FAO/WHO Consultation on Combined Exposure to Multiple Chemicals for JECFA and JMPR

Alan R Boobis

Imperial College London

London, UK

a.boobis@imperial.ac.uk

EFSA International Workshop on Risk Assessment of Combined Exposure to Multiple Chemicals

18-19 October 2021
Online

Disclosure Statement

- Member of several science advisory boards (public and private sector): ILSI, ILSI Europe, Cosmetics Europe LRSS, MSU Center for Research on Ingredient Safety, A*STAR Food and Chemical Safety Programme Singapore, Owlstone Medical, PCPC Expert Group on Carcinogenicity
- Member/chair of several national and international scientific advisory committees: UK COT, UK COMEAP, JMPR, JECFA, WHO TobReg, ISO TC126 WG10 Intense Smoking Regime
- I have no financial or other conflicts of interest related to the subject matter of the session

EuroMix Project

- Euromix was an Horizon 2020-funded project, involving 22 partner organisations and 4 third party organisations (non-European), which ran from 2015–2019
- The objective was to develop approaches and methods for the assessment of risks posed by combined exposures to multiple chemicals
- A key objective of Euromix was to identify and promote opportunities to harmonize different approaches taken to such assessments
  - Developed a freely available web-based toolbox and handbook to provide databases and methods for the tiered assessment of combined exposure to chemicals whatever the level of data available on each substance
  - Organised a series of four international workshops on harmonization
    - London, Oct 2016; Brussels, May 2017; London, Oct 2018; Geneva, April 2019

This project is funded by the Horizon 2020 Framework Programme of the European Union

Conclusions from EuroMix international harmonisation workshops

- Currently there is no overarching approach to the risk assessment of combined exposures to chemicals in Europe (or elsewhere) but there is ongoing work in this area (e.g. OECD, EFSA)
- Approaches to the risk assessment of combined exposures to chemicals vary across sectors and with geography, reflecting the needs of the risk manager
- The most common approach for grouping chemicals is based on structural similarity and/or co-occurrence (in products) and/or designed function
- The EuroMix toolbox and handbook will enable different tiers to be applied for hazard and for exposure for data-rich and data-poor chemicals
- EuroMix has provided tools to enable the implications (i.e. uncertainty) of different exposure and toxicology choices, e.g. in grouping chemicals, to be determined

FAO/WHO Workshop
16-18 April 2019

Food and Agriculture Organization of the United Nations

World Health Organization

- Complimentary to EuroMix, an expert consultation was convened by FAO and WHO to develop appropriate guidance for risk assessment of combined exposures to multiple chemicals at an international level and make recommendations for implementation by FAO/WHO expert committees

Aims:

- Develop a practical approach to the risk assessment of combined exposures to multiple chemicals to be piloted by JMPR and JECFA in 2019
- Propose a process for application to substances that are not DNA reactive mutagens (for DNA reactive mutagens special considerations required)
- Synergistic interactions between chemicals may need to be considered separately on a case by case basis, as appropriate

FAO/WHO Workshop
16-18 April 2019

Food and Agriculture Organization of the United Nations

World Health Organization

Participants	
Ms Janis Baines (FSANZ, retired) (rapporteur)	Mr Soren Madsen (WHO)
Prof Alan Boobis (Imperial College London) (chair)	Dr Bette Meek (University of Ottawa)
Dr Eloisa Dutra-Caldas (University of Brazil)	Prof Angelo Moretto (University of Milan)
Dr Amelie Crépet (ANSES, France)	Dr Roland Solecki (BfR, Germany)
Dr Jean-Lou Dorne (EFSA)	Dr Philippe Verger (WHO)
Dr Vittorio Fattori (FAO)	Dr Gerrit Wolterink (RIVM, The Netherlands)
Dr Natalie Von Gotz (Federal Office of Public Health, CH)	Dr Liu ZhaoPing (CFSA, China)
Prof Jacob van Klaveren (RIVM, The Netherlands)	

