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

17 May 2017, Thon Hotel EU, Rue de la Loi 75, 1040 Bruxelles, Belgium

Background

EuroMix organised the second of a series of workshops on the international harmonisation of the risk assessment of combined exposures to chemicals on 17 May, 2017 at the Thon Hotel EU, Brussels, Belgium. The specific objectives of the workshop were to discuss current and impending regulation, across different chemical sectors (e.g. pesticides, contaminants) and regions (e.g. USA, Europe) and how and when new science might impact on future regulation. The necessary steps to implement an internationally harmonised, scientific approach to the risk assessment of combined exposures to chemicals in the diet in relevant legislation were explored. The focus of the meeting was on those policies impacting not only on public health but also on international trade of food commodities. The meeting also sought to identify those topics of most relevance for further consideration at the next workshop in the series. Participants involved experts from North America, Europe and South America, as well as national and international organisations such the European Commission (DG SANTE, DG Environment), EFSA, OECD, Codex Alimentarius, WHO, US FDA 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
Annamaria Bruno	International	Codex Alimentarius
Evisabel Craig	USA	US EPA
Jean-Lou Dorne	Europe	EFSA
Eloisa Dutra Caldas	Brasil	University of Brasilia
Suzanne Fitzpatrick	USA	US FDA
Peter Korytar	Europe	DG Environment
Eeva Leinala	International	OECD
Bette Meek	Canada	University of Ottawa
Angelo Moretto	Italy	University of Milan
Paul Price	USA	US EPA
Stefanie Rotter	Germany	The German Federal Institute for Risk Assessment (BfR)
Jiri Sochar	Europe	DG SANTE

Roland Solecki	Germany	The German Federal Institute for Risk Assessment (BfR)
Jacob van Klaveren	The Netherlands	The Netherlands National Institute for Public Health and the Environment (RIVM)
Veerle Vanheusden	Europe	DG SANTE
Philippe Verger	International	WHO
Frans Verstraete	Europe	DG SANTE
Andrew Worth	Europe	The Joint Research Centre of the European Commission (JRC)

The meeting room was arranged in board room style. The meeting was chaired overall by Alan Boobis. Stephanie Rotter 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 understand current and upcoming legislative needs for cumulative risk assessment of chemicals (with a focus on the diet); how this varies across chemical sectors (e.g. pesticides, additives, contaminants) and the extent to which this might be harmonised; how this varies across geographical regions and the opportunities for harmonisation; the role that scientific research, and particularly that of EuroMix, might play in the development and implementation of legislation in this area. The meeting was organised into three sessions. Session 1 was on current and impending legislation in the area of cumulative risk assessment. Session 2 was on the potential contribution from EuroMix. Session 3 was on implementation of EuroMix advances. During each session, a number of speakers presented their perspectives, each followed by discussion. Copies of the introductory presentations are available from the EuroMix website.

Session 1: Current and impending legislation

The session opened with an **analysis of legal requirements for mixtures of chemicals** both within and outside Europe, together with a review of current frameworks and research for cumulative risk assessment of chemicals. In general, whilst mixture risk assessment is required in a number of regulatory sectors and geographical regions for intentional mixtures (e.g. formulations), this is not always required. Even where mandated, testing of the mixture itself is not always necessary, but a prediction from the components would be accepted. Where there is a legislative requirement to assess the risks of mixtures, guidance is not always available. In some chemical sectors, assessment of certain unintended/incidental mixtures is required, for example run-off from contaminated sites (Superfund sites in USA) and for pesticides in the USA and in Europe, where suitable methodology is under development. Several different approaches are being used to group chemicals for cumulative risk assessment, and this is an area where ongoing research could be very informative. Several frameworks have been developed for cumulative risk assessment, most utilising a tiered approach. Both OECD and EFSA are developing new, overarching frameworks for cumulative risk assessment. A significant limitation of the tiered approach is the lack of relevant information and hence, it is often not possible to progress to higher tiers. Various possibilities have been discussed, such as use of the threshold of toxicological concern (TTC) and application of an additional uncertainty factor to allow for possible exposure to additional chemicals sharing toxicological effects. Often, exposure from uses of the same chemical in different regulatory sectors and/or by different routes (aggregate exposure) is not taken into account. One approach to this is to reserve a fraction of the health based guidance

value, but a better solution would be more accurate exposure assessment. Identifying the key drivers (active substances) responsible for cumulative risk would enable focussed risk management with most impact.

