SITOX- XIX Congresso Nazionale
Bologna, 11-12 febbraio 2020

SESSIONE: CO-ESPOSIZIONE A RESIDUI DI PRODOTTI FITOSANITARI

Problemi di armonizzazione dell'approccio alla valutazione delle co-esposizioni.

Angelo Moretto

Department of Biomedical and Clinical Sciences
Università degli Studi di Milano
International Centre for Pesticides and Health Risk Prevention (ICPS)
ASST Fatebenefratelli Sacco, Milano
angelo.moretto@unimi.it

Outline

- General considerations
- Grouping
- Co-exposure
- Toxicology
- FAO/WHO workshop (April 2019)
- Recommendations
- Further steps

Cosa armonizzare?

- Non solo prodotti fitosanitari ma anche
  - Contaminanti
  - Additivi alimentari
  - Farmaci veterinari
  - Biocidi
  - …
- Non solo UE ma anche resto del mondo
  - Commercio delle derrate agricole
  - …

Le co-esposizioni nella legislazione dell'UE

Reviewed Regulations and Directives of the EU law		Principals of the regulations	Mixture assessment for human health required?	Guidance for implementation of CRA available?
Biocidal products	Reg. EU No. 528/2012	Procedure: appr. of substance & author. of products	Yes	Yes ECHA, 2015a
CLP	Reg. EC No. 1272/2008	Classification of substances & mixtures	Yes	Yes ECHA, 2015b
Plant Protection Products	Reg. EC No. 1107/2009 Reg. EU No. 283/2013 Reg. EU No. 284/2013	Procedure: appr. of substance & author. of products	Yes	No
MRL`s	Reg. EC No. 396/2005	Setting of maximum residue levels	Yes	No
Medicinal Prod. for Human & Veterinary Use	Direct. 2001/83/EC Direct. 2001/82/EC	Author. procedure of products	Yes	Yes, drug interactions
Cosmetics	Reg. EC No. 1223/2009	Author. procedure of products	Yes	No
REACH	Reg. EC No. 1907/2006	Registration, authorisation of chemicals	No	No
Food and Feed Additives	Reg. EC No. 1333/2008 Reg. EC No. 1831/2003	Author. procedure of products	No	No

USA EPA

Siti contaminati: procedura a step

- «Exposure first»:

  ⇨ co-occorrenza

- «Toxicology second»:

  ⇨ Tossicità comune con MoA comune
  (eventualmente stesso organo bersaglio)

EPA: **Pesticide** cumulative risk assessment: framework for screeening analysis purpose (2016)

Approccio in due fasi:

