Exposure assessment to multiple chemicals and future mixture testing

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Content

1. Risk assessment vs epidemiology
2. About EFSA work on (dietary) risk assessment of mixtures
3. Mixture testing and how risk assessment can be refined with new test results (EuroMix project)
4. How epidemiology can confirm risk assessment results
5. Platform of models and data
Dietary risk Assessment

Exposure assessment
national databases
- Exposure sources
- Exposure route
- Exposure level
- Highly exposed groups

Effect assessment
Hazard identification
Identification of negative health effects
- target organ and critical effect

Hazard characterization
- Selection of critical data
- Mechanism of toxicity
- Dose-response for critical effect
- "Point of departure"
- Kinetic and dynamic variability
- Sensitive groups

Risk characterization
ACCEPTABLE DAILY INTAKE
SAFETY FACTORS APPLIED (10x10)
No harm is expected, but what about epidemiologic findings?

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EFSA Cumulative Risk Assessment


2015 2016

Colloquium

Scientific Opinion
Evaluating CRA methodologies

Scientific Opinion
Testing CRA methodologies

Guidance assessment

EFSA info-session on Cumulative risk assessment

11th February 2014

2010/2011 EU Report
CRA exercises

Framework partnership agreement

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LEVEL 1

EFSA grouping pesticides into cumulative assessment groups (CAGs or mixtures)

16 organs identified

- Adrenal glad
- Bone marrow
- Bones/skeleton
- Cardiovascular system
- Eye
- Gallbladder
- Haematological system
- Kidney
- **Liver**
- Muscles
- Nervous system
- Parathyroid gland
- **Reproductive system**
- Developmental toxicity
- Spleen
- Thyroid
- Urinary bladder

1) EFSA finalized cumulative assessment group
2) EFSA Proposed cumulative assessment group, EuroMix test cases
Concept testing strategy

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Adverse Outcome Pathways

Useful concept to:

- Organize current scientific knowledge
- Consistent documentation and evaluation
- Translate information from lower tier testing into something that actually matters from a regulatory perspective
Advanced AOP for liver steatosis

**Molecular effects**

- ER binding
- PPAR-α antagonism binding
- LXR activation
- PPAR-γ activation
- AHR agonism
- Activation of: ChREBP, SREBP-1c, FAS, SCD1
- Increase of fatty acid influx from peripheral tissues
- CD36
- Differentiation
- Inhibition of respiration = NAD+ depletion
- Inhibition of the mitochondrial β-oxidation
- Inhibition of the microsomal β-oxidation
- De novo fatty acid synthesis
- Triglyceride accumulation
- *Cytoplasm displacement
- *Nucleus distortion
- *Mitochondrial disruption
- *Endoplasmatic reticulum stress

**Cellular effect**

- ER transactivation assay (DLO-R)
- reporter gene assays (BfR)

**Tissue/organ effect**

- parameters related to mitochondrial function (UGENT)
- neutral lipid content (INRA/DLO-R)
- Oil Red O staining (BfR)
- GC/MS measurement DLO-R
- gene level: PCR arrays (BPI)
- protein level: proteomics (ETHZ)

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Concept extrapolation to humans
Random sampling from a concentration and a consumption database
EFSA – RIVM partnership agreement

- EFSA collects consumption data of all European countries
- EFSA collates all (dietary) monitoring data
- Data organisation Cumulative Assessment Group Thyroid and Neuro System
- Scalability, reproducibility, accessibility and tutorials
Confusion, too many national approaches, not up-to-date data

- DE and UK methods (<2016)
- EFSA calculator (=>2015)
- BROWSE (>2014)

- EFSA calculator (lower tier, deterministic, worst-case and only for authorization)
- BROWSE (higher tier, probabilistic, for authorisation and for real exposure)

Other ad hoc models

Onderzoek Bestrijdingsmiddelen en Omwonenden (OBO)

Paul Hamey presentation BfR 2014
Occupational exposure EuroMix

BfR and Fera : Pesticides from CAG steatosis
  – Operator and Bystander exposures

ETHZ and ANSES : Substance to be selected regarding diet and cosmetic exposures
  – General population exposed by food and non-dietary sources such as cosmetics or personal care products
  – PB-PK model for bisphenol A
  – General population exposed by food and non-dietary sources such as dust, air, etc.
Dietary and occupational exposure

EFSA calculator and non-dietary exposure model(s)
EuroMix platform with data and models

Exposure to multiple chemicals via multiple routes (aggregated exposure)
- Food and occupational exposure
- Link between external and internal exposure (PB-PK models)
- Link with effect modelling
- Links with molecular fingerprints (omics)

Web-based infrastructure data and models available to all stakeholders (also beyond the lifetime of the project)
HBM4EU partners

22 EU Member States
3 Associated States
1 Partly Associated State

(3 candidates to join in later)

109 Partners
41 Participants

Financial volume: ~ 73 M €

Management Board Member
Activities on mixtures in HBM4EU

- Identification of most relevant chemical mixtures for risk assessment
  - development of aggregated mixture indicators
  - integration of various approaches and conventions of countries
  - database of existing HBM mixture data

- Joint survey on HBM mixtures in 3-5 countries, and apply overarching analysis across priority substances to get aggregated HBM profiles
  - study populations enrolled based on exposure gradient
  - priority substances and pesticides (due to EU/EFSA approach)

- Identification of mixture health effects, translation of aggregated indicator analysis into policy recommendations and future research recommendations, and risk assessment of the observed mixtures in existing / newly collected HBM data
  - close co-operation with ongoing EU projects
  - liaison with EFSA activities
  - use and/or development of effect markers
1. Many chemicals might share a common effect

2. New developments testing mixture effects of chemicals

3. EFSA is responsible for European risk assessment
   - consumption and monitoring data collection
   - risk assessment opinions
   - EFSA-RIVM partnership agreement on exposure modelling

4. Link between epidemiology and risk assessment
   - epidemiology can confirm of risk assessment (preferable not)
   - exposure calculations and biomarkers of exposure/biomarkers
   - challenge to link data and results of both research areas

Summary
Further reading

Scientific Opinion on Risk Assessment for a Selected Group of Pesticides from the Triazole Group to Test Possible Methodologies to Assess Cumulative Effects from Exposure through Food from these Pesticides on Human Health (2009)


Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile (2013)


Scientific Opinion on the relevance of dissimilar mode of action and its appropriate application for cumulative risk assessment of pesticides residues in food (2013)
Further reading

Info Session on Applications - Pesticides – Technical meeting on Cumulative Risk Assessment. Parma 11-02-2014

ACROPOLIS website: acropolis-eu.com

Scientific publications ACROPOLIS project: Food and Chemical Toxicology
Volume 79, Pages 1-80 (May 2015) Toxicity testing and model development for estimating cumulative and aggregate exposure to pesticide residues in Europe
Edited by Susan M. Barlow and Polly E. Boon

http://www.euromixproject.eu/
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EuroMix participants

22 beneficiaries from 16 countries linked to international organisations including WHO, FAO and EFSA. EuroMix is coordinated by RIVM.