Food and Agriculture Organization of the United Nations

World Health Organization

FAO/WHO Expert Consultation on Dietary risk assessment of chemical mixtures

(Risk assessment of combined exposure to multiple chemicals)

WHO, Geneva, 16-18 April 2019

Final Report

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[1]). 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

Recommendation	**Action**
Database development	
Add the JECFA/JMPR summary for evaluations to the EFSA database (OpenFoodTox)	FAO/WHO secretariat to contact EFSA
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. 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.	FAO/WHO secretariat JECFA/JMPR to consider at future meetings
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)	FAO/WHO secretariat
Ensure that databases of individual food consumption data for different countries (CIFOCOss and GIFT) and corresponding food concentration data are compatible so that dietary exposures and co-exposures can be undertaken in a consistent manner	FAO/WHO
Reporting of risk assessment outcomes	
Explore the use of summary reporting templates, for example, those from the EFSA MIXTOX Guidance document, to describe	FAO/WHO secretariat JECFA/JMPR to consider at future meetings

outcomes of the risk assessment for combined exposures of multiple chemicals in the final report	
The EFSA Guidance reporting format would be useful to add to standard outputs for the EuroMix tool	FAO/WHO secretariat to contact RIVM
Future work	
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	FAO/WHO secretariat
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	JECFA/JMPR
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	FAO/WHO secretariat with JECFA/JMPR
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	FAO/WHO secretariat
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	FAO/WHO secretariat
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	FAO/WHO secretariat
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	FAO/WHO secretariat

Annex 1 Agenda and list of participants

Food and Agriculture Organization of the United Nations

World Health Organization

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

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Annex 2 Summary of contributions

1. Selecting mixtures on the basis of dietary exposure and hazard data (Amelie Crepet)

Through their diet, populations are exposed to mixtures of chemicals which can cause health diseases. Due to the complexity of mixtures, the question of which substances should be assessed together remains a big challenge. The EuroMix project developed a strategy for mixture risk assessment and proposed an original method combining exposure and hazard information to identify the key mixtures of chemicals to which populations are exposed. The principle is to reduce the number of substances in a defined cumulative assessment group (CAG) using risk-based identification of co-occurring substances in diet for a given time frame. The method is based on sparse non-negative matrix factorization under approximation (SNMU) to decompose the co-exposure matrix into two non-negative matrices. The method is illustrated on the liver steatosis CAG using exposure data to pesticide residues of children and adults in 9 European countries. Food consumption and pesticide residues in food and drinking water came from national surveys. Exposures to 144 pesticides were evaluated through scenarios related to chronic/acute exposure and merged/country specific concentration data. Relative potency factors were calculated to express the potency of each substance relative to the flusilazole and multiplied by the exposure.

Considering chronic exposure, one mixture explained the major part of the total variance for each country, while in acute exposure, several mixtures were often needed to explain the major part of the total variance. The results showed that 15 pesticides were mainly observed in mixtures, with a high contribution of imazalil and dithiocarbamates.

It was also shown how the method in studying correlations between individual profiles of exposure to several substances is a relevant tool to group substances in mixture compared to the Maximum Cumulative Ratio (MCR) and the risk drivers identification. The MCR is a useful tool for assessing the value of performing a cumulative risk assessment and can be used as a first step but did not specifically study individual correlations between exposures. The risk drivers are based on the mean percentage of the contribution of each substance to the cumulative exposure but do not take into account for combined exposures. It was also presented the possibility to cluster individuals by their specific diet and link it to specific mixtures of substances.

Finally, the method can be applied to exposure only i.e without considering relative potency factors, to concentrations in food or in the body, to non-dietary exposure or to aggregate exposure from several sources.

2. EFSA'S MIXTOX Guidance Document (Jean Lou Dorne)

In march 2019, the European Food Safety Authority (EFSA) has published the MIXTOX guidance document describing "harmonised methodologies for the human health (HRA), animal health (ARA) and ecological risk assessment (ERA) of combined exposure to multiple chemicals ("chemical mixtures"). The guidance document is focused on the food and feed safety areas while its application can be broadened to other regulatory areas and across regulatory silos. Key challenges to harmonization of such methodologies included the diversity of regulations and associated RA frameworks, the large number of chemicals involved, variations in associated exposure patterns and diverse toxicological profiles in humans and species of veterinary and ecological relevance.

First, a harmonised framework has been proposed for HRA, ARA and ERA. This framework aims to be fit for purpose and is based on the principles of tiering for each step of the risk assessment: problem formulation, exposure assessment, hazard assessment, risk characterisation and uncertainty analysis. A key aspect of such an exercise is the prioritisation of multiple chemicals for which a combined exposure assessment would be needed using available information on exposure. Overall, the applications of tiering principles range from qualitative, semi-quantitative to fully probabilistic approaches and are flexible and depends on the purpose of the RA, and the availability of data availability, time and resources.

During the problem formulation phase, the purpose of the RA, methodological approaches used and analysis plan are described and provide a decision point to undertake the RA using a whole mixture (WMA), a component-based approach (CBA) or a combination of both approaches. For the WMA, the the approach is similar to that for single compounds. For the CBA, the default model for assessing combined toxicity is dose addition model. Under some specific and uncommon circumstances, evidence for deviation from dose addition needs to be assessed using a weight of evidence (WoE) approach particularly for synergistic effects. This WoE analysis allows for the (semi-)-quantification of the magnitude of the interaction through an extra uncertainty factor or a biologically-based model (e.g. toxicokinetic-toxicodynamic model) in the hazard assessment and the risk characterisation steps.