1. Valutazione dei dati tossicologici disponibili
2. Se necessario, screening basato sul rischio

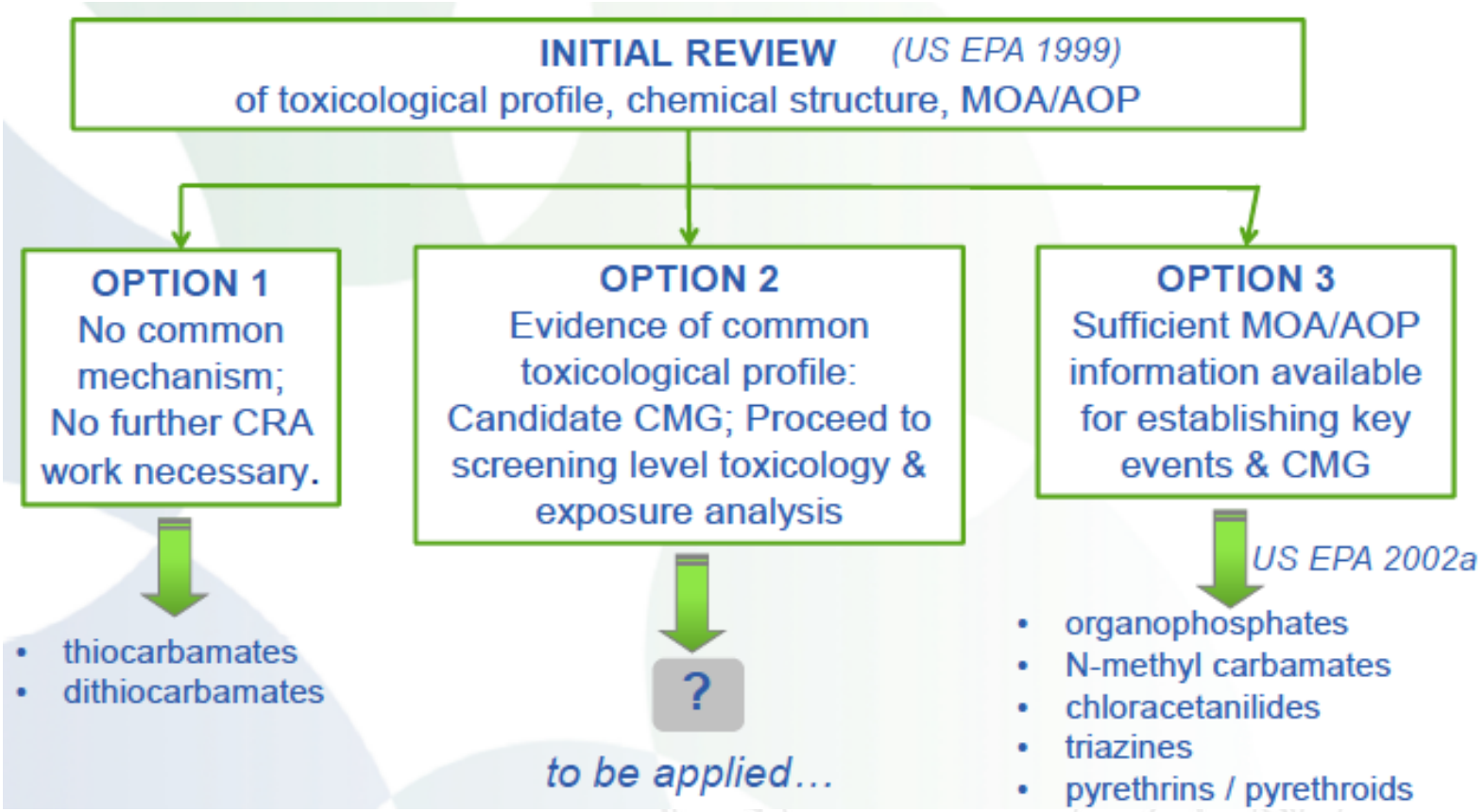
EPA: **Pesticide** cumulative risk assessment: framework for screeening analysis purpose (2016)

Se la tossicologia suggerisce inclusione (Common Mechanism Group, CMG)

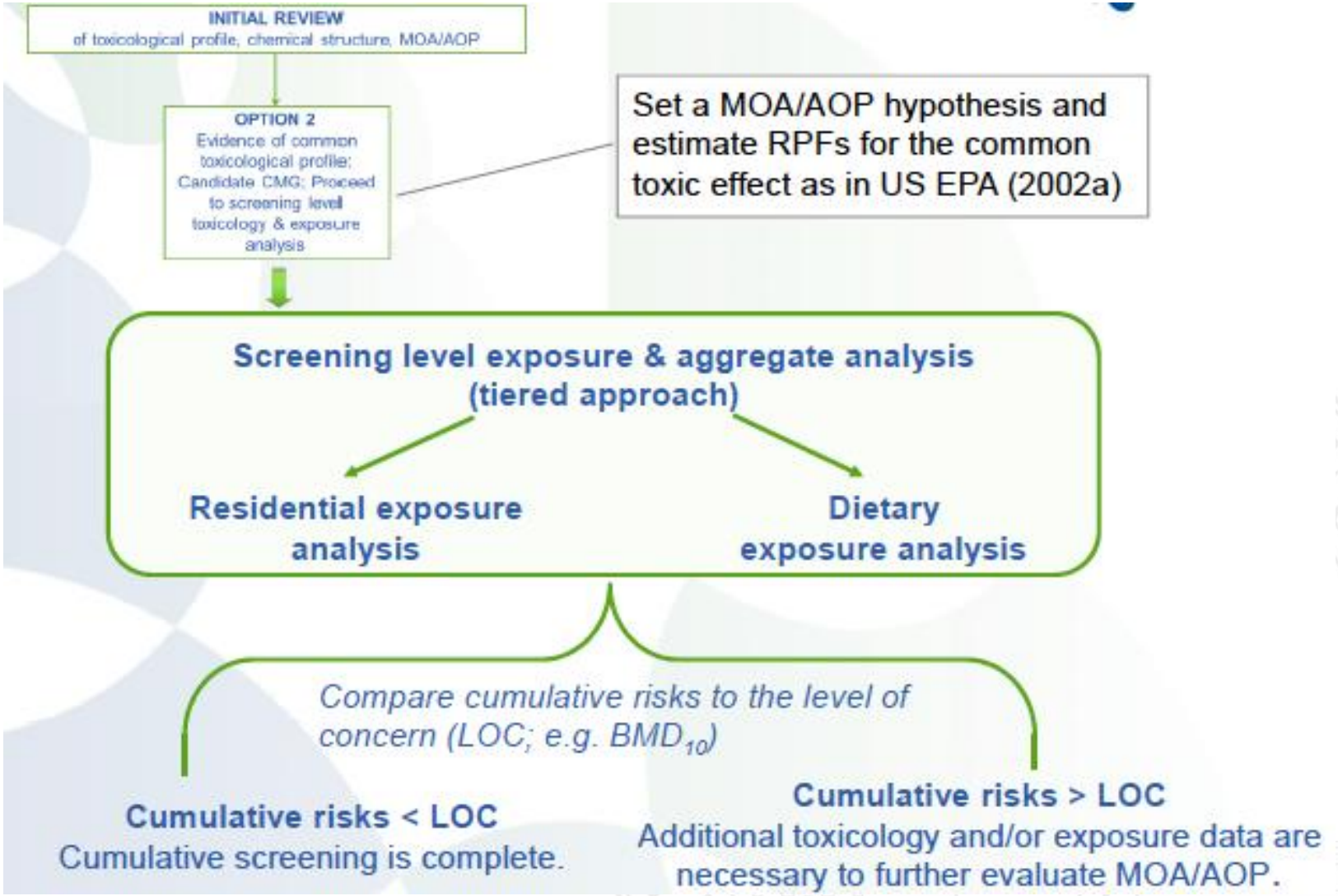
→ screening iniziale per esposizione (rischio)

