Background

The WHO Department of Food Safety and Zoonoses (FOS), is participating in a project entitled “EuroMix” funded by the European Commission (EC), under the Horizon 2020 research programme. This project, coordinated by the Dutch National Institute for Public Health and the Environment (RIVM), aims to develop a tiered strategy for the risk assessment of combined exposure to multiple chemicals derived from multiple sources across different populations.

One important objective of EuroMix is to propose a methodology to assess the human health risks of combined exposure to multiple chemicals in food. EuroMix’s aim was to help harmonize such assessments at EU, but also at global, level.

EuroMix has developed an experimentally verified, tiered strategy for the risk assessment of mixtures of multiple chemicals derived from multiple sources across different life stages. The need to integrate exposure to mixtures of chemicals in the risk assessment framework to ensure adequate public health protection has been raised by WHO in many reports and in particular in: “Principles and methods for the risk assessment of chemicals in food” (EHC 240). This approach has also been discussed during the EuroMix stakeholder meetings with FAO and the Codex Alimentarius Secretariat, who both expressed a mutual interest to harmonize the approaches globally and better understand the underlying principles of grouping chemicals based on their modes of action.

The strategy, developed by the EuroMix project and described in the EuroMix Handbook, is driven by data and methods available in EU countries and more generally in most developed countries but not necessarily readily accessible for developing countries or even for emerging economies.

The World Health Organization (WHO) is the directing and coordinating authority for health within the United Nations system. It is responsible, together with FAO and through the Codex Alimentarius, for setting international norms and standards, articulating evidence-based policy options and providing technical support to countries. According to its agreement with RIVM, WHO was responsible, within the EuroMix project, for organizing an expert consultation involving experts from EU and non-EU Countries on the development of guidance for the risk assessment of combined exposure to multiple chemicals.

1 https://www.who.int/foodsafety/publications/chemical-food/en/
WHO and FAO convened an expert consultation to develop such guidance at an international level and make recommendations for implementation by FAO/WHO expert committees (see Annex 1 for the agenda and list of participants). An overview of the JECFA and JMPR processes and a summary of the EuroMix Handbook and Toolbox were presented. The consultation reviewed specific case studies proposed by the Steering Committee. A practical approach to the risk assessment of combined exposures to multiple chemicals was developed to be piloted by JMPR and JECFA in 2019.

The proposed approach is summarised in this report, including recommendations for FAO and WHO.

**Risk assessments of combined exposure to multiple chemicals**

For JECFA and JMPR evaluations, when the estimated dietary exposure(s) for a single substance exceeds the relevant HBGV or is below an adequate MoE in the risk characterisation step, then standard risk assessment practice applies and the outcomes would be referred to the risk managers (relevant Codex committee) for their appropriate consideration.

A proposed process for substances that are not DNA reactive mutagens is described below. For DNA reactive mutagens special consideration will be needed and they are not included in this proposal.

The Experts agreed that, if a substance under evaluation by JECFA/JMPR, has sufficient similarity to an established chemical group previously considered in a risk assessment of combined exposure to multiple chemicals (e.g. organophosphates)*, the substance should be considered for assessment as part of that group.

If a substance under consideration is not part of an established chemical group previously considered, the JECFA/JMPR should then determine whether there was a need to include it in a risk assessment of combined exposure to multiple chemicals. The Experts proposed that the assessment of these compounds should be piloted prior to general implementation of the methodology.

*Pragmatic decision point for undertaking the proposed approach for chemicals not part of a previously established group*: if the estimated dietary exposure for a single compound under evaluation is more than 10 percent of the relevant health based guidance value (HBGV) or, in the absence of a HBGV, the calculated Margin of Exposure (MoE) is less than 10 fold of the MoE considered adequate for such a compound for at least one population, the need to include the compound in a risk assessment of combined exposure to multiple chemicals should be considered. The decision point (i.e. 10% of HBGV or 10 x MoE) should be reviewed following piloting of the process by JECFA and JMPR.

For this purpose, 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. It is important to understand the level of uncertainty around the dietary exposure estimate, which will depend on the quality of data inputs, to assess where there may be a concern about an estimated dietary exposure exceeding the proposed decision point.

If a risk assessment for combined exposure to multiple chemicals is considered, then the following questions need to be answered, to determine which other substances should be included in an indicative assessment group:

*Is there toxicological evidence for combined effects?*

The assessors should use a weight of evidence analysis and/or expert judgement on structural similarities, toxicological profiles for similar mode of action (MoA)/adverse outcome pathways (AOPs)
or shared adverse effects, referring to previous assessments at a national or regional level as necessary.

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

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

The assessors should review potential sources of information on co-exposure, for example:

- regulations for permissions for use (food additives/ag vet chemicals)
- import tolerances
- use profiling
- existing data on mean dietary exposure for the general population (mean/median concentration data such as trial data or monitoring data or use levels in food additives) for other compounds to determine whether the population is exposed to the chemicals of interest from dietary sources.
- toxicokinetic data for internal exposure considerations
- biomonitoring data.

