

Report of EuroMix Fourth Workshop on International Harmonisation of the Risk Assessment of Combined Exposures to Chemicals

10.00-17.00, 15 April 2019
WHO HQ, Avenue Appia 20, 1202 Geneva, CH

Background

EuroMix organised the fourth of a series of workshops on the international harmonisation of the risk assessment of combined exposure to multiple chemicals on 15 April, 2019 at WHO HQ, Avenue Appia 20, 1202 Geneva, CH. The specific objective of the workshop was to explore the potential of the EuroMix Handbook to contribute to harmonised scientific approaches to the risk assessment of combined exposure to multiple chemicals in the diet and more generally, in relevant legislation. Perspectives on the Handbook (and the Toolbox) were invited from representatives of international organisations. Issues that might arise in utilising the Handbook and the Toolbox at international level were identified, for consideration at the Expert Consultation, 16-18 April, 2019. Participants involved experts from Europe, North America, South America and Asia, as well as national and international organisations such as EFSA, JRC, OECD, WHO and FAO. The programme of the workshop is provided in the **Annex**. The following individuals participated in the workshop:

Name	Country/Region	Organisation
Janis Baines	Australia	Food Standards Australia New Zealand (retired)
Alan Boobis	UK	Imperial College London
Stephanie Bopp	Europe	JRC (The Joint Research Centre of the European Commission)
Eloisa Dutra-Caldas	Brazil	University of Brasilia
Amelie Crépet	France	ANSES (Agency for Food, Environmental and Occupational Health & Safety)
Jean-Lou Dorne	Europe	EFSA (European Food Safety Authority)
Vittorio Fattori	International	FAO (Food and Agriculture Organization of the United Nations)
Natalie Von Gotz	Switzerland	Federal Office of Public Health
Jacob van Klaveren	The Netherlands	RIVM (National Institute for Public Health and the Environment)
Eeva Leinala	International	OECD (Organization for Economic Cooperation and Development)
Soren Madsen	International	WHO (World Health Organization)
Bette Meek	Canada	University of Ottawa

Angelo Moretto	Italy	University of Milan
Roland Solecki	Germany	BfR (Federal Institute for Risk Assessment)
Philippe Verger	International	WHO (World Health Organization)
Gerrit Woltering	The Netherlands	RIVM (National Institute for Public Health and the Environment)
Liu ZhaoPing	China	CFSA (China National Center for Food Safety Risk Assessment)
Johanna Zilliacus	Sweden	Karolinska Institute, Stockholm

1. Introduction

The Meeting was the fourth, and last, of a series of workshops organised by EuroMix to explore options and potential limitations in the international acceptance of harmonised approaches to the risk assessment of combined exposure to multiple chemicals. The previous meetings were as follows:

- First Workshop: 20-21 October 2016, Imperial College London, London W12 0HS
- Second Workshop: 17 May 2017, Thon Hotel EU, Brussels, Belgium
- Third Workshop: 25 October 2018, Imperial College London, London W12 0NN

The meeting was chaired by Alan Boobis. Angelo Moretto served as rapporteur. Participants introduced themselves. **Alan Boobis** then briefly outlined the aims of the EuroMix project and specifically the outcomes of the previous workshops. While the meetings involved mainly risk assessors, the second workshop also included a number of risk managers, whose involvement proved to be very informative.

The main conclusions from the previous workshops were:

- Currently there is no agreed approach to the risk assessment of combined exposure to multiple chemicals in Europe (or elsewhere), although there is alignment of the general principles
- Approaches to the risk assessment of combined exposure to multiple 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
- There is agreement that dose-addition is an appropriate default assumption and that synergy is rare at human-relevant exposures
- There is currently no general agreement on how information on mode of action (MOA)/adverse outcome pathway (AOP) should be used in the risk assessment of combined exposure to multiple chemicals
- There is potential for the EuroMix Handbook and Toolbox to contribute to harmonisation of the risk assessment of combined exposure to multiple data rich and/or data poor chemicals

The aim of the present workshop was to evaluate the EuroMix Handbook, section by section. On this basis, a number of risk assessment bodies were asked to provide (i) their perspectives on the potential utility of the Handbook in the risk assessment of combined exposure to multiple chemicals by their own organisations and (ii) their feedback on how the Handbook could be improved.