→ prioritizzazione (o anche esclusione)

L'approccio aggiornato dell'EPA (1)



L'approccio aggiornato dell'EPA (2)



EFSA approach for pesticides

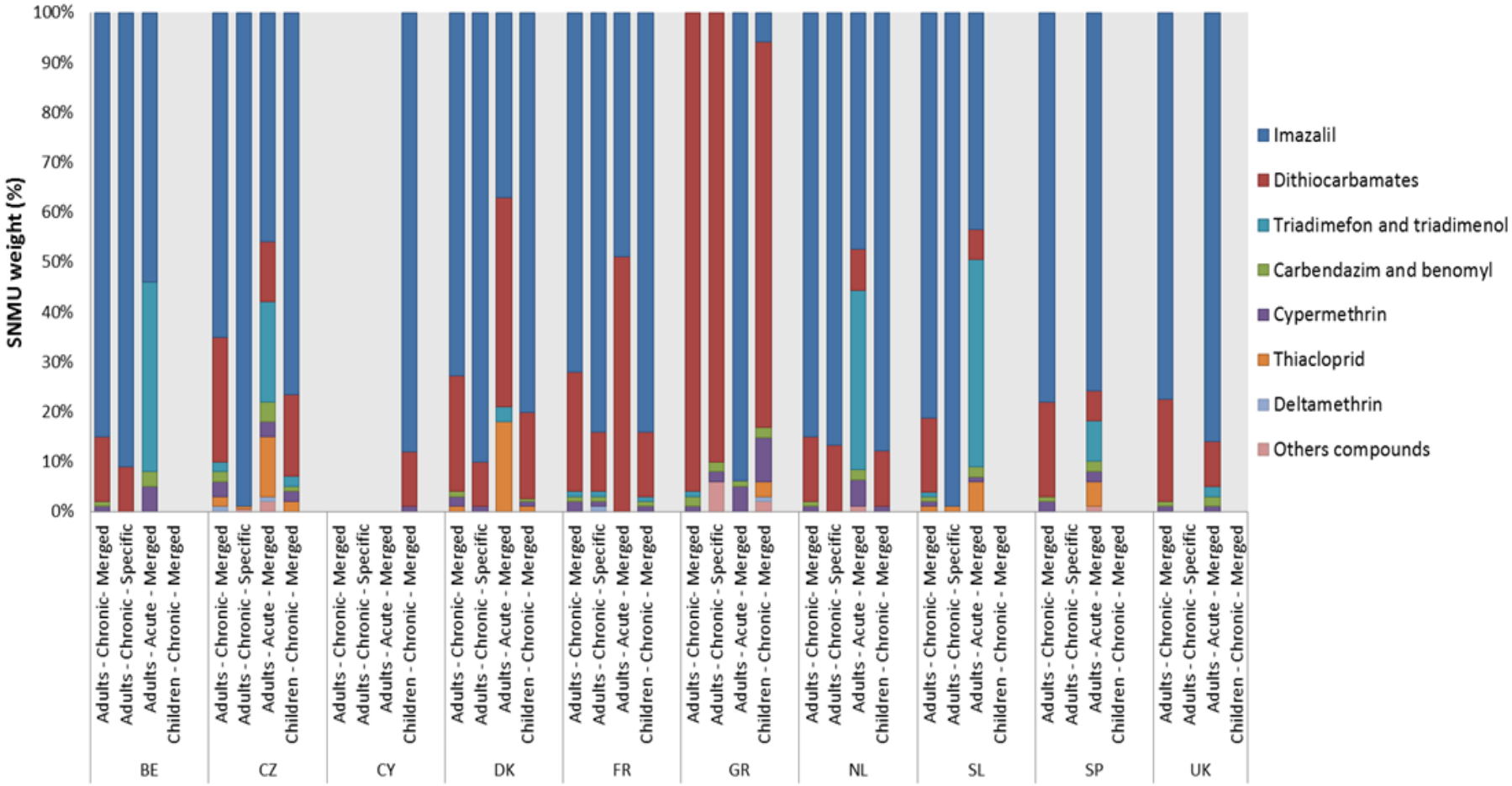
1. HAZARD IDENTIFICATION: Identify specific and unambiguous toxic effects that adversely affect an organ or system
2. HAZARD CHARACTERISATION: identify the most appropriate indicator(s) for the specific effect
3. DATA COLLECTION: gather data on the indicator(s) for the specific toxic effect
4. GROUPING: include all substances that exhibit a similar toxicological effect (phenomenology)