If concentration data from monitoring, total diet studies or agricultural trial data (supervised trial median residue, STMR) and individual food consumption data are available, the assessors could use a statistical method to study correlations in dietary exposure estimates to identify which chemicals are likely to be found together in the diet for a given population, for example, the Sparse nonnegative matrix underapproximation (SNMU) method, implemented in the EuroMix Toolbox.

In a risk assessment of combined exposure to multiple chemicals, dual use compounds (e.g. used as a veterinary drug and as a pesticide) and discontinued persistent pesticides that occur as contaminants (POPs) may need to be considered when grouping chemicals into indicative assessment groups since they may contribute to total dietary exposure.

**Hazard identification and characterisation step**

Standard procedures should be followed, including derivation of relative potency factors for chemicals in the assessment group where appropriate (Chapters 4, 5 EHC240).

**Dietary exposure estimates**

A probabilistic approach is recommended for estimating exposure to multiple chemicals, 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.

Different procedures are required for calculating acute and chronic dietary exposure estimates (Chapter 6 EHC240). For total internal exposure estimates, physiological based kinetic models, such as the EuroMix COSMOS model, may be applied.
Risk characterisation step

For risk characterisation, suitable procedures using dose addition can be applied using either deterministic or probabilistic approaches, to identify key risk drivers, including the main 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. EuroMix has developed a suitable tool, based on earlier work.

The assessment groups may be refined based on these results and the risk assessment revised.

Summary of recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Action</th>
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<tbody>
<tr>
<td><strong>Database development</strong></td>
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<tr>
<td>Add the JECFA/JMPR summary for evaluations to the EFSA database (OpenFoodTox)</td>
<td>FAO/WHO secretariat to contact EFSA</td>
</tr>
<tr>
<td>Develop a database with a simple list of parameters required to systematically investigate potential assessment groups for consideration of combined exposures to multiple chemicals, including substance IDs (name, CAS, structure code), HBGVs, critical effects, PODs for HBGV (NOAEL, BMD), MoAs, Functional classes (uses), estimated dietary exposures, part of established chemical group (Y/N), name of chemical groups.</td>
<td>FAO/WHO secretariat JECFA/JMPR to consider at future meetings</td>
</tr>
<tr>
<td>Information to be extracted from the JECFA/JMPR summary of evaluations databases and/or available databases such as Open FoodTox, using a standardised format and units.</td>
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<tr>
<td>Establish structured databases for JECFA/JMPR evaluations from the last 15 years to enable enhanced searches for required parameters for a risk assessment of combined exposure to multiple chemicals (using a common design format to organise data in a way that is compatible with existing databases)</td>
<td>FAO/WHO secretariat</td>
</tr>
<tr>
<td>Ensure that databases of individual food consumption data for different countries (CIFOCOs and GIFT) and corresponding food concentration data are compatible so that dietary exposures and co-exposures can be undertaken in a consistent manner</td>
<td>FAO/WHO</td>
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<tr>
<td><strong>Reporting of risk assessment outcomes</strong></td>
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<td>Explore the use of summary reporting templates, for example, those from the EFSA MIXTOX Guidance document, to describe risk assessment outcomes</td>
<td>FAO/WHO secretariat JECFA/JMPR to consider at future meetings</td>
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<tr>
<td>Outcomes of the risk assessment for combined exposures of multiple chemicals in the final report</td>
<td>FAO/WHO secretariat to contact RIVM</td>
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<tr>
<td>The EFSA Guidance reporting format would be useful to add to standard outputs for the EuroMix tool</td>
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<td><strong>Future work</strong></td>
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<tr>
<td>The report of the expert consultation should be presented and discussed at the upcoming FAO/WHO expert committees i.e. JECFA 87, JECFA 88 and JMPR 2019</td>
<td>FAO/WHO secretariat</td>
</tr>
<tr>
<td>As a pilot exercise, JECFA 88 and JMPR 2019 should start identifying which compounds under evaluation should be considered for potential risk assessment of combined exposure to multiple chemicals in the future</td>
<td>JECFA/JMPR</td>
</tr>
<tr>
<td>The results of the pilot exercise using the proposed approach should be reviewed and the approach revised as appropriate, with particular consideration of the choice of decision point</td>
<td>FAO/WHO secretariat with JECFA/JMPR</td>
</tr>
<tr>
<td>Once agreed, the approach to risk assessment for combined exposure to chemical mixtures should be included in the updated FAO/WHO EHC240, in Chapter 6 Dietary exposure assessments and Chapter 7 Risk characterisation</td>
<td>FAO/WHO secretariat</td>
</tr>
<tr>
<td>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</td>
<td>FAO/WHO secretariat</td>
</tr>
<tr>
<td>The standard JECFA/JMPR call for data process can include a request for completed risk assessments of combined exposure to multiple chemicals by other agencies to assist future evaluations</td>
<td>FAO/WHO secretariat</td>
</tr>
<tr>
<td>Access to a suitable tool and any associated computational facilities for probabilistic modelling of combined exposures to multiple chemicals should be made available to JECFA/JMPR experts, with associated training</td>
<td>FAO/WHO secretariat</td>
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Annex 1 Agenda and list of participants