Participants were also asked to consider which sections of the Handbook would be most relevant for discussion at the Expert Consultation, 16-18 April 2019 and to identify any potential limitations.

The presentations are available on the EuroMix website.

2. EUROMIX HANDBOOK

Johanna Zilliacus then presented in detail the content of the EuroMix Handbook.

2.1. INTRODUCTION

The EuroMix Handbook describes approaches to the risk assessment of combined exposure to multiple chemicals, drawing upon tools in the Euromix Toolbox. The EuroMix Toolbox provides a suite of web-based tools and data, which can be used to perform such an assessment. The EuroMix Handbook consists of a main text with a description of the methodology and tools, and a number of Annexes that cover the methodology in detail and provide templates, examples and training material for the EuroMix Toolbox. The EuroMix Toolbox comprises a number of modules, includes a data repository, and there is a separate Toolbox user manual.

The EuroMix Handbook took into consideration and is aligned with recent activities in CRA (note CRA (cumulative risk assessment) is used here to mean “risk assessment of combined exposure to multiple chemicals”), particularly the OECD’s Considerations for Assessing the Risks of Combined Exposure to Multiple Chemicals and EFSA’s Guidance on Harmonised Methodologies for Human Health, Animal Health and Ecological Risk Assessment of Combined Exposure to Multiple Chemicals.

The main features of the Handbook include:

- Component-based approach
- Grouping based on toxicological considerations
- Dose addition as default model
- Relative potency factors (RPF) approach
- Probabilistic exposure assessment
- Mainly, but not exclusively, dietary exposure

Whilst the Handbook is currently focused on grouping based on toxicological considerations, it is possible to input groupings based on other parameters and tools, such as co-exposure or both co-exposure and toxicological considerations, with modules in the Toolbox. The Handbook is applicable to a wide range of problem formulations because it can be applied using different grouping principles (structure, exposure...), to any chemical, (relative) potency of chemicals can be derived using different approaches (e.g. using acceptable daily intake (ADI)/tolerable daily intake (TDI), or no observed adverse effect level (NOAEL)/benchmark dose (BMD) for critical or specific effect), and provides methodology to handle data poor substances.

The Toolbox is based on previous software (MCRA) and allows the uploading of the user’s own or other data, as necessary, to perform CRA.

The software will be made freely available to users and a web-based manual and training will be provided. The software includes many modules that address the different aspects of CRA (hazard characterisation, exposure assessment, risk characterisation, uncertainty analysis), which can be used as needed.

The Toolbox includes food consumption data, from 11 European countries, and food monitoring data, mainly on pesticides, from the same countries. These data are owned by individual countries and can be used in web-based assessments, but they cannot be downloaded (unless specific permission of the data owner is provided). Users can upload their own data, provided the data are in the format required by the Toolbox, and templates are available to assist in achieving this. The EuroMix Toolbox will initially

include data on the toxicological endpoints: hepatic steatosis, craniofacial malformation and feminization.

COMMENTS from the participants

The question of verification of the data in the Toolbox was raised. Verification and peer review of data are needed, even if the data are proprietary. Currently the data provided in the Toolbox are “as is”. Users need to satisfy themselves as to their reliability, as appropriate. For example, some of the data, such as the results of national food consumption surveys, will have been verified by the owner. The use of the Toolbox for regulatory risk assessment will further require that the modules/models meet certain requirements, such as transparency. Not all of the code is publicly available, but it might be possible to rely on performance verification by EuroMix, but this will depend on the type and quality of information in the Toolbox. There is a need to follow guidance, such as on the use of quantitative structure-activity relationships (QSARs) (perhaps from EFSA or JRC) and on AOPs (OECD) to ensure the acceptability of such information in the Toolbox. Whilst guidance on these topics exists, it is not always suitable for the areas addressed by EuroMix.

Data in each module should be described and made publicly available (e.g. in Zenodo) with a description of the metadata that feed the module. This will greatly enhance the prospects of the tool being used in practice.