The session continued with a **summary of the work undertaken by the Joint Research Centre** (JRC) of the European Commission as follow-up actions to the Commission Communication on the combined effects of chemicals (COM(2012)252 final), to support the Fitness check of chemicals legislation (REFIT) and as part of the 7th Environment Action Programme – a strategy for a non-toxic environment. To date, JRC has conducted a review of regulatory requirements and guidance, an expert survey, a review of novel approaches and a review of literature case studies on the assessment of chemical mixtures. Currently, JRC is conducting experimental case studies on mixtures of developmental neurotoxicants and of (anti-)androgenic compounds, a literature review of physiologically-based toxicokinetic (PBTK) models for mixtures, a case study on the use of human biomonitoring data and biomonitoring equivalents and a systematic literature review and evaluation of evidence for interactions between environmental chemicals. In an effort to increase harmonisation of assessment, JRC is developing an uncertainty framework for risk assessment of combined exposures, that will provide a transparent means of documenting the entire workflow, including problem formulation, assumptions, constraints, methodological choices, conclusions, and identification and characterisation of uncertainties.

A key issue is how emerging methods in toxicology, such as high throughput screens, will be used in cumulative risk assessment. This will likely be linked to key events in AOPs, and ongoing work within EuroMix should establish proof of principle, but harmonisation on the application of such methods in cumulative risk assessment will need further discussion. Similarly, the incorporation of information on systemic exposure, including the use of PBTK models, will require further discussion.

Problem formulation in cumulative risk assessment is critical. It is therefore important that the frameworks used are flexible and there is a suite of tools to deal with range of policy needs.

EU approaches to the **assessment of the cumulative exposure to contaminants** in food were reviewed, following an introduction by DG SANTE. EFSA is already addressing the risk from mixtures of contaminants, to a certain extent, through the scientific advice provided by the CONTAM Panel to DG SANTE. There are no *a priori* criteria for grouping. This is case-by-case, based on exposure, structural and toxicological considerations; the criteria used being clearly explained in the advice provided. Examples include dioxins and dioxin-like compounds (the Toxic Equivalency Factor or TEF approach), non-dioxin-like PCBs (6 markers substances out of 197 possible congeners), polycyclic aromatic hydrocarbons (marker substance approach), brominated flame retardants (e.g. PBDEs, PBBs) and perfluorinated alkylated substances. In addition, several groups of related mycotoxins have been assessed for their respective combined risks. These include aflatoxins, fumonisins, zearalenone and related toxins, ergot alkaloids, pyrrolizidine alkaloids and tropane alkaloids. There are considerable difficulties in such assessments due to the lack of data on toxicity and occurrence, analytical issues and other uncertainties. Presently, the risk assessment and risk management of mixtures of structurally and toxicologically “similar” contaminants are being addressed to some extent, albeit with considerable difficulties and uncertainty. However, the risk assessment and risk management of mixtures of "non-similar" contaminants (e.g. different mycotoxins, different metals) is not yet being addressed.

One of the difficulties is that only those contaminants that are monitored can be controlled, and the choice of which contaminants to monitor is based on feasibility and the relevance of individual compounds to health. Risk management is based on a pragmatic view of the relative importance of exposure to related compounds, e.g. among fumonisins it was decided to address exposure to only

fumonisins B1 and B2, as B3 is only a minor constituent. Work is ongoing to address dual use of veterinary drugs and pesticides, where there may be co-exposure to residues from both uses.

Current approaches in the EU to the **assessment of combined exposure of food additives** were then discussed following an introduction by DG SANTE. At present, there is only limited consideration of the risk from such combined exposures, and there is no consideration of the risk in combination with chemicals from other uses. Within the EU, there is a very specific definition of "food additives", which are substances added to food for technological purposes. Other substances, such as flavours and vitamins, are excluded. In some other parts of the world, the term is used more broadly and in some cases, applies to any substance added to food. Food additives require approval (authorisation) before marketing, part of which includes their safety assessment. Substances that are classified as CMR (carcinogenic, mutagenic or toxic to reproduction) will not be approved (but this excludes impurities). Some combination effects are taken into account, for example, certain food colourings, mixtures of benzoate and ascorbate, which can lead to UV-catalysed formation of benzene, and group ADIs for compounds that share a mode of action, e.g. phosphates, sorbates, benzoates. In the case of caramel colours, three of these have been combined for risk assessment and one other has been considered separately, due to differences in their characteristics. In general, substances with completely different structures and toxicological effects would not be considered together, though if there some reason for concern this is permitted within the legislation. Examples would be when mechanistic consideration of toxicokinetics or toxicodynamics indicates some potential for interaction. Some food additives contain secondary food additives, which will enter the food chain. The possible risk from such chemical combinations is not currently assessed by EFSA.