For a given RA, once the risk characterisation has been performed, important aspects for interpretation need to be considered and the constant cross-talk between risk assessors and risk managers is highlighted. Reporting the results is of key importance for transparency and a reporting template has been proposed and illustrated for the HRA, ARA and ERA areas in the guidance. The reporting template has been further tested for the HRA area using available exposure and hazard data for regulated compounds and contaminants and case studies have been presented during the WHO workshop.

Future perspectives for mixture RA are discussed in the light of the integration of historical data and mechanistic alternatives to animal testing such as in silico and in vitro biologically-based tools and models. Open source platforms are also discussed as means to: (1). Provide scientific tools directed towards the RA and regulatory community, (2). Apply harmonised methodologies and (3). Train the current and next generation of risk assessors.

Finally, examples of open source physiologically-based kinetic models for the HRA, ARA and ERA, that are under development in EFSA, have also been highlighted to refine methods for the risk assessment of combined exposure to multiple chemicals. It is foreseen that these tools will provide biologically-based means to move from external dose to internal dose using a quantitative metric for extrapolation between subgroups of the human population and species of animal and ecological relevance.

3. <u>Cumulative dietary risk assessment of pesticides using the Monte Carlo Risk Assessment (MCRA): The Brazilian experience (Prof. Eloisa Dutra Caldas)</u>

A summary of the most recent cumulative probabilistic dietary risk assessments of pesticides conducted in Brazil using the MCRA 8.2 was presented. National individual consumption data corresponded to individuals 10 years or older (2 non-consecutive days' survey, 2008-2009), and residue data were from Brazilian governmental monitoring programs (Ministries of Health and of Agriculture) and data generated by the Laboratory of Toxicology at the University of Brasilia (2005-2015).

Acute assessments were performed for the cumulative assessment group (CAG) stablished by the EPA for organophosphorus, carbamates and pyrethroids (Jardim et al., 2018a) and for the CAGs of triazoles for chronic hepatotoxic effects and cranium-facial malformation, relevant for women of child bearing age, following the methodology proposed by EFSA (Jardim et al., 2018b). Additionally, assessment for the triazole CAG for skeletal variation (women of child bearing age) and chronic assessment for dithiocarbamates (measured as CS2) were also conducted (Jardim et al., 2018b). The source of the CS2 in the sample was related to the dithiocarbamates used in Brazil, which is mostly mancozeb. In the chronic assessments, the non-normal/multimodal exposure distributions were adjusted using the model-than-apply (MTA) tool included in the MCRA 8.2. In all assessments, no appreciable risks were found for the population at the 99.9P of the exposure distribution.

The MCRA 9 (beta) Euromix toolbox

Using the same Brazilian consumption and residue data, a cumulative chronic assessment was conducted for the liver steatosis CAG proposed in the MCRA 9 (beta) Euromix toolbox, which has flusilazole as the reference compound (PoD=530 µg/kg bw/day). This CAG contains 144 pesticides from different chemical classes, from which 52 were found to be positive in the Brazilian residue data.

The Exposure Mixture module of the toolbox (sparse non-negative matrix underestimation, SNMU) identified three main risk mixtures (total exposure) in the data base:

- Mixture 1 (53.5%): dithiocarbamates (83%) and carbendazin (0.17%)
- Mixture 2 (20.6%): carbendazin (98%) and tebuconazole (2%)
- Mixture 3 (16.2%): imazalil (93%), dicofol (6%) and captan (2%)

The Dietary Exposure module of the toolbox indicate an exposure of 1.1 µg/kg bw/day at the P99.9 of exposure, representing a margin of exposure (MOE) of 490 in relation to the flusilazole PoD, indicating no appreciable risk to Brazilian consumers 10 years or older. Dithiocarbamate intake accounted for 52.8% of the total cumulative exposure. At the upper tail of the exposure distribution, the risk drivers were dithiocarbamates in apple (55.8% of the exposure), papaya (7.6%) and lettuce (5.5%), imazalil in orange (4.2%), and carbendazin in papaya, orange and beans (7.4%). As expected, these results agree with the Exposure Mixture module results.

It is important to highlight, however, that the only dithiocarbamate included in the CAG is ziram, and it is very unlikely that the CS2 detected in the Brazilian samples by the indirect method used in monitoring program comes from the application of this pesticide. In Brazil, ziran is used only for seed treatment or soil application, and no residues are expected in the food samples from these treatments. When the dithiocarbamate intake (as ziran) was not considered in the assessment, the intake at the P99.9 was 0.52 µg/kg bw/day at the P99.9 of exposure, with a MOE of 1019.

As dithiocarbamates (measured as CS2) are frequently found in food samples, it is important that assessments for the steatosis CAG conducted at either national, regional or international levels consider whether or what percent the CS2 detected in the samples really come from the use of ziran based on the use pattern of this pesticide in the field.

Assuming that the steatosis CAG or any other CAG is agreed on, the main challenge to use the Exposure Mixture and Dietary Exposure modules of the MCRA 9 (beta) Euromix toolbox is to prepare the consumption and residue tables in the appropriate formats. Fortunately, the tables prepared for the MCRA 8.2 were suitable for MCRA 9, with very few changes needed, but for a first time MCRA user,

table preparation will demand quite a lot of time. Training and support is necessary to prepare the tables and to run the toolbox.

The two modules tested in the toolbox run very quick (about 2 minuts), and the total outcome of the results can be saved in pdf (over 600 pages each), and includes the raw data submitted and the individual results. Additionally, the main outcome of the reports can be saved separately. Some improvements in the outputs of the tested modules are suggested:

- Include the basis and assumption of the SNMU in Exposure Mixture
- Include the basis and assumptions of the CAG in the Dietary Exposure module report
- Include a summary report, containing all the relevant information in a single document with a reasonable number of pages (no more than 20, for example)

References

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