The toxicological data in the Toolbox needs to be expanded. Currently it contains *in vitro* and *in vivo* data generated by EuroMix as well as *in vivo* data from the literature collected by EuroMix, only on the three endpoints, hepatic steatosis, craniofacial malformation and feminisation used in the EuroMix exploratory studies. It was noted that OECD has a template to harmonise data collection of intermediate effects and adverse outcomes (OECD OHT 201). It was recommended that this be included in the Handbook.

Currently, the Toolbox includes information on toxicity only when it is available in English.

Many of these points are subject to discussion with EFSA and in the EuroMix follow-up. EFSA will assess the performance of the EuroMix Toolbox using its own software. RIVM has an agreement with EFSA for data collection. EFSA is currently collecting toxicological data using the OECD harmonised templates (OHTs) that include AOP and kinetic data (OECD OHT 58). Linkage to this information from the Toolbox would be very helpful.

2.2. PROBLEM FORMULATION

The template for problem formulation, which includes provision for an analysis plan, and an example, which are provided as annexes to the Handbook, were described. These are not included in the Toolbox, but the template was developed based on the methodology implemented in the Toolbox.

COMMENTS from the participants

It was suggested that the template for problem formulation and the example should be included in the Toolbox.

It was noted that the template includes a mixture of risk management and risk assessment elements. In conventional risk analysis, problem formulation is the responsibility of the risk manager, albeit in

dialogue with the risk assessor, to avoid a mismatch between what is asked by the risk manager and what is feasible or scientifically sound, from the point of view of risk assessment. In addition, existing legislation will dictate some aspects of problem formulation. It was suggested the template should clarify what is the responsibility of risk management and of risk assessment (i.e. scientific issues) in the analysis plan.

Both the problem formulation template and the Toolbox should be sufficiently flexible to allow a variety of questions to be addressed, depending on the needs of the risk manager. Suitable problem formulation is an essential prerequisite for CRA to be useful and, hence, to enable an appropriate answer to the problem to be provided.

The template includes a field for description of the mixture (components of potential concern), but there is no explicit mention of a gatekeeper step as such, which is included in all of the recent frameworks, including those from WHO, EFSA and OECD.

2.3. IDENTIFICATION AND ASSESSMENT OF AOP NETWORKS

This section covers grouping of compounds based on toxicity data (CAGs) and determination of relative potency factors (RPFs). The Handbook focuses on the use of data on AOPs both for grouping and for RPF determination. The methodology for identification and assessment of AOPs (AOP networks) is based on the OECD AOP handbook (2018).

If AOPs are not available in the AOP wiki, they should be developed, if possible. Such AOPs should then be coded (according to the AOP wiki) and uploaded to the Toolbox. When this is done, the information can be used to conduct CRA because individual quantitative KE data will be automatically connected in the relevant modules. In this respect, it is important to be very clear about the reliability of the KE data and the AOP used.

Modules are available in the Toolbox for key event (KE) quantitative data (note: to make more general, the term “effect” is used for a KE in an AOP, and “response” is used for what is measured experimentally to assess a KE). Such data can be used for potency estimates, if data on adverse outcomes per se are not available.

The default assumption is dose-addition for a common adverse outcome, independent of differences in molecular initiating event (MIE) and some of the KEs.

The Toolbox allows CRA to be performed for a single AOP or for a network of AOPs (e.g. similar and dissimilar acting compounds). This is in recognition that in different regulatory domains, the criteria for grouping may differ.

COMMENTS from the participants

There is a need to clarify how information on AOPs can be used in the grouping of multiple chemicals for risk assessment of their combined exposure. It is possible to perform CRA in the absence of information on AOPs or even RPFs. Some explanation of how to perform such an assessment, and the use of the Toolbox, in such situations, should be provided.

Some of the terminology used in the Handbook could be more explicit. For example, MOA and AOP are sometimes used synonymously and sometimes differently. It would be helpful if such terms were defined, consistent with international usage.

