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

25 October 2018, Hammersmith Campus, Imperial College London, London W12 0NN, UK

Background

EuroMix organised the third of a series of workshops on the international harmonisation of the risk assessment of combined exposures to chemicals on 25 October, 2018 at the Hammersmith Campus of Imperial College London, London, UK. The specific objectives of the workshop were to explore ways in which the EuroMix toolbox can contribute to harmonised scientific approaches to the risk assessment of combined exposures to chemicals in the diet, in relevant legislation. In support of this objective, illustrative case studies were presented and discussed, and used to inform guidance for consideration at the final workshop. Participants involved experts from North America, Europe and South America, as well as national and international organisations such EFSA, JRC, OECD, WHO and US EPA. The programme of the workshop is provided in the Annex. The following individuals attended the workshop:

Name	Country/Region	Organisation
Alan Boobis	UK	Imperial College London
Stephanie Bopp	Europe	The Joint Research Centre of the European Commission (JRC)
Eloisa Dutra Caldas	Brazil	University of Brasilia
Jean-Lou Dorne	Europe	EFSA
Takaaki Ito	International	OECD
Jacob van Klaveren	The Netherlands	The Netherlands National Institute for Public Health and the Environment (RIVM)
Anna Lowit	USA	US EPA
Bette Meek	Canada	University of Ottawa
Luc Mohimont	Europe	EFSA
Angelo Moretto	Italy	University of Milan
Emiel Rorije	The Netherlands	The Netherlands National Institute for Public Health and the Environment (RIVM)
Roland Solecki	Germany	The German Federal Institute for Risk Assessment (BfR)

Name	Country/Region	Organisation
Philippe Verger	International	WHO
Hilko van der Voet	The Netherlands	Wageningen University & Research (WUR)
Johanna Zilliacus	Sweden	Karolinska Institutet

The meeting was chaired by Alan Boobis. Angelo Moretto served as rapporteur, together with Alan Boobis. The meeting started with participants introducing themselves. **Alan Boobis** then provided a brief introduction to the objectives of the workshop, which were: to review the outcome of the first two workshops; to review ongoing work on harmonisation elsewhere; to explore ways in which the EuroMix toolbox can contribute to the risk assessment of combined exposures to chemicals; to compare and contrast different approaches to the risk assessment of combined exposures to chemicals in the diet, in relevant legislation by means of illustrative case studies; to consider how the EuroMix toolobox might contribute to the different needs to risk assessors and promote greater harmonisation in the approaches used. The meeting was organised into three sessions. Session 1 was on Conclusions from the first two workshops and EuroMix contribution. Session 2 was on Illustrative case studies. Session 3 was on Conclusions and next steps. During each session, a number of speakers presented their perspectives, each followed by discussion. Copies of the presentations are available on the EuroMix website.

Session 1: Conclusions from the first two workshops and EuroMix contribution

The session opened with a review of **What have we learned from the first two workshops (A Boobis).** In general, an overall objective of the workshops was to identify to what extent the process of the assessment of combined exposures to multiple chemicals can be harmonized across geographical regions and regulatory domains. How can this be done assuring consumer safety without restricting international trade unnecessarily, on the basis of sound science? The scope of the assessment needs to include exposure sources and routes, the bases for grouping substances, and the chemical sector(s) to be considered.

At the first Workshop (London, 20-21 October 2016), it was concluded that, in general, problem formulation for the assessment of combined exposures to chemicals is not well developed, and often lacks transparency in a number of elements. For example, the chemical scope (which sectors and chemistries) is often not explicitly identified, and not all of the factors used as a basis for grouping chemicals are always explicitly stated. Problem formulation should include chemical sector/space to be covered, regulatory context, timescale, resources available, acceptable level of uncertainty; percentiles of concern when using probabilistic approaches.

There was general agreement that a tiered approach should be used, which was likely to vary depending on the chemical sector and available information. Areas in which further discussion was considered necessary included the scope (e.g. which sectors/“silos”) of the assessment; criteria for grouping chemicals for assessment; how information on MOA/AOP should be used in assessments. All agreed that further harmonization was desirable, and indeed was necessary in some areas, including pesticides (international trade).

