substances)*

Hypothyroidism
(CAG-TCF, 124 substances)

Nervous system

5 effects of relevance

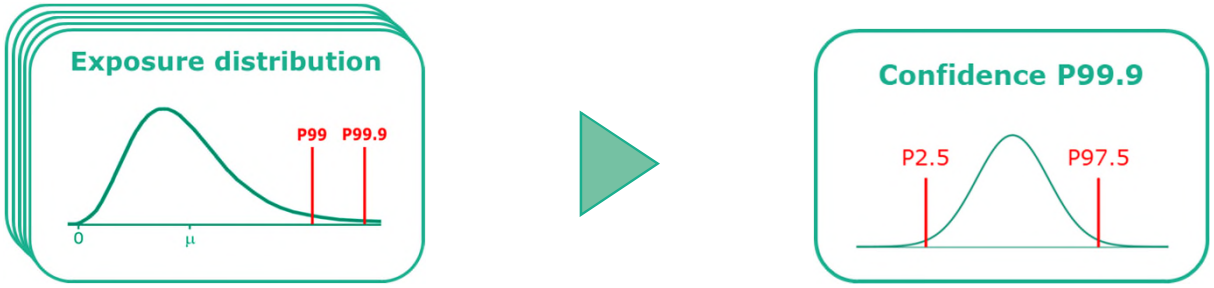
2 CAGs retained for assessment

Brain and/or erythrocyte AChE inhibition *(CAG-NAN, 47 substances)*

Alterations of the motor division *(CAG-NAM, 100 substances)*

CRA Pesticides – Exposure assessment

- **Two-dimensional probabilistic method:**



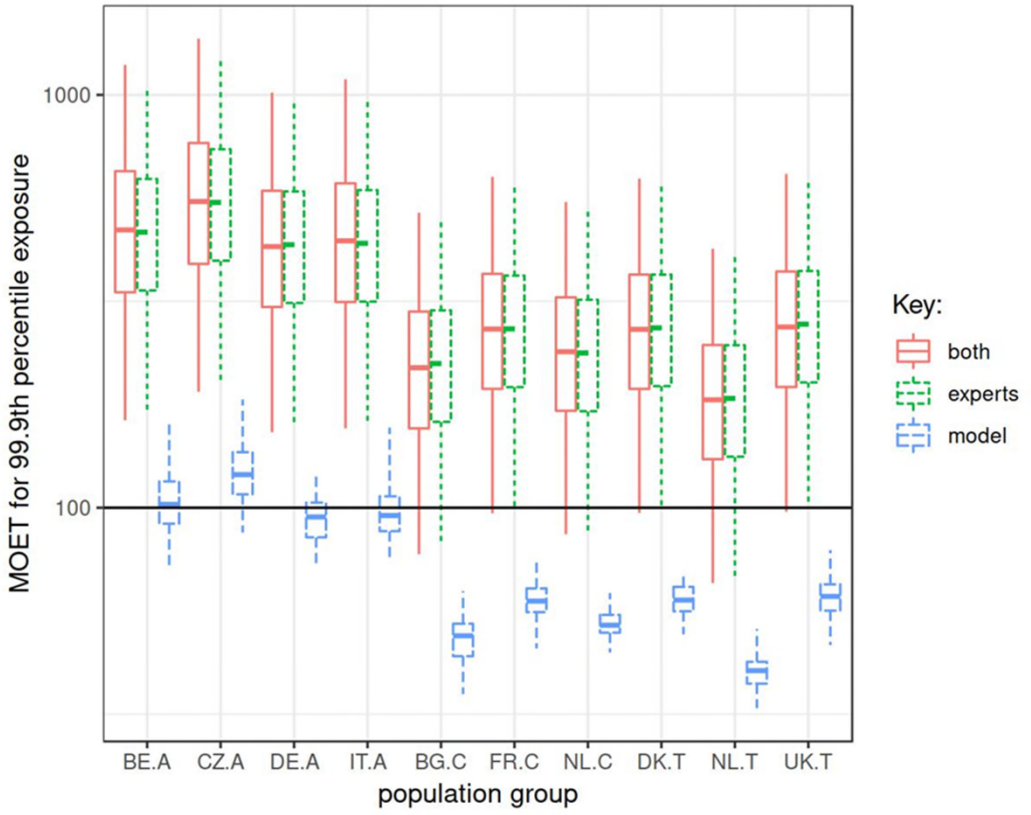
- **Assumptions and criteria (defined by SC PAFF):**
  - Conservative assumptions to compensate for missing or limited data
  - Tier I & Tier II scenarios
  - Combined/total margin of exposure (MOET)
- **Threshold for regulatory consideration (agreed by SC PAFF):**
  - 99.9th percentile of the exposure distribution
  - MOET ≥ 100