2.4. COLLECTION OF TOXICITY DATA

The Handbook recommends use of systematic review and weight of evidence for data collection. Any type of data can be used or uploaded to the Toolbox. The Handbook provides a template for data collection (but see above).

COMMENTS from the participants

It was suggested that the section on data collection could perhaps be shortened and the emphasis on systematic review should be removed, as systematic review is often not necessary. Instead, the emphasis should be on the need for transparency in the approaches, assumptions and data used in the assessment, whatever they are. The approach to data collection will be driven by problem formulation. Some guidance on when systematic review might be needed and other possible options would be helpful.

The templates are very KE/AOP focused. It might be helpful to summarise the assays used in different tiers in a CRA in a table for use in the Toolbox.

2.5. TIERED TESTING STRATEGY

Tiered testing based on an AOP network is also described. This requires selection of suitable assays (*in vitro*).

The methodology suggested in the Handbook includes:

- Identification of KEs in the AOP network that can provide information for grouping or for determination of RPFs
- Identification of *in silico*, *in vitro* and *in vivo* assays for the KEs or AOs
- The need to assess the
 - relevance of the assays
 - reliability of the assays
 - availability and feasibility in terms of costs and resources
 - information provided for grouping, RPFs, prioritisation for further testing
- Selection of assays to be included based on the assessments
- Description of the assays (test systems and responses) in the tables for use in the Toolbox

A template for description of a tiered testing strategy when used is provided in the Handbook.

COMMENTS from the participants

The Handbook could perhaps be clearer that the Toolbox can be used with any data for hazard characterisation (e.g. raw data to assess RPFs using the Toolbox or independently (externally) derived RPFs which are then uploaded; the use of AOPs is not a prerequisite).

As noted above, when developing new AOPs, these should be assessed according to the OECD process, but one option is to indicate different levels of reliability/confidence in an AOP depending on its maturity. There is some concern about the reliability of some of the AOPs currently in the Toolbox, as these have not yet been verified according to the OECD procedure. Hence the need for a formal process, and also for providing a very clear explanation of the confidence in these AOPs.

It was noted that confidence in the output of a CRA will differ depending on the confidence in the AOP, and its acceptance, especially if the AOP has not been independently verified. This should be clearly reported in the uncertainty analysis. It should also be made clear that, as the AOPs currently in the Toolbox are not verified, Toolbox outputs using such information should be considered as preliminary examples of proof-of-principle of the Toolbox and the proposed approaches. EuroMix examples/case studies are really for illustrative purposes. All methods will need to have been suitably characterised/verified before use in risk assessment for regulatory purposes. Concern was expressed that, despite this, CRA using non-validated AOPs could lead to unreliable conclusions, and once the conclusions are available, it will be difficult to counter their interpretation. When using the Toolbox, this should be made clear as appropriate, particularly in the output.

The Handbook should be clearer on the role of AOPs, since these are not currently being used even in the risk assessment of individual chemicals. Specific for CRA is that AOPs are of potential value in refining assessment groups. It should be born in mind that EuroMix is an innovation project, which tried to anticipate the evolution of risk assessment. That is why an AOP-based approach has been included. However, the Handbook should make clear what is applicable now and what might be possible in the future.

New approach methodologies (NAMs) (*in silico* and *in vitro*) used for KE event characterisation in CRA should be appropriately verified before such application. The Handbook should cross-reference existing guidance on approaches to verification of these methods for individual chemicals, as this would be relevant to their use in CRA.

2.6. GROUPING

The methodology proposed in the Handbook includes a number of considerations such as:

- Level of grouping (target organ, common effect/AO, common specific mode of action /AOP)
- AOP network
- Substance category
- Collect toxicity data (*in silico*, *in vitro*, *in vivo*, human epidemiology)
- Organise data in lines of evidence
- Assess data for relevance and reliability
- Decide on group membership using weight of evidence approach
- Report group membership in table for use in EuroMix toolbox (either 0 (not included) or 1 (included) or a value between 0-1 indicating the probability for belonging to the assessment group)

Different methodological considerations are possible for grouping off-line, using essentially any criteria as appropriate. A filtered (include/exclude) list of chemicals can then be uploaded to the Toolbox. It should be noted that with respect to OECD guidance on grouping, the Handbook addresses also the use of QSAR for this purpose.