At the Second workshop (Brussels, 17 May 2017), participants discussed the legislative needs for the assessment of combined exposures to chemicals in different chemical sectors within the EU and across different geographical regions for the same sector. Participants also considered the role that scientific research plays as a determinant of future legislation. Perspectives of risk managers were presented in

the areas of pesticides, contaminants, additives, industrial chemicals and chemicals in general. It was agreed that the work of EuroMix could contribute in a number of areas, such as a tiered approach to grouping; and the assessment of uncertainty.

It was concluded that there is currently no overarching approach available for the assessment of combined exposures to chemicals. Different approaches are in use across chemical sectors and geographical regions. It was noted that the most common approach for grouping chemicals is a combination of structure, co-occurrence, and designed function. EuroMix will explore the consequences of different choices and assumptions in conducting such assessments.

The session continued with an **Update on ongoing work on harmonisation** (T Ito). OECD activities in the area of Environment, Health and Safety aim at the development of harmonized, high quality instruments, work-sharing to avoid duplication, prevent unnecessary non-tariff trade barriers, and to shorten time to market. The combined exposure assessment project started in 2014, following up on a WHO/OECD/ILSI HESI International Workshop in 2011. The goal of the project is technical convergence between member countries in the assessment of combined exposures to multiple chemicals. The expected deliverables include an outline of considerations for assessing combined exposures to multiple chemicals, which is addressed primarily to regulatory authorities and should not be considered strict guidance. The composition of the expert group, the structure of the document and the approach adopted were described. Key components are problem formulation; use of a tiered approach; hazard and exposure assessment; and risk characterisation. It is hoped that the document will be published by the end of 2018.

As of the present, there is no specific plan for follow-up, but one of the expectations is for the sharing of case studies amongst countries and organisations and that the OECD will continue to gather experience and knowledge on CRA activities. Possible follow-up activity will depend on suggestions of expert group members and feedback from countries

It was agreed that an inventory of case studies would be useful, identifying lessons learnt and those areas (chemical sector, geographical, regulatory) that are not covered by the developed case studies. Different groups have requested case studies (EFSA/OECD/EuroMix/WHO, etc), and there are clearly opportunities for sharing these, ideally using a common platform. OECD may discuss the possibility of devloping a standard template for problem formulation and possibly for other aspects of CRA such as uncertainty analysis and weight of evidence. In addition, to share case studies optimally, data would need to be organized using a common template. There may be a role for EuroMix here.

The session continued with several presentations on the EuroMix toolbox. The first of these was on **Retain and refine based on expert opinion and applied to pesticides using the EuroMix model and data platform** (H van der Voet). The final version of the EuroMix toolbox will provide an open web-based platform enabling integration of all data types and sources necessary for CRA. The toolbox includes modules for exposure, hazard and risk, and provides for data input and derived calculations. Visualisation includes use of the “RISK21 matrix” and it is proposed that boundaries for variability and for uncertainty should be included. Participants ageed that some further consideration needs to be given to the implementation of this feature.

The “Retain and Refine” approach was described. This includes consideration of the following in creating CAGs

- uncertainty on membership;
- missing hazard data;
- missing exposure data.

With this approach "Refine" indicates that a probability of membership of a CAG is given to all compounds and none is dropped from the calculation. An analysis is then conducted for potential risk drivers (e.g. using mixture selection).

Uncertain of membership is estimated by a combination of:

- expert elicitation
- QSAR
- Molecular docking
- Any combination

Uncertainty for missing hazard data, including that of the RPFs, is also estimated. EuroMix proposes use of the TTC, generic or specific, to estimate the POD/RFP, with associated uncertainty, in the absence of chemical-specific information.

While technically feasible, this approach should tested by applying it to realistic case-studies to determine its practicality and conservatism. Key assumptions used in applying the probabilistic approach proposed should be clearly identified and a sensitivity analysis conducted to determine which are the risk drivers. The generation of the data required for input for this approach is resource intensive and, therefore, this has to be balanced with pragmatism and feasibility. It was suggested that the EuroMix toolbox could be used to determine the contribution of each factor or assumption to the final outcome, to determine whether its inclusion was necessary. While the "Retain" approach is recognized as scientifically sound, it might be that a number of retained substances contribute so little to the total risk that they may be safely ignored in the CRA, and criteria should be developed for such a decision.