CRA Pesticides – Uncertainty analysis

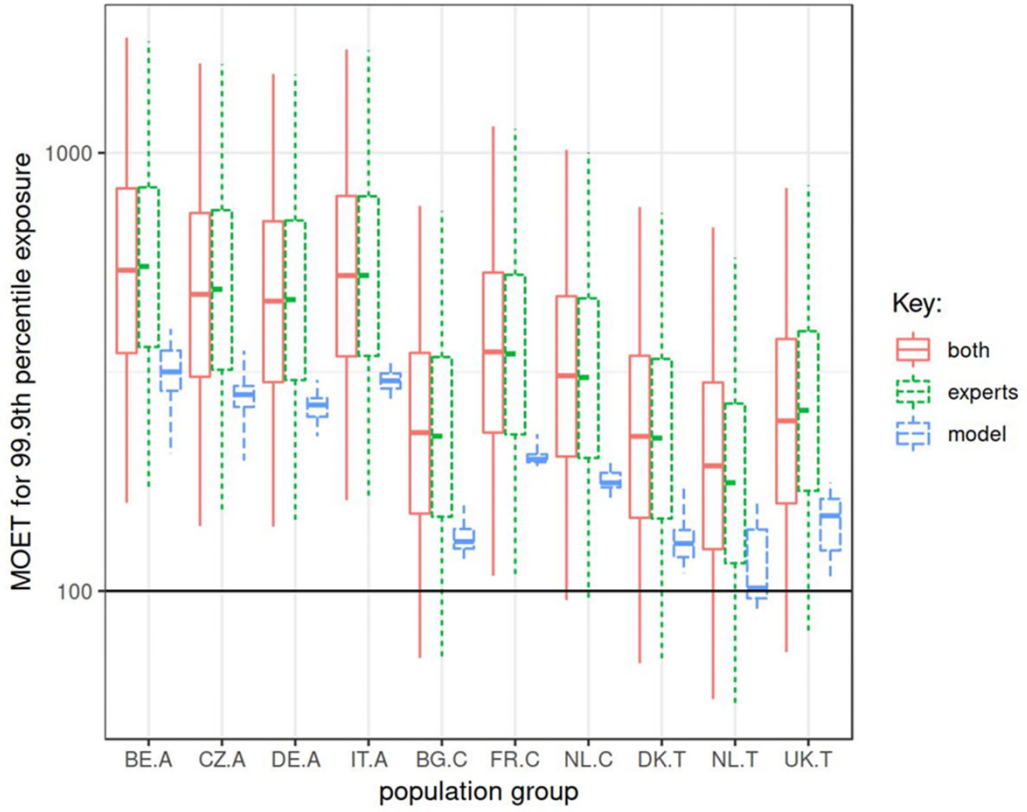
- **Starting point:**
  - MOET at the 99.9th percentile of the exposure distribution calculated for the Tier II scenario (confidence interval for sampling uncertainty only)
- **Purpose:**
  - Determining what would be the MOET at the 99.9th percentile of the exposure distribution if all uncertainties were resolved
  - Determining the probability that the MOET for the 99.9th percentile of exposure for each population in 2014-2016 is below 100
- **Expert knowledge elicitation:**
  - Preliminary step: Identification of all sources of uncertainties
  - Step 1: Evaluation of individual uncertainties
  - Step 2: Combined impact of exposure and toxicology uncertainties
  - Step 3: Effect of dependencies

CRA Pesticides – Results

AChE inhibition



Hypothyroidism



CRA Pesticides – Conclusions

- **Overall conclusion**

  Taking account of the available data and the uncertainties involved, it is concluded that cumulative exposure to pesticides that have acute effects on the nervous system or chronic effects on the thyroid does not exceed the threshold for regulatory consideration established by risk managers.

- **Degree of certainty on this statement**
  - Adults: almost certain (> 99% certain)
  - Children and toddlers: likely to very likely (≈ 80-95% certain)
- **Factors driving the acute exposure distributions**
  - Single substances in a specific commodity (75% of the upper part)
  - Commodities exceeding the MRL (40 to 95%)

CRA Pesticides – Recommendations

- **Reduction of uncertainties:**
  - Use Benchmark Dose (BMD) modelling to characterise the active substances
  - Consolidate the list of processing factors
  - Collect information on use frequency
  - Include in probabilistic calculations the sources of uncertainties which can be modelled (e.g. CAG membership)
  - Include relevant commodities and active substances that were not included so far
- **Others:**
  - Identify scientific strategies to optimize future CRAs
  - Establish a CAG and perform a CRA for developmental neurotoxicity
  - Perform a chronic CRA for AChE inhibition