DIETARY RISK ASSESSMENT OF CHEMICAL MIXTURES
WHO/HQ Geneva, Room D, 16-18 April 2019

Agenda

DAY 1 – 16/04/2019

- 9:30-10:30
  - Welcome and introductions
  - Election of the Chair and Rapporteur
  - Declarations of Interests
- 10:30-11:00 Coffee break
- 11:00-11:45 EuroMix Handbook (Jacob van Klaveren)
- 11:45-12:30 Selecting mixtures on the basis of dietary exposure and hazard data (Amelie Crepet)
- 12:30-13:30 Lunch break
- 13:30-15:30 Presentation of results from Brazil (Eloisa Dutra Caldas) and the EU (Jean-Lou Dorne) and discussion
- 15:30-16:00 Coffee break
- 16:00-17:30 Presentation of results from Brazil and the EU and discussion (cont.)

DAY 2 – 17/04/2019

- 09:00-10:30 Presentation of results from Brazil and the EU and discussion (cont.)
- 10:30-11:00 Coffee break
- 11:00-13:00 Presentation of results from Brazil and the EU and discussion (cont.)
- 13:00-14:00 Lunch break
- 14:00-15:30 Preparation of the meeting report and recommendations
- 15:30-16:00 Coffee break
- 16:00-17:30 Preparation of the meeting report and recommendations
DAY 3 – 18/04/2019

- 09:00-10:30 Preparation of the meeting report and recommendations (cont.)
- 10:30-11:00 Coffee break
- 11:00-13:00 Preparation of the meeting report and recommendations (cont.)
- 13:00-14:00 Lunch break
- 14:00-16:00 Adoption of the meeting report and recommendations

Participants

Ms Janis Baines (rapporteur)
FSANZ (retired)
Canberra, Australia
Email: bainej1@grapevine.com.au

Prof Alan Boobis (chair)
Centre for Pharmacology & Therapeutics
Department of Medicine, Faculty of Medicine
Imperial College London, Hammersmith Campus
Ducane Road
London W12 0NN
United Kingdom
Email: a.boobis@imperial.ac.uk

Dr Eloisa Dutra-Caldas
University of Brasilia
College of Health Sciences
Pharmaceutical Sciences Department
Campus Universitario Durci Ribeiro
Federal District 70910-900
Brazil
Email: eloisa@unb.br

Dr Amelie Crépet
ANSES
14 rue Pierre et Marie Curie
94701 Maisons-Alfort Cedex
France
Email: amelie.crepet@anses.fr

Dr Jean-Lou Dorne
European Food Safety Authority (EFSA)
43126 Parma
Italy
Email: Jean-Lou.DORNE@efsaeuropa.eu
Dr Vittorio Fattori  
Food Safety and Quality Unit  
Agriculture and Consumer Protection Department  
Food and Agriculture Organization of the United Nations  
Viale delle Terme di Caracalla  
00153 Rome  
Italy  
Email: vittorio.fattori@fao.org

Dr Natalie Von Gotz  
Federal Office of Public Health  
Schwarzenburgstrasse 157  
3097 Liebefeld  
Switzerland  
Email: natalie.von.goetz@chem.ethz.ch

Pr Jacob van Klaveren  
National Institute for Public Health and the Environment (RIVM)  
Antonie van Leeuwenhoeklaan 9  
3721 MA Bilthoven  
The Netherlands  
Email: jacob.van.klaveren@rivm.nl

Mr Soren Madsen  
JMPR Joint Secretary  
Department of Food Safety and Zoonoses (FOS)  
World Health Organization  
1211 Geneva 27  
Switzerland  
E-mail: madsens@who.int

Dr Bette Meek  
McLaughlin Centre  
University of Ottawa  
600 Peter Morand Crescent  
Room 216  
Ottawa ON K1G 5Z3  
Canada  
Email: bette.meek@uottawa.ca

Prof Angelo Moretto  
Department of Biomedical and Clinical Sciences  
University of Milan  
And  
International Centre for Pesticides and Health Risks Prevention (ICPS)  
Luigi Sacco Hospital  
ASST Fatebenefratelli Sacco  
Via GB Grassi 74  
20157 Milano  
Italy  
Email: angelo.moretto@unimi.it
Dr Roland Solecki  
Federal Institute for Risk Assessment  
Max-Dohrn Strasse 8-10  
D-10589 Berlin  
Germany  
Email: Roland.Solecki@bfr.bund.de

Dr Philippe Verger  
Advisor Food Safety  
WHO/EMRO/CEHA  
P.O. Box 811547  
Amman 11181  
Jordan  
Email: vergerp@who.int

Dr Gerrit Wolterink  
National Institute for Public Health and the Environment (RIVM)  
PO Box 1  
3720 BA Bilthoven  
The Netherlands  
Email: Gerrit.Wolterink@rivm.nl

Dr Liu ZhaoPing  
China National Center for Food Safety Risk Assessment (CFSA)  
No.37 Guangqu Road  
Chaoyang District  
Beijing 100022  
China  
Email: liuzhaoping@cfsa.net.cn