Previous and ongoing **work at EFSA on generic approaches to cumulative risk assessment** were reviewed. The Panel on Plant Protection Products has published a number of opinions on the risk assessment of combined exposure to residues of pesticides and is currently compiling information on assessment groups based on phenotypic endpoints. The Scientific Committee of EFSA published an opinion in which a generic approach to cumulative risk assessment was described. These outputs were discussed at a scientific colloquium in 2014, which served to inform a new activity of the Scientific Committee, the development of guidance on harmonised risk assessment methodologies for human and ecological risk assessment of combined exposure to multiple chemicals. A tiered approach will be used. Areas where harmonisation is not possible will be identified. Information and models are being developed to improve toxicokinetic assessments, which will also help identify the possibility of interactions.

DG Environment's perspective on cumulative risk assessment and ongoing activities within the EU were next discussed. A key focus is the EC Communication of 2012 on the Combined Effects of Chemicals (COM(2012)252 final). Whilst methodology already exists for assessing the risks from combined exposures to chemicals, a substantial limitation is the paucity of available data, particularly on occurrence of the chemicals. In addition, there is currently no systematic process for assessing combined risks across the range of chemicals to which humans are exposed. To help address this, an inter-service group has been established to promote cross-sector activity, but progress to date has been somewhat limited. Nor has guidance across regulations yet been developed. However, the issue of mixtures more generally is currently under review.

Horizon 2020 is supporting a number of research projects, e.g. EuroMix, to expand the tools and approaches necessary for cumulative risk assessment. In addition, efforts are underway to improve the availability of occurrence data through IPCheM (EU Information Platform for Chemical Monitoring). All relevant EU databases have been connected to this portal and information on chemicals in food, the environment, indoor and outdoor air and from human biomonitoring studies is

available. Both monitoring data and research data on chemical occurrence should be available from IPCheM.

Whilst REACH does not address all possible incidental/unintentional mixtures routinely, this is undertaken if required, e.g. phthalates. The risk management of industrial substances comprising intentional mixtures already considers possible combined effects of the constituents. However, whilst a whole mixture approach is taken to the registration of multi-component substances of unknown composition, environmental monitoring is problematic, as the most toxicologically relevant compounds are often not known.

In the Water Framework Directive, the cumulative risk of groups of structurally-related chemicals is assessed, analogous to the approach taken for contaminants in food. Effect-based tools can also be used on the whole mixture (water sample). If positive, identification of the chemical(s) contributing most to the effect would enable risk management.

A number of additional activities relevant to the cumulative risk assessment and risk management of chemical mixtures are underway. In the Fitness Check of Chemicals Legislation (Regulatory Fitness and Performance Programme, REFIT), the fitness-for-purpose of current frameworks, including those for mixture risk assessment, are being assessed. REFIT is due for completion by the end of 2017. Also, under the 7th Environment Action Programme, to help achieve the objective of a non-toxic environment, the European Commission should, by 2018, develop a strategy to minimise exposure to endocrine disrupting chemicals; and to chemicals in products; to address the safety of nanomaterials; and combination effects of chemicals and minimise exposure. The strategies proposed will need to be agreed by Member States.

Harmonisation across chemical sectors will not be possible overnight, and is best achieved step by step. Risk assessment in the European Union is science-based. The legislation reflects the state of the science. Hence, scientists need to understand the frameworks, for example for risk assessment of combined exposures to chemicals. To facilitate the implementation and utilisation of such frameworks, researchers should develop suitable tools for this purpose. This is one of the key objectives of EuroMix.

In mixture risk assessment, profiling of chemicals is important. This may be for toxicology, but also for exposure, depending on the framework. One possibility is exposure banding, or worst-case exposure estimates (cf TTC). A case study of an incidental/unintended mixture where the chemicals are regulated under different legislative mandates (sectors) would be of value. The default assumption would be concentration/dose addition for chemicals with a similar mode of action.

The approach being implemented in the EU for **the cumulative risk assessment of dietary exposure to pesticides residues** was outlined by DG SANTE and discussed. The need for cumulative risk assessment of pesticide residues as part of the approval process is mandated by European legislation (Reg. (EC) No. 1107/2009 and Reg. (EC) No. 396/2005), with the proviso that the methods used must be scientifically acceptable by the Authority. It is envisaged that once developed, cumulative risk assessment of pesticide residues will be used for several different purposes: approval of active substances, MRL setting, authorisation of PPPs, assessment of high residue events and annual reviews of monitoring data.