PHENOMENOLOGICAL APPROACH WITH DIFFERENT DEGREES OF REFINEMENT

EFSA Comments on Grouping

- Large CAGs
- The majority of pesticides might NOT contribute significantly to total combination (low potency/low exposure)
- Combination driven by few A.I.s
- Uncertain, but «higher level of protection» (meaning: more conservative?)

Steatosis CAG (154 pesticides): drivers of exposure



Crépet, et al. International Journal of Hygiene and Environmental Health, 2019: 222(2):291-306

FAO/WHO Workshop

16-18 April 2019

Food and Agriculture Organization of the United Nations

World Health Organization

- Involved 15 experts from EU and non-EU countries
- Expert consultation convened to:
  - develop appropriate guidance for risk assessment of combined exposures to multiple chemicals at an international level
  - make recommendations for implementation by FAO/WHO expert committees (JMPR, JECFA and others)

FAO/WHO Workshop

Participants observed that:

- the strategy developed by the EuroMix project is driven by data and methods available in EU countries (and most developed countries);
- These data are not necessarily readily accessible for low-income countries or emerging economies;
- That a pragmatic approach should be adopted for a pilot exercise before developing any guidance

FAO/WHO Workshop

- Participants agreed to restrict their recommendations to substances that are not DNA-reactive mutagens;
- These will be addressed by the WHO working group on Guidance for the Evaluation of Genotoxicity of Chemical Substances in Food (soon to be incorporated in EHC 240).

FAO/WHO Workshop: Grouping

- If a substance under evaluation has sufficient similarity to an established chemical group previously considered (e.g. organophosphates, triazines, …):

  ➜ include in the group;

- If not: determine if there is a need for a risk assessment of combined exposure to multiple chemicals;
  - A pragmatic approach was developed to select chemicals under evaluation by JECFA/JMPR to be included in a pilot exercise prior to developing a final methodology for implementation

FAO/WHO Workshop: Identification

Pragmatic decision point for grouping in piloting the proposed approach

A compound under evaluation should be considered for risk assessment for combined exposure if for at least one of the populations/cluster diets:

- the estimated dietary exposure is >10% of the HBGV (e.g.: ADI, TDI, …)

OR

- the calculated MoE is <10 fold of the adequate MoE

FAO/WHO Workshop: Identification

- The mean dietary exposure for general population (consumers and non-consumers) should be calculated assuming
  - mean/median concentration
  - mean food consumption levels for individual countries or cluster diets
- This decision point would be reviewed in the future following piloting of the process by JECFA and JMPR.

FAO/WHO Workshop

Pragmatic decision point for piloting the proposed approach

If a risk assessment for combined exposure to multiple chemical is considered then need to ask:

- *Is there toxicological evidence for combined effects?*
- *Is there potential for co-exposure (from co-occurrence or internal exposure)?*

FAO/WHO Workshop: Toxicology

Is there toxicological evidence for combined effects?

Use Weight of Evidence analysis and/or expert judgement on

- structural similarities,
- pesticidal mode of action,
- toxicological profiles for similar mode of action (MoA)/adverse outcome pathways (AOPs)

Refer to previous national/regional assessments

Derive relative potency factors (RPF) for chemicals in the assessment group or use Hazard Index (HI) approach, where appropriate.