COMMENTS from the participants

There should be clear information in the output of the CRA of what criteria were used as the basis for grouping.

Another key issue is the harmonisation of grouping. Some of the approaches outlined in the Handbook might not be generally accepted internationally.

There is a need to harmonise terms used in the Handbook (and the Toolbox) to the extent possible, to facilitate understanding and uptake of the Handbook. For example, the term “active substances” is understood by many to refer to pesticides. If a more general meaning is implied, perhaps a different term could be used, such as “chemicals”.

The Handbook should be checked to ensure that the OECD considerations for grouping have been adequately addressed.

2.7. RELATIVE POTENCY FACTORS (RPFs)

A number of options for determining RPFs are described on the Handbook. *In vivo* data should be used if available, for the time being, until reliable extrapolation of *in vitro* data becomes routinely possible (for both toxicokinetics and toxicodynamics). The RPF can be calculated using the NOAEL/LOAEL or BMD_x. Any value can be used for the BMR to determine the RPFs, depending on the shape of the dose-response curves. Normally it should be between 20 and 80%, as this is the statistically most reliable part of the curve.

If the BMD is to be used as a point of departure, the EFSA guidance on BMD should be used to decide on an appropriate BMR.

The choice of index compound should be based on the quality of the data, and this should be from *in vivo* studies.

If there is more than one point of departure (POD) for a compound, some basis for the choice of the POD will need to be decided, e.g. the lowest, the mean value. Is it for an upstream of a downstream key event? Guidance on this would be helpful.

IVIVE should be used to convert an *in vitro* POD to an external POD *in vivo*.

If toxicological information is not available, the threshold of toxicological concern (TTC) or a variant, such as an endpoint-specific TTC, can be used.

The Toolbox enables calculation of RPFs for multiple compounds based on their respective dose-response curves, and designation of one of the compounds as the index compound.

The Handbook explains how to design mixture studies based on RPFs to select various dose proportions for the chemical combinations. The methodology described in the Handbook includes:

- The use of equipotent doses/concentrations of substances
- The need to derive RPFs of individual substances
- The use of several doses of individual substances and binary mixtures
- The analysis of the results using the benchmark dose method

2.8. EXPOSURE

The Handbook proposes probabilistic exposure assessment, based on the previous MCRA tool and in line with EFSA guidance. The Toolbox provides distributions for both acute and chronic exposure with uncertainty estimates. Food consumption data are available from consumption surveys in 11 countries while concentration data are available from monitoring (i.e. measurement of levels of substances in raw agricultural commodities and conversion of food-as-eaten) with application of processing factors, in the same countries.

In the absence of measured concentrations of a specific chemical, either extrapolation from other foods or legal limits in food can be used.

Estimates of non-dietary exposures can be imported and used for aggregate exposure assessment in the Toolbox.

The results should be expressed as a margin of exposure (MOE), relative to the index compound.

Uncertainty in the assessment should be described and quantified to the extent possible. Templates are provided for this.

The Toolbox enables identification of substances commonly found together in the exposure (from the diet) and to which the studied population is mainly exposed. The approach is based on individual exposure correlations estimated from individual food consumption patterns, concentration data and RPFs. This information can be used for grouping, prioritisation, refinement of the risk assessment and prioritisation of mixtures to be tested. The statistical method implemented in the Toolbox for this purpose is the Sparse Nonnegative Matrix Underapproximation (SNMU). This appears to be a unique implementation in the EuroMix Toolbox and was considered by the participants to be a valuable contribution to CRA methodology.

COMMENTS from the participants

Consideration of exposure vs toxicology criteria for grouping chemicals should be addressed up-front in the Handbook, since refinement of exposure is an essential tier in a number of problem formulations. At present, grouping is considered largely in the section on hazard assessment. Grouping based on exposure can sometimes be easier than that based on hazard, since there are usually not that many driver compounds and it might be possible to decide *a priori*, based on MOE, whether to even consider including a compound in an assessment group. If the margin of safety (i.e. exposure/health-based guidance value (HBGV)) (based on the critical effect) is less than an agreed percentage (i.e. saturation of HBGV is < x%), should the substance even be considered for inclusion in the assessment group?