E Rorije next described EuroMix **In silico tools for lower tier CAG membership and potency estimates**. The approaches being developed were illustrated using hepatic steatosis as an example. Several methods can be used to assess CAG membership in the absence of higher tier data. These include:

- Generic QSAR models based on apical endpoints. This has been applied to over 600 compounds

  These are not very specific and CAG membership is rather inconclusive. There are no QSAR models for the prediction of MOA, but EuroMix is developing some models for this purpose

- Molecular Docking (MD)

  MD is useful in predicting MIEs, however it is assumed that binding results in activation. The models cannot differentiate between agonism and antagonism. MD does enable activity (binding) to different nuclear receptors (MIEs) to be distinguished.

Low tier for Potency estimation:

- NOAEL, if available;
- Read-across;
- TTC (generic or CAG specific);
- Docking (use binding energy).

Potency estimates based on binding energy are generally very conservative, with estimates almost always lower than the 5th percentile NOAEL for steatosis (i.e. the threshold for a CAG-specific TTC]

All of the data and calculations are available in the EuroMix toolbox.

The session continued with a presentation on **Examples of multiple routes of exposure and how these might affect the Margin of Exposure** (J van Klaveren). The EuroMix toolbox now includes considerable information on exposure. Consumption data (diet) from different EU countries, organized in EFSA is available. A concentration (of pesticides) database is also available in which processing factors are provided.

The impact of using relative potency factors based on different data sets, including the EFSA reports on CAG groups, in vitro studies and in silico (QSAR) predictions to calculated MOEs has been assessed. The consequences of using different approaches for RPF determination and of the breadth of chemical space used in the exposure assessment were also assessed. The MOEs for the CAG group of pesticides causing steatosis, as an example, were all > 500. In general, MOEs were lower, sometimes much lower, when additives and, particularly, contaminants were considered together with pesticides. This is, to a large part, a consequence of how poor/missing exposure data are addressed.

The calculations were performed assuming dose-additivity for CAG members, based on phenotypic effects (EFSA level 2) and including compounds for which this effect was not the critical effect (i.e. the effect used for the Point of Departure/Reference Point for establishing the health-based guidance value).

Non-food exposures (e.g. farmers, applicators, bystanders, residents) cannot presently be estimated using the EuroMix toolbox itself, and hence to conduct a full aggregate exposure assessment requires the appropriate estimates to be imported. The toolbox has provision for this. For example, it is possible to link the BROWSE model (Bystanders, Residents, Operators and WorkerS Exposure models for plant protection products) from the toolbox.

The consequences of the different assumptions used in these calculations should be explored by EuroMix, for both combined and aggregate exposure to chemicals.

Discussion of the EuroMix toolbox continued with a presentation on **Kinetics and IVIVE (In vitro to in vivo extrapolation)** (E Rorije). EuroMix has developed a generic physiologically-based toxicokinetic (PBTK) model, based on that developed by the EU COSMOS project. Chemical specific parameters are estimated in silico, using QSAR and from physicochemical properties. This has been undertaken for all of the substances in the EuroMix inventory.

The approach was illustrated using cypermethrin as an example. Most parameters were predicted within a factor of 10 but some, particularly plasma protein binding, were not well predicted. The reasons for this need to be explored. Prediction of metabolic rates is under development, using read across from an existing QSAR model for fish metabolism. The possibility of developing a similar model for rat or human could be considered. The current model assumes that the parent is the toxic moiety.

The final presentation in this session was on the **Applicability of EuroMix tools for other regulatory sectors** (B Meek). The Canadian Government has mandated the evaluation of a large number of industrial chemicals. Therefore, the approach adopted has to be tiered and very pragmatic, both for prioritization and for assessment. In general, many of these chemicals are data poor, yet prioritization and, if necessary, assessment is required using the data available. Hence, read across from within chemical categories is of considerable importance. Criteria are needed for grouping chemicals. Characteristics that can be used are:

- Structural similarity;
- MOA;
- Physicochemical properties, environmental fate, human/environmental effects;

- Qualitative/quantitative comparison.

OECD IATAs (Integrated Approaches to Testing and Assessment) provide a pragmatic means to integrate available data and target testing strategies. OECD is developing case studies, using defined templates to increase the collective experience. In reviewing case studies to date, read across was the most frequently used approach in the assessments.