EFSA is currently finalising cumulative assessment groups (CAGs) for hazard assessment of combined exposures to pesticides. These are based on grouping for common target organ/system effect (pathological outcome). The first target organs addressed were the nervous system and the thyroid. In additional CAGs for effects on the liver, reproduction and development, the adrenal and the eye are

being prepared. There are several (up to 16) CAGs for each target organ/system, because of the number of distinct toxicological/pathological outcomes. Some of the CAGs are quite large, comprising over 100 chemicals.

EFSA decided to group pesticides that could plausibly act in combination, causing a common specific adverse effect, rather than on mode of action. In part, this was because modes of action are often unknown. There is also concern that compounds acting by different modes of action might still contribute to the common adverse effect and use of common effect for grouping would be precautionary. However, this would give rise to the potential to overestimate the risk for acute exposure. It is envisaged that further refinement might be possible when more detailed information on toxicological modes of action becomes available. In addition, PBTK and PBTD modelling might be utilised as a further development

Relative potency factors (RPFs) will be added to updated annexes on the cumulative assessment groups (CAGs) for effects on the nervous system and the thyroid by the end of 2017. This will be followed by RPFs for the CAGs for effects on the liver, reproduction and development, adrenal and eye. The approach used for determining RPFs for members of a CAGs was discussed. If this is to be based on the common effect (use of the critical effect would be very conservative), agreement will be needed on how the points of departure for the common effect are to be determined. Since this POD will not have been discussed in establishment of the ADI/ARfD, separate consensus will be needed, which could be very resource intensive.

Exposure assessment will be performed probabilistically, using the ACROPOLIS on-line IT tool, which is referred to as the Monte Carlo Risk Assessment (MCRA) software, for this purpose. The assumption is that each component of the CAG contributes to the combined effect in proportion to its exposure and potency for the common effect, based on the assumption of dose addition.

Once the assessment groups have been agreed, the methodology will first be applied to the risk assessment of consumers, based on the exposure assessments in the annual report (the European Union Report on Pesticide Residues in Food, prepared by EFSA). Longer term, the intention is to use the methodology for regulatory purposes, i.e. for pesticide approvals and MRL setting. However, this will depend on the demonstration of the fitness-for-purpose of the methodology, development of detailed procedures, completion of the establishment of all CAGs by EFSA, and an assessment of the new methodology for its impact on health, agriculture and international trade.

There are a number of risk management decisions involved in final implementation of the methodology. These include the assumptions to be made, e.g. on non-detects; imputation of missing values; variability factor to be used; information on use, processing, etc; which toxicological values to use; consumption and occurrence data; exposure distribution confidence interval. These issues have been discussed by a working group of DG SANTE and the Member States and many of them were resolved. The working group also agreed that the combined margin of exposure should be used for expressing the risk, with a probabilistic assessment, rather than an ADI or ARfD for the CAG (the margin of exposure is the ratio between the estimated exposure and a relevant toxicological endpoint taken from an animal study). In addition, a threshold for regulatory consideration should be identified: X^{th} percentile of the population should have a combined margin of exposure above Y. The working group proposed a two-stage approach, in which a conservative scenario would first be assessed, followed by a less conservative scenario, should a potential risk be identified with the first scenario. If a potential risk is identified in the second scenario, risk management decisions will need to be taken as to whether regulatory action is necessary, taking into account the uncertainties in the assessment, or whether further, refined analyses should be undertaken.

Following this discussion of EU approaches to cumulative risk assessment, the meeting addressed some of the approaches in use internationally, starting with the **US EPA approach to the cumulative risk assessment of pesticides**. EPA defines cumulative risk as "the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity." To date, cumulative risk assessment has been performed on five common mechanism groups (CMGs): organophosphates, N-methyl carbamates, triazines, chloroacetanilides, and pyrethrins/pyrethroids. Establishing such CMGs is very data and resource intensive. Hence, EPA has recently introduced a screening framework for cumulative risk assessment to assist in identifying potential candidate CMGs and conducting screening-level assessments (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework). The framework follows the same principles as the WHO/IPCS framework. All pesticides undergoing registration review are assessed for membership of a candidate CMG (or an existing CMG), on the basis of pesticidal MOA, structural similarity, target organ toxicity and apical outcomes, and MOA for mammalian toxicity, on the basis of submitted data and published information. It is envisaged that high throughput screening in ToxCast will be of value in candidate CMG construction. If screening indicates that the evidence is against a group of pesticides sharing a common mechanism, no cumulative risk assessment is necessary. If there is evidence for a common mechanism, the candidate CMG is subject to screening level toxicology and exposure assessment. If the margin of exposure is not adequate, further refinement of exposure and/or toxicity is needed. If sufficient evidence is available for a MOA/AOP and the causal key events, a CMG is established and assessed. Screening level assessments are currently being performed for multiple candidate CMGs, including the mectins.