The Handbook could expand on possible options once the key risk drivers have been identified. Should one progress to higher tier assessment, should additional *in vitro* testing be undertaken, should the focus be on risk management options? Some indication of the factors that would help determine the next steps would be helpful (this would presumably depend to some extent on problem formulation).

It was noted that refinement of exposure estimates is essential in CRA. Aggregate exposure can also be relevant when defining the groups.

The section on uncertainty assessment could perhaps be expanded slightly in the Handbook, with cross-reference to relevant guidance.

It was suggested that the text on the SMNU method might fit better in the risk characterisation section.

2.9. RISK CHARACTERIZATION

The dose-addition model is the default model. Response addition and synergy may be considered on a case-by-case basis.

2.10. UNCERTAINTY ANALYSIS

Uncertainties are related to the different steps in the mixture risk assessment and the Handbook provides a template for the uncertainty analysis, where uncertainties should be identified and described, and quantified if and when possible.

COMMENTS from the participants

It is important to distinguish quantifiable variability in model parameter estimates vs “real” uncertainty (unknowns). Much of the current reference to “uncertainty” in the Handbook refers to variability. Hence, the meaning of uncertainty analysis as described in the Handbook should be more clearly explained.

3. PERSPECTIVES OF DIFFERENT RISK ASSESSMENT BODIES

Individuals from a number of risk assessment bodies were invited to provide their comments on the likely utility of the Handbook in the risk assessment of combined exposure to multiple chemicals by their own organisations. Any suggestions as to how the Handbook might be improved would also be welcome.

3.1. OECD

OECD develops methodology but does not carry out risk assessment of single or multiple chemicals. OECD has recently published some “Considerations for risk assessment of combined exposure to multiple chemicals”, which includes discussion on points to address in problem formulation and on the risk assessment of exposure to multiple chemicals. It covers a wide range of scenarios.

The EuroMix Handbook is very complimentary to the OECD publication.

There is a need to include more mechanistic data and AOPs in risk assessment, which have considerable potential in the grouping of chemicals. NAMs can help in assessing AOPs, which in turn can help in better use of such data, although these have yet to be validated. There is a good measure of agreement on the general methodological approaches to CRA. However, decisions on how the methodology should be applied take place in different decision contexts (i.e. the problem formulation), so that sometimes the approach used will vary. It is proposed that we should start to use the methodologies now, and then refine the approach as necessary, with experience.

It is important to continue to develop a range of case studies (which is ongoing in different regions), and it would be helpful to increase the number of case studies available. Perhaps the ones developed by EuroMix and by EFSA will inform application.

With respect to data collection and storage, there is a need to harmonise how this is done, building on work already done at the OECD with the OECD Harmonised Templates, to enable data sharing.

3.2. WHO

The need for WHO is to be able to assess chemical risk and to provide robust advice to risk managers. This requires technical guidance that translates the results of research such as from EuroMix into risk assessment practice.

The Handbook and the Toolbox are closely linked, and it is not always easy to distinguish what refers to which.

With respect to the Handbook, some of the recommendations are not very applicable for international risk assessment, i.e. by JECFA/JMPR. But there are some parts of the Handbook that, it is hoped, could be used as the basis of practical guidance.

Regarding the Toolbox, this is a very powerful platform, but it needs to be determined whether it allows sufficient flexibility for the approach necessary in the work of WHO, especially JMPR and JECFA. An important question is how the platform is to be maintained after EuroMix finishes. There are also issues of transparency and of validation if the Toolbox is to be used in international risk assessment.

3.3. FAO

In addition to the views of the WHO, the need for a flexible approach, that covers both data rich and data poor compounds, was emphasised.

Approaches for the risk assessment of dual use compounds (pesticides and veterinary drugs) have recently been harmonised by FAO/WHO. It is important that these can be accommodated in the Toolbox and could perhaps be addressed in the Handbook.