FAO/WHO Workshop

Proposed approach for JECFA/JMPR

- If a substance under evaluation has sufficient similarity to an established chemical group previously considered it should be considered for assessment as part of the existing group (e.g. organophosphates, pyrethroids, triazines)
- If not, then determine if there is a need to include it in 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
  - If the estimated dietary exposure for a single compound under evaluation is >10 percent of the HBGV (or < 90 times the MOE) then consider the need to include it in a risk assessment of combined exposure to multiple chemicals grouped by similar structure and/or mode of action

FAO/WHO Workshop

Hazard identification and characterisation step

- Standard procedures to be followed, including derivation of relative potency factors for chemicals in the assessment group where appropriate

Dietary exposure estimates

- A probabilistic approach is recommended for estimating exposure to multiple chemicals, ideally using individual food consumption and concentration data
- Different procedures will be needed for chronic and acute estimates
- For chronic risk, the mean dietary exposure for the general population (consumers and non-consumers) should be calculated assuming mean/median concentration and mean food consumption levels for individual countries or cluster diets

FAO/WHO Workshop

Risk characterisation step

- Suitable procedures using dose addition can be applied to 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

Pilot exercise

- Present workshop report at JECFA88 and JMPR 2019 and identify possible chemicals under evaluation for pilot process
- The results of the pilot exercise should be reviewed and the approach revised as appropriate, with particular consideration of the choice of decision point

Implementation

- Update EHC240 once process for risk assessment of combined exposure to multiple chemicals agreed
- Include requests for completed risk assessments of combined exposure in future JECFA/JMPR data calls
- Access to a suitable tool and computer facilities for probabilistic modelling of combined exposures to multiple chemicals should be made available to JECFA/JMPR experts, with associated training
- Risk assessments for combined chemical mixtures where chemicals are DNA reactive mutagens should be referred to the FAO/WHO Working Group updating Chapter 4, EHC240

Workshop recommendations

- Develop a database with a simple list of parameters required to systematically investigate potential assessment groups for consideration of combined exposures to multiple chemicals
  - Parameters to include 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
- Establish structured databases for JECFA/JMPR evaluations from the last 15 years to enable enhanced searches for required parameters Explore the use of summary reporting templates, for example, those from the EFSA Guidance document, to describe outcomes of the risk assessment for combined exposures of multiple chemicals
- - spreadsheet prepared for JMPR 2019

Joint FAO/WHO Meeting on Pesticide Residues (JMPR), Geneva, Switzerland, 17 - 26 September 2019

- The 2019 Meeting agreed to pilot the approach based on chronic dietary exposure for compounds being evaluated for the first time at the meeting
- Of the 8 compounds evaluated by JMPR for the first time, the only one for which the estimated dietary exposure (IEDI) exceeded 10% of the upper bound of the ADI was pyflubumide
  - Pyflubumide does not belong to an established assessment group for combined exposure to multiple pesticides
- https://www.who.int/foodsafety/areas_work/chemical-risks/JMPR_2019_Sep_Report.pdf?ua=1

88th meeting of JECFA (Residues of veterinary drugs), 22–31 October 2019, Rome, Italy

- The 88th JECFA agreed to pilot the approach based on chronic exposure for compounds being evaluated at the meeting, but concluded that 2–3 years would be insufficient to judge the utility of the approach. Moreover, estimating combined exposure at an international level would be challenging with respect to both the availability of suitable data and the application of the methodology (e.g. where distributions for consumption are available from some countries but not others).
- Neither of the compounds evaluated for both safety and residues (diflubenzuron and halquinol) belonged to an established assessment group for combined exposure to multiple chemicals
- For neither of the compounds did the estimated dietary exposure from veterinary use exceed 10% of the upper bound of the ADI in any population or subpopulation
- http://www.fao.org/3/ca7512en/CA7512EN.pdf

Conclusions

- FAO and WHO have developed a pragmatic approach for identifying compounds for which there might be a need for the risk assessment of combined exposures to multiple residues
- The approach has been agreed in principle by JMPR and JECFA (veterinary drugs) and has been piloted by both meetings to identify candidate compounds that might require such an assessment
- The next step, identifying suitable data and conducting the assessment of the risk from combined exposures has been hampered by the Covid-19 pandemic
  - Several key issues will need to be resolved before such an assessment can be completed, though highlighting the possible need for such assessment may be of value in itself
  - JECFA and JMPR will continue to pilot this approach whenever feasible