The possibility of synergistic interactions between chemicals should be considered separately, on a case by case basis.

FAO/WHO Workshop: Co-exposure

Sources of information:

- regulation for permission of use (e.g.: fodd additives, veterinary chemicals, agrochemicals, …);
- import tolerances;
- use profiling;
- existing data on mean dietary exposure for the general population;
- toxicokinetic data for internal exposure considerations;
- biomonitoring data.

FAO/WHO Workshop: Co-exposure

Dietary exposure estimates

- A probabilistic approach recommended, ideally using individual food consumption and concentration data
- Recent developments in data collection and dietary exposure methodology undertaken by FAO/WHO committees, EFSA and/or research agencies are available to implement probabilistic modelling.
- Deterministic methods can be used, but result in a higher level of uncertainty in the dietary exposure estimates, especially in the context of combined exposures to multiple chemicals.

FAO/WHO Workshop: Co-exposure

Is there potential for co-exposure (from co-occurrence or internal exposure)?

When grouping chemicals into indicative assessment groups consider:

- dual use compounds (e.g. used as a veterinary drug and as a pesticide)
- discontinued persistent pesticides that occur as contaminants (POPs).

Statistical method to identify which chemicals are likely to be found together in the diet for a given population are available (e.g.: the Sparse nonnegative matrix underapproximation (SNMU) method, implemented in the EuroMix Toolbox).

These may require a number of data including

- data from monitoring,
- total diet studies
- agricultural trial data (supervised trial median residue, STMR)
- individual food consumption.

FAO/WHO Workshop: Risk characterisation

- Use dose addition
- identify key risk drivers using either deterministic or probabilistic approaches,
- including the key chemicals contributing to total dietary exposure and/or foods contributing to exposure from each chemical
- Probabilistic models for single chemicals are available in several tools, but few tools are publicly available for multiple chemicals

Discussions with RIVM/EC/WHO to be held on the future availability and validation of EuroMix Handbook and toolbox for use by FAO/WHO expert committees

Workshop recommendations

- Databases
- Reporting
- Future work

Workshop recommendations: databases

- Develop a database with a simple list of parameters
  - ID (name, CAS, structure code),
  - HBGVs,
  - critical effect,
  - POD for HBGV (NOAEL, BMD),
  - MoA,
  - Functional class (use),
  - estimated dietary exposure,
  - part of established chemical group (Y/N),
  - name of chemical group (if applicable)
- This should include JECFA/JMPR evaluations from the last 15 years
- Ensure compatibility of databases of individual food consumption data for different countries (CIFOCO and GIFT) and corresponding food concentration data to ensure consistency in dietary exposures and co-exposures assessment.

Workshop recommendations: reporting

- Explore the use of available summary reporting templates (e.g.: those from the EFSA Guidance document) to describe outcomes of the risk assessment for combined exposures of multiple chemicals
- The EFSA Guidance reporting format would be useful to add to standard outputs for the EuroMix tool

Workshop recommendations: Future work

(2019) Report to JMPR 2019/JECFA 87&88 (2019)

→ (2019-2021) Pilot exercise by JMPR 2019 and JECFA 87&88

→ (2021?) Review pilot exercise

→ (2021?) Agree on the approach

→ (2022?)Update EHC 240

Workshop recommendations: Implementation

- Include requests for completed risk assessments of combined exposure in future JECFA/JMPR data calls;
- Provide access to a suitable tool and computer facilities for probabilistic modelling of combined exposures to multiple chemicals for use by JECFA/JMPR experts (with associated training);
- Refer to the FAO/WHO Working Group updating Chapter 4, EHC240, the risk assessments for combined chemical mixtures where chemicals are DNA reactive mutagens.

Outcomes of the 2019 JMPR

- One compound identified with >10% ADI at least one population;
- No action taken yet, because of lack of time;
- Need to adapt the working modality, with respect to timing, to apply the proposed pilot approach;
- Need to develop the database of JECFA/JMPR evaluations from the last 15 years

Sfide per l'armonizzazione

Definizione di CAG/CMG	rilevante
Criteri di esclusione (risk-based)	potenzialmente rilevante
Metodo di valutazione dell'effetto (additività)	non rilevante
Metodo di «calcolo» (IC/MoE)	non rilevante
Stima dell'»intake»	potenzialmente rilevante
Approccio deterministico vs probabilistico (definizione di sicuro)	rilevante

Thank you for your patience and attention

angelo.moretto@unimi.it

The report of the consultation can be found at www.who.int/foodsafety/areas_work/chemical-risks/Euromix_Report.pdf.

The report of the 2019 JMPR can be found at http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmpr/jmpr-rep/en/