3.4. JRC

JRC has undertaken work on methodology for risk assessment of combined exposure to multiple chemicals, covering both dietary and non-dietary exposure. The flexibility of being able to use and import one's own data into the Toolbox is appreciated.

Use of NAMs and AOPs in such assessments is important.

With respect to the Handbook, it is not always clear what can be done in the Toolbox and what cannot be done at the moment (or at all).

The Handbook is easy to read. But there is some imbalance in the detail, for example the section on the identification of mixtures vs the one on IVIVE, where the latter is quite brief. There could perhaps be a better balance in the Handbook for data rich and data poor chemicals.

The Handbook could provide more guidance on communication and working across silos. This is not always clear, for example on how and when non-dietary exposure should be integrated into assessments.

Most of the documents cited in the Handbook are from EFSA and related to pesticide CRA. Perhaps this should be broadened to other key documents for non-dietary exposure and other chemical sectors.

Overall, it was felt that the Toolbox would contribute to the harmonisation of approaches to the risk assessment of combined exposure to multiple chemicals.

3.5. EFSA

The recent EFSA guidance on risk assessment of combined exposure to multiple chemicals addresses systematically problem formulation, hazard characterisation, exposure assessment, risk characterisation and the reporting summary. This guidance was applied by EFSA in the case study on four compounds for the WHO Expert Consultation.

EuroMix should give careful thought to dissemination of its different outputs and achievements, in scientific journals and in open source platforms, for each individual model developed, to maximise the incorporation of these tools into other platforms and so optimise their use in risk assessment by a range of scientific advisory bodies.

Training in the methodology is important and some thought needs to be given to how this can be accomplished.

With respect to the use of the Toolbox within EFSA, there is a formal process, described in the procedure for new tools, by which such innovations are assessed. There would need to be a critical appraisal of the individual models and methods. This is context dependent. Models used by EFSA need to be open source. A recommended option is to connect relevant EuroMix models and data in the Toolbox to EFSA's OpenFoodTox.

In general, the Handbook and Toolbox were positively received. There are possibilities of applying the Toolbox in the European context. This could be facilitated by submission of a project idea to the EU Risk Assessment Agenda and by integration of the EuroMix tools with other EU tools.

3.6. GENERAL DISCUSSION

There are various mentions of the Handbook, Toolbox and User Manual for the Toolbox, but they are not always clearly distinguished. Each of these needs to be clearly described, particularly the role of the Handbook. How do these all map to each other?

How should AOPs for endpoints not covered during the EuroMix project be addressed?

OECD could perhaps co-ordinate the development of AOPs for endpoints of specific regulatory concern, to ensure that these are adequately covered. Could this be a research focus within Horizon Europe?

Suggested enhancements to the Toolbox include: provision for the generation of transparent summaries of the model outputs, enabling trace-back to the relevant inputs; clear explanations for the selection of parameters, decisions, input data; perhaps link modules to relevant templates (and vice versa). There could be more modules on exposure, for grouping and for lower tier exposure estimation.

P450-specific metabolism of chemicals and physiologically-based kinetic models should also be addressed.

The output of the Toolbox should be independently verifiable and replicable: the Toolbox provides all of the details necessary for this.

4. KEY MESSAGES AND POINTS FOR DISCUSSION AT THE UPCOMING WHO EXPERT CONSULTATION

It is noted that, at present, the format of consumption data used by JMPR and JECFA is not compatible with the Toolbox (summary statistics vs raw data for individuals) because they are not based on individual food consumption data. In addition, since distributions of monitoring data are generally not available to JMPR/JECFA, usually a full probabilistic assessment cannot be performed. At international level, performing a full probabilistic assessment would require using a distribution of occurrence either from residue trials or from monitoring data. What sources could be used for suitable residue and food consumption data for this?

The presence of several metabolites as residues of a single substance can also be of concern for assessments by JMPR/JECFA. What assumptions can be made about shared and different MOAs, and hence membership or not of an assessment group?

Whilst the focus of JECFA and JMPR is chemical exposure from the diet, WHO also has activities related to Drinking Water, and Indoor Air Quality and Ambient Air Quality. The implications of this may need to be considered at the Expert Consultation.