In the US, substances that are not detected in monitoring for residues are excluded from cumulative risk assessments and chemicals must share a common mechanism of toxicity to be included in a CMG, which contrasts with the approach used/proposed in the EU. It is apparent that there are significant differences between the EU and the USA in the approaches being taken to group pesticides for cumulative risk assessment. If the European and US criteria lead to very different group sizes, cumulative risk assessment is likely to result in different conclusions on human health protection. Ideally, common criteria for grouping chemicals should be developed and applied, based on fundamental scientific principles.

A brief explanation of how the **Codex Alimentarius Commission addresses risks from exposure to chemicals in food** was provided. Codex Alimentarius develops food standards that, whilst not mandatory, are the benchmark for international harmonisation to protect human health and ensure fair practices in the food trade. These standards are based on the principle of sound scientific analysis and evidence, involving a thorough review of all relevant information, in order that they assure the quality and safety of the food supply. Codex Alimentarius is responsible for risk management advice, relying on input from WHO/FAO scientific advisory committees for risk assessment, i.e. JECFA, JMPR, JEMRA, JEMNU, and ad hoc expert consultations on emerging issues. Lower tier assessments are often very conservative, but the lack of data make it difficult or impossible to refine the assessment. Hence, balancing protection of human health whilst ensuring fair trading practices is complex.

To date, cumulative risk assessment has not been a major consideration by Codex Alimentarius or any of the WHO/FAO committees, although there are some instances where this has been undertaken, for example assessment of dioxins and dioxin-like compounds by JECFA. In addition, the topic has been discussed by the committees on a number of occasions. For example, JMPR noted in 2008 that it would continue to monitor ongoing activities in the field and eventually advise on the need for cumulative risk assessment for certain groups of pesticides. In 2014, following a request from the 46th

session of the Codex Committee on Pesticide Residues (CCPR), JMPR reviewed the various approaches for assessing cumulative risk of chemicals in food that are currently under development or in use worldwide. JMPR recommended that the Secretariat identify relevant developments in cumulative risk assessment and place them on the agenda for discussion at the next appropriate JMPR. Generic issues in the area of cumulative risk assessment are being explored by the WHO Chemical Risk Assessment Network Coordinating Group on Combined Exposures. At Codex Alimentarius level, discussion has started within the Codex Committee on Contaminants in Food on the need for cumulative risk assessment of certain groups of mycotoxins and the issue has been identified as an emerging one by the coordinating committee for Europe.

Session 2: Potential contribution from EuroMix/Session 3: Implementation of EuroMix advances

The session started with an outline of **approaches being developed within EuroMix for the assessment of combined exposure to chemicals**. EuroMix is developing a tiered approach to exposure assessment, comprising: screening tier, deterministic tier and Hazard Index approach, probabilistic approach, probabilistic approaches including likelihood of co-exposure. In the screening tier, chemicals are grouped based on QSARs, e.g. all food additives predicted to cause liver steatosis; worst case for hazard (e.g. TTC); rough estimate of exposure, e.g. worst case from deterministic assessment. If the MOE exceeds specified (high) value, e.g. 10,000, there might not be a need for testing, depending on the risk managers decision. This would be a highly unrealistic and conservative scenario. In the first tier, deterministic exposure models, such as those from EFSA, are used for each regulatory sector only. Examples include PRIMo for pesticides, the Food Additive Intake Model and the GEMS Food diets, which models are based on different conservative data and assumptions. There is no overarching deterministic approach covering all regulatory sectors and this will raise many practical challenges and/or extremely conservative outcomes. In higher tiers, probabilistic assessments of exposure are used, with random sampling from distributions of both consumption and occurrence. Guidance on the conduct of probabilistic exposure assessment has been published by EFSA and suitable software (MCRA) has been developed; access is freely available through a partnership between EFSA and RIVM for the member states involved in the in the implementation of cumulative risk assessment of pesticides. All consumption and monitoring data from all EU member States held by EFSA can be utilised in the modelling since EFSA has harmonised the formats. This will help in combining assessments over different regulatory sectors. Case studies on probabilistic assessments of combined exposure are currently being conducted within and across chemical sectors. A key factor is the available of relevant data, which varies markedly from chemical sector to chemical sector. This may necessitate imputation of missing values, the consequences of which are being explored. EuroMix is investigating a number of possible refinements, among which are: exposure driven approaches, inclusion of toxicokinetic information (e.g. is co-exposure likely?), use of information on AOPs to refine CAGs, integration of exposure and hazard estimates (deterministically and/or probabilistically), aggregate and combined exposure, comparison between calculated intake and observations in humans.