Further guidance is necessary, and the EuroMix toolbox could be of value in addressing some of the existing needs. Such areas include:

- the definition of analogues/category boundaries, and uncertainty analysis and reporting;
- assessment of industrial chemicals (not occupational), in data-poor situations;
- exposure assessment;
- contaminated sites, where predictive application to data poor situations is necessary;
- development of case studies for industrial chemicals (e.g. PBDEs/phthalates);
- application to the OECD IATA case studies on CRA and on chemical categories

Session 2: Illustrative case studies

The first case study was on the **Implementation of CRA of pesticide residues by EFSA** (L Mohimont). The CAGs for pesticides used by EFSA are based on phenotypic effect, dose-addition is applied to all members of the CAG, and it is assumed that there is no interaction among members of the CAG (indeed, none is expected). Suitable methodology was developed by the PPR Panel from 2007-2013. All relevant data for assessing combined exposure to members of such a CAG are available (i.e. on toxicology, consumption, residues) and the necessary tools have been developed, i.e. MCRA (RIVM) and an internal EFSA model (SAS-based).

Initially a retrospective CRA will be conducted. During 2019, in a pilot phase, CAGs for the nervous system and the thyroid will be assessed. From 2019-23, CAGs for eight other organs/systems (adrenals, development, eyes, haematopoietic system, kidneys, liver, reproduction and testes) will be assessed. Prospective CRA awaits kick-off by the EC and member states.

There will be four reports on the nervous system CAG. One report will be on the CAGs, describing the identification and characterisation of the common effects. There will be two reports on combined exposure assessment (from RIVM, using MCRA and from EFSA, using SAS). The fourth report will be on characterization the risk from combined exposure to CAG members. Considerations included will be identification on the index compounds, and analysis of uncertainties associated with CAG membership and the assumption of dose-additivity.

General criteria have been identified for CAGs for the nervous system and for thyroid effects. Criteria for identification of index compounds have been defined, which include potency. RPFs have been calculated for all CAG members, based on NOAELs (or adjusted LOAELs, if necessary), where the lowest NOAEL from acceptable studies was used. 420 Active Substances (AS) have been assessed for effects on the nervous system and the thyroid. Seven effects of relevance were identified (five for nervous system, two for thyroid) and seven CAGs were created. The CAG for hypothyroidism included changes in T3/T4/TSH and induction of adenomas/carcinomas. There was no exclusion based on human relevance (e.g. thyroid adenomas due to increased T4 elimination).

Within a CAG, some of the members had a known (or presumed) MOA, whilst others did not, but shared at least one of the indicators identified for the common effect. For example, within the nervous system - motor effects CAG there are 85 AS with a known MOA and 35 for which the MOA was not

known. Within the thyroid – hypothyroidism CAG, the percentage of active substances with known MOA is much lower.

An assessment of the uncertainty in grouping compounds into the CAG for hypothyroidism was undertaken, as a case study. This was based on weight of evidence and expert knowledge elicitation. First, possible lines of evidence were identified. Each line of evidence was then weighted for its contribution to determining CAG membership. An overall score for each AS was calculated by multiplying the scores for all lines of evidence. Based on these scores AS were sub-divided into 7 sub-groups, members of which had an approx. similar level of evidence. Expert knowledge elicitation was then used to assess what percentage of members in each of the sub-groups caused hypothyroidism (true positives). The estimated probabilities of true CAG membership could then be taken into account when conduct CRA. Key risk drivers will be identified, and if there is concern (low margin of safety (MOS - ratio of reference value for index compound to exposure, or low MOE), then a more detailed analysis on the probability of CAG membership will be undertaken.

The appropriateness (uncertainty) of assuming dose-addition for CAG members will be assessed. Considerations upon which this assessment will be based include empirical information on the combined effects of the AS, MOA and toxicokinetics.

Risk managers have agreed that the threshold for regulation is the 99.9th percentile of the population with a protection goal of a combined MOE of at least 100. Uncertainty analysis of hazard characterisation, exposure assessment and model uncertainties will form an essential part of the assessments.

A number of points were noted with regard to the approach described.

Inclusion of all members of a CAG in an assessment, based only on hazard, implies an assumption of co-occurrence/exposure. Information on actual co-occurrence would be of value (work on this is ongoing within EuroMix). In addition, inspection of the tail of acute exposure distributions reveals that this comprises a very small number of compounds, usually only one. Such information could be used in a refined assessment.