Problem formulation needs to be clearly defined for JMPR and JECFA.

It is noted that the EU Commission is willing to use the monitoring data as background to assess the saturation of the remaining ADI for a new compound to be authorized. It remains to be determined whether this approach can be applied or is even feasible at JECFA/JMPR.

CRA for pesticide or veterinary drug residues at international level is complicated by national/regional difference in GAP, and by the lack of residue data for some of the compounds belonging to the same assessment group, at a given meeting. Relevant data are usually submitted by sponsors in response to a data call. Ways of addressing these issues will need to be explored.

JMPR/JECFA might prefer to use MOA for endpoints considered relevant as a basis of grouping chemicals. However, experience in recent years has shown that sponsors generally do not provide mechanistic data, despite repeated calls for such data. This makes it difficult to identify MOAs, although data might be available in the literature. A related issue is how data generated using NAMs should be used for this purpose.

Organisational aspects within the JECFA/JMPR process will need to be carefully considered: e.g. flow of data via WHO; standard of reporting; compatibility of data collection. It would be helpful to agree on common templates, to help in harmonisation and to ensure data format compatibility.

How can FAO/WHO facilitate training, if at all?

5. Conclusions

The Handbook was generally well received. Participants felt that it was clearly laid out and that, together with the Toolbox, it should make a significant contribution towards international harmonisation of approaches and methods used in the risk assessment of combined exposure to multiple chemicals.

Participants made a number of suggestions on how the Handbook might be clarified or extended. These included:

- Ensure that the Handbook is “neutral” in the approach and methods used, to provide maximum flexibility for the range of problem formulations that arise in different chemical sectors and regions
- Clarify the difference among the Handbook, the Toolbox and the User Manual for the Toolbox, and their respective roles
- Improve the balance of the text, which is extensive in some areas but relatively short in other, equally important, areas
- Provide guidance on options where AOPs are not available for the chemicals being assessed, including assessing confidence in AOPs developed *de novo* for an assessment and options where AOPs cannot be developed
- Discuss options also for exposure-based grouping rather than only toxicologically-based grouping of chemicals
- Expand the section on exposure to consider approaches in addition to the full probabilistic assessment described
- Ensure that templates are suitable for data exchange, for example are harmonised with the OECD templates for data collection
- Provide some guidance on reporting standards, including suitable summaries for risk assessors and for risk managers

The participants concluded that there were several sections of the Handbook and modules in the Toolbox that could potentially contribute to risk assessment of combined exposure to multiple chemicals by JECFA/JMPR and that would merit discussion at the Expert Consultation. However, potential limitations were also identified, including availability of suitable data on exposure, formats for consumption data, transparency of the models used in the Toolbox, and the need for verification of methods, algorithms and software.

Annex

Fourth EuroMix workshop on international harmonisation on the risk assessment of combined exposures to chemicals

Program

The objective of the fourth workshop is to explore the extent to which the EuroMix guidance serves the needs of harmonised scientific approaches to the risk assessment of combined exposures to chemicals in the diet, in relevant legislation.

15 April 2019: Room D (7th floor), WHO HQ, Geneva, Switzerland

Day 1		
09:00-10:00	Registration	
Chair/Rapporteur	Alan R Boobis (<i>Imperial College London</i>)/Angelo Moretto (<i>University of Milan</i>)	
10:00-10:15	Welcome and introductions	Alan R Boobis (<i>Imperial College London</i>) and All
10:15-10:30	Background and objectives of meeting	Alan R Boobis (<i>Imperial College London</i>)
10:30-11:30	The EuroMix Handbook	Johanna Zilliacus (<i>Karolinska Institute</i>)
11:30 -12:30	General discussion	All
12:30-13:30	Lunch	
13:30-15:30	Perspectives of risk assessors (including) <ul style="list-style-type: none"> - OECD - EFSA - WHO - FAO - JRC 	Short presentations (5-10 min) and general discussion
15:30-16:00	Refreshment break	
16:00-17:00	Implications for WHO Expert Consultation	All