CRA Pesticides – Scientific reports

Target organ	Author	Subject	Status
Thyroid	EFSA	Establishment of *cumulative assessment groups*	Published
Thyroid	RIVM	Cumulative dietary *exposure assessment using MCRA software*	Published
Thyroid	EFSA	Cumulative dietary *exposure assessment using SAS® software*	Published
Thyroid	EFSA	Cumulative dietary *risk characterisation*	Public consultation
Nervous system	EFSA	Establishment of *cumulative assessment groups*	Published
Nervous system	RIVM	Cumulative dietary *exposure assessment using MCRA software*	Published
Nervous system	EFSA	Cumulative dietary *exposure assessment using SAS® software*	Published
Nervous system	EFSA	Cumulative dietary *risk characterization*	Public consultation

CRA Pesticides - What about the US?

EU

- ***Regulation (EC) No 1107/2009:*** "ensure that the chances of failing to detect adverse effects or of under-estimating their importance are reduced to a minimum"
- Grouping based on the similarity of ***mode of action*** or ***phenomenological effects***
- Cumulative effects of N-methyl carbamates and organophosphorus assessed ***jointly*** for AChE inhibition

US

- ***Food Quality Protection Act:*** "cumulative effects of such [pesticide] residues and other substances that have a common mechanism of toxicity."
- Grouping based on the similarity of ***mode of action***
- Cumulative effects of N-methyl carbamates and organophosphates assessed ***separately*** for AChE inhibition

▶ **Difference is in the problem formulation**

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Future perspectives – Lessons learned

1. **Planning the hazard, exposure and risk assessment**
   - Strengthen project governance
2. **Alignment with generic activities (MixTox, EuroMix)**
   - Integration of methods development in project governance
   - Integration of stakeholder involvement in project governance
3. **Resourceful scientific process (for CAGs in particular)**
   - Leaning the process with clear priority setting

Future perspectives – Project governance

Project Steering Committee

Project Sponsor
RASA HoD

Project manager (DATA)	**SCER** HoU	**PRES** HoU	**PREV** HoU	**DATA** HoU	**COMCO** HoD	**REPRO** HoD

Project Management Office (DATA)
Overall coordination, liason with RAM-Pro and cooperation with Stakeholders

WP1 (SCER) Methods development	**WP2 (PREV)** Prioritisation of organs and leaning of CRA approach	**WP3 (PREV)** Hazard characterisation of CAGs	**WP4 (DATA)** Exposure assessment	**WP5 (PRES)** Risk characterisation	**WP6 (COM)** Communication

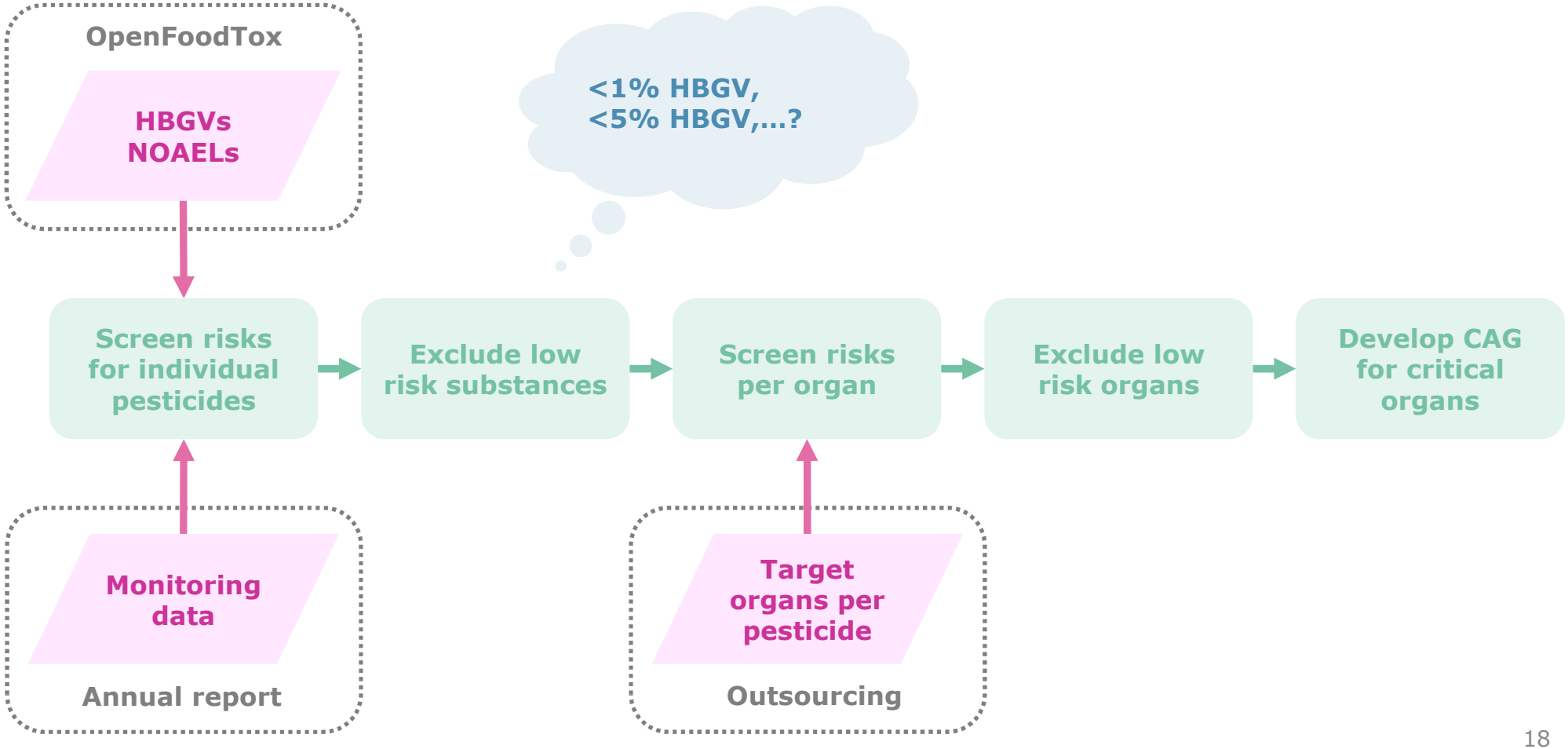
Future perspectives – Methods development