It was noted that compounds can fall into more than one CAG (e.g. for nervous system), and that the effect of an AS on which CAG membership is based is not necessarily the critical effect on which its reference value is based. Since CRA will be performed only after assessment of each compound has shown that there is no concern for the compounds taken individually, this could be a consideration in refinement of the methodology.

The question of whether and how account will be taken of the human relevance of certain effects, such as some of those on the thyroid in rodents, in CAG membership was raised.

The appropriateness of basing CAG membership on a single indicator showing a statistically significant change in one study was questioned. Additional issues where further consideration might be merited include the use of the NOAEL of the most sensitive indicator as POD for CRA, the way in which the lines of evidence are used to assess weight of evidence, and the aspects addressed in expert elicitation.

The second illustrative case study was on the **Cumulative risk assessment of pesticides in the US** (A Lowit). EPA cumulative risk assessments for pesticides are risk based. The mechanism of pesticidal activity is used as an indicator of potential mode of action for human health effects.

Key principles in a refined CRA are:

- integration of toxicity and exposure data; i.e. time-frame
- realistic assessment, e.g. use monitoring data, avoid compounding conservativism (especially in CRA vs individual compound assessment)
- maintain geographical, temporal and demographic specificity
- be able to "track back" sources of exposure for sensitivity analysis

To date, refined CRA has been performed for five CMGs: organophosphates (OPs), N-methyl carbamates, pyrethroids, triazoles, and choloroacetanilides. In each case, members of a CMG were shown to share the same MOA. In some cases, for example for carbamates, EPA conducted specific studies to confirm dose-additivity. For each CMG, an index compound was selected, based on the quality and quantity of data available. Uncertainty in the POD of the IC propagates throughout the CRA. Potency is not a consideration in the choice of IC by EPA.

Temporality is a key consideration in CRA. It is important to consider biological time, i.e. toxicodynamics. This helps determine the relevant dose metric, e.g. C_{max}, AUC and likelihood of co-exposure. For example, N-methyl carbamates show peak toxicity at 30 min and recovery by 2 hours. Hence, whilst 24-hour exposure estimates would be sufficient in most cases, if necessary, refinement would be possible, based on eating pattern.

Models are available to estimate aggregate exposure from multiple sources.

Compounds may be excluded from a CAG because of low hazard potential, e.g. some pyrethroids show no effects up to a limit dose of 5000 mg/g bw. Similarly, pyrethroids with no residues in any crop were excluded from the dietary assessment. For residential uses, only those uses likely to give rise to significant exposure were included in the assessment. For hazard characterization of pyrethroids, severity scores in animal studies for behavioural and other signs were used.

In the triazine assessment of 2018, a PBPK model was developed for the IC, atrazine, and this was used to determine PODs for all of the triazine herbicides, including chlorotriazine metabolites, in the CAG. The model was used to allow for different age groups and different exposure scenarios (routes of exposure).

EPA has recently developed a screening framework to identify candidate CMGs. This uses the same principles as in the previously published guidance for CMG creation, i.e. chemical structural similarity, hazard profile, pesticidal mode of action and mammalian MOA/AOP. Shared chemical structure is not sufficient on its to support a candidate CMG. Rarely is apical outcome used as the sole basis for determining a candidate CMG, e.g. OPs and pyrethroids would not be considered in the same CMG. In the absence of good evidence for a common mechanism of action, no CRA would be necessary (Option 1 in the Framework), e.g. sulfonylureas. Where a candidate CMG supports a common mechanism of action, but there are insufficient data to define the key events in the MOA, a screening level tiered exposure assessment is conducted (Option 2 in the Framework), e.g. anilinopyrimidines. If this assessment gives rise to no concern, the CRA can be concluded. If there is potential concern, the CMG would be refined, to enable a higher tier assessment to be undertaken (this has not been necessary to date). EPA is preparing a publication on use of ToxCAST data to support identification of candidate CMGs.

Session 3: Conclusions

The workshop closed with a brief presentation on **Integration with other activities such as WHO/EuroMix workshop and EuroMix guidance** (J Zilliacus). WHO is organising an expert consultation within the frame of EuroMix. This will be held 16-19 April, 2019 in Geneva. The workshop

will comprise a series of case studies, in which different organisations will have assessed combined exposure to the same group of chemicals, using their own choice of methodology and inputs. One option will be to use the tools and data available in the EuroMix toolbox. Based on the outcome of this exercise, guidance will be prepared on when and how a risk assessment of combined exposure to multiple chemicals should be undertaken within an international context, for example by JMPR. The guidance will be produced according to WHO procedures and will not be complete until after EuroMix has ended.

A EuroMix Handbook is being prepared describing the approach for mixture risk assessment developed by EuroMix. This will provide practical guidance for the implementation of Euromix tools in risk assessment of combined exposure to multiple chemicals under a variety of problem formulations, and will cover both data-rich and data-poor situations. The aim is to ensure that the Handook is aligned with the OECD document and (draft) EFSA framework, and to avoid unnecessary repetition. There will be further training sessions for stakeholders in early 2019 on the EuroMix toolbox and Handbook. Finally, EuroMix is organising a joint stakeholder workshop with the sister H2020 project, EDC-MixRisk. This will be 26-27 March, 2019 in Brussels.

Conclusions

There is considerable alignment of the principles for assessment of combined exposure to multiple chemicals in the guidance of IPCS, OECD, EFSA and other organisations. These all emphasise the importance of problem formulation, including specification of the objectives and acceptable degree of uncertainty for assessment, and the basis for grouping and the selection of assessment approach. There was general agreement on the need for tiered approaches for both hazard and exposure assessment, to avoid overly conservative assumptions. The use of mode of action information in refining assessment groups has also been broadly incorporated, as has been transparent delineation of uncertainties at each tier. In a number of chemical sectors, there is common application of these principles. However, in the area of pesticides, there are significant differences between the proposed approach in Europe and that which is in use in the USA.

The EuroMix toolbox has potential application, regardless of the approach used in different sectors or geographical regions. Whilst harmonisation of the specific risk assessment methodology might not be possible, at least in the short term, it should be possible to harmonise the principles used, the standard of reporting and data templates. The EuroMix guidance will seek to provide best practice for the range of problem formulations that might concern risk managers and will encourage further harmonisation, to the extent possible.

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

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

Program

The objective of the third workshop is to explore ways in which the EuroMix toolbox can contribute to harmonised scientific approaches to the risk assessment of combined exposures to chemicals in the diet, in relevant legislation. In support of this objective, illustrative case studies will be discussed, and used to inform guidance for consideration at the final workshop.

09:00-17:00, 25 October 2018: Hammersmith Campus, Imperial College London, London W12 0NN

08:30-09:00	Welcome coffee and registration	
Chair/Rapporteurs	**Alan R Boobis *(Imperial College London)*/TBD**	
SESSION 1: Conclusions from the first two workshops and EuroMix contribution		
09:00-09:15	Introduction and objectives of meeting ***Alan R Boobis (Imperial College London)***	15 min
09:15-10:00	What have we learned from the first two workshops ***Alan R Boobis (Imperial College London)***	25 min + 20 min discussion
10:00-10:30	Update on ongoing work on harmonisation ***Takaaki Ito (OECD)***	20 min + 10 min discussion
10:30-11:00	Refreshment break	
11.00-13.05	Outline of the EuroMix toolbox 1. Retain and refine based on expert opinion and applied to pesticides related to pesticide regulation ***Hilko van der Voet (WUR)*** 2. Approaches for less extensive CAGs based on mode of action using tools such as QSARs/molecular docking and cost-effective and reliable *in vitro* assays ***Emiel Rorije (RIVM)*** 3. Examples of multiple route exposure and how these might affect the Margin of Exposure ***Jacob van Klaveren (RIVM)*** 4. Kinetics and IVIVE ***Emiel Rorije (RIVM)*** 5. Applicability of tools for other regulatory sectors/chemical classes/grouping principle ***Bette Meek (University of Ottawa)***	5 x (15 min + 10 min discussion)

13:05-14:00	Lunch	
SESSION 2: Illustrative case studies		
14:00-15:45	- EFSA: Implementation of CRA of pesticide residues ***Luc Mohimont (EFSA)*** - EPA: Organophosphates; carbamates; pyrethroids ***Anna Lowit (EPA)***	2 x (30 min + 20 min discussion)
15:45-16:15	Refreshment break	
SESSION 3: Conclusion		
16:15-16:45	Integration with other activities such as WHO/EuroMix workshop and EuroMix guidance ***Johanna Zilliacus (Karolinska Institute)***	20 + 10 min dicussion
16:45 -17:00	Conclusions and next steps	15 min