- **Priorities for exposure routes and chemicals**

Dietary exposure to multiple **pesticides** → **Dietary** exposure to multiple **chemicals** → **Aggregated** exposure to multiple **chemicals**

- **Scientific criteria for grouping chemicals into assessment groups**
  - Cross-cutting working group of the Scientific Committee
  - Applicable to all chemicals in the remit of EFSA
  - Terms of reference adopted in June 2019
  - Public consultation in Autumn 2020
  - Scientific opinion in Spring 2021

Future perspectives – Leaning CRA approach



Future perspectives – Leaning CRA approach

1. **Consolidate data on the target organs for pesticides**
   - Build on data previously collected (224 pesticides)
   - To be finalised in Autumn 2020
2. **Validation of the screening method**
   - Use data for the thyroid and the nervous system
   - Impact assessment for different thresholds
   - To be finalised in Autumn 2020
3. **Close collaboration with Scientific Committee**
   - Alignment with grouping criteria
   - Draft scientific opinion expected in Autumn 2020

▶ **Lean approach for pesticides expected end-2020**

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Engagement MSs – Partnerships with RIVM

- **On-going partnership**
  - Validation of the screening method for individual substances
  - Operational plan to transform MCRA into open MCRA
  - Enhancement of data-integration into MCRA
  - Prospective scenarios in view of setting MRLs for pesticides
  - Expires end-2020
- **Shape future partnership**
  - Allow for a more dynamic exchange
  - Involvement of other Member States' agencies

Engagement MSs – Future of MCRA software

efsa
European Food Safety Authority

Step 1
Modular & Open Source

- Composed of separate modules (e.g. BMDL calculator)
- Access to programs codes and re-use
- Modules can be used independently if needed
- MCRA interface for sequential use of modules
- Multiple interfaces possible (e.g. EuroMix)

Step 2
Shared platform

- Platform currently hosted by RIVM
- Platform accessible to pre-defined user groups (incl. Member States)
- Transfer MCRA to interagency platform
- Direct access to input data while maintaining confidentiality
- Computational cost

Step 3
Co-creation

- Co-creation of modules by EFSA, RIVM and other Member States
- Updating existing modules or creating new modules
- MCRA governance to ensure coordination among Member States

Engagement MSs – Other opportunities

- **Other partnerships envisaged**
  - Consolidation of EU database on processing factors (BfR)
  - Consolidation of toxicological databases for the different chemicals under EFSA's remit, incl. target organs for pesticides (partners to be identified)
  - MYCHIF: Integrated and innovative modelling methodologies for the risk assessment of mycotoxin mixtures in food and feed (Universities of Piacenza, Parma, Minho, Belfast and INRA Toulouse)
- **Public consultations**
  - Cumulative dietary risk characterization for pesticides that have effects on the thyroid or on the nervous system (ongoing)
  - Scientific criteria for grouping chemicals into assessment groups (Autumn 2020)
- **International EFSA MIXTOX Workshop (Autumn 2020)**

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