The final topic discussed was EuroMix research on **how to group chemicals for cumulative risk assessment**. The default assumption is that exposure to each individual compound in a CAG is below its respective health based guidance value (risk management considerations will apply to each chemical) and the combined effect of the group is a consequence of dose addition, unless there is good evidence otherwise. However, prior to such an assessment, consideration needs to be given to what is meant by common toxicity, the basis for grouping. For some chemicals, there is a wealth of information, data-rich compounds, whereas for others there is a dearth of information, data-poor

compounds. Approaches to formation of CAGs should be sufficiently flexible to recognise this, and take account of the available information in the various assessment tiers.

The approach adopted by EFSA for formation of CAGs for pesticides (data-rich compounds) comprises four levels: target organ (level 1), phenotypic effect (level 2); common MOA/AOP (level 3), common mechanism (level 4). In practice, the distinction between level 3 and level 4 has not been clearly defined, and it is likely that robust evidence for level 3 would make level 4 redundant. Inclusion in a CAG is independent of whether the common effect is the critical (i.e. basis of health based guidance value) effect or not. Currently, EFSA is working on constructing level 2 CAGs for pesticides. Those of the nervous system and the thyroid have been published and work is advanced on another 4 target organs/systems. Eventually, CAGs will be created for 15 different target organs/systems. As an example, over 200 pesticides have been identified that affect the liver. Eleven different level 2 CAGs have been created to cover these effects, for example hypertrophy (189 members), fatty change (steatosis) (106 members), cell degeneration/cell death (139 members). There is appreciable overlap in CAG membership. A key question is how/if information on AOPs can help refine the CAGs. EuroMix is working on several AOP-based case studies, one of which is liver steatosis. The different AOPs, with associated key events (KEs), responsible for steatosis have been mapped and methods for determining key event involvement are being developed and applied to selected compounds. An important question that EuroMix is seeking to address is whether effects on different MIEs/KEs "cumulate" at environmentally relevant doses (exposures). This is being investigated both in vitro and in vivo, over an appropriate range of exposures.

For data-poor compounds there are fewer options. For such compounds, in silico (QSARs and/or molecular docking simulations) and in vitro approaches may be necessary. EuroMix is investigating how/if to combine QSAR models that address adverse outcomes or specific KEs. It is likely that QSARs will be more specific for KEs (particularly the molecular initiating event, MIE) than for adverse outcomes, as there may be competing structural requirements for the MIEs leading to the same adverse outcome. In silico approaches could be used qualitatively, to assess the likelihood of (different levels of) CAG membership. Confidence in this approach can be enhanced by the use of multiple models.

Similarly, EuroMix is investigating how best to utilise in vitro information on KEs and/or MIEs to develop CAGs. Such information can be used to assess probability of belonging to level 3 CAGs and, *inter alia*, the probability that compounds will exhibit dose additivity.

Each predicted or measured data value and conclusion (e.g. CAG level 2 membership) has associated with it a degree of uncertainty. This needs to be addressed and quantified to the extent scientifically possible (e.g. EFSA framework, WHO/IPCS framework, Codex Alimentarius framework).

The most scientific approach to CAG membership would be the "retain and refine" method, in which broad criteria are used to identify CAG membership but members are then weighted (refine) for a number of probabilities (e.g. common AOP). However, the practicality of such an approach needs to be weighed against problem formulation. In some scenarios, the number of compounds involved and/or the time available to provide advice/take action, may mean that there are insufficient resources to pursue this approach in full (or even in part). However, in order to determine which pragmatic assumptions (e.g. exclusion of chemicals with different AOPs for the same adverse outcome) are still health protective, comparison with the 'full' model will be necessary. In this way, information on the degree of conservatism associated with different options can be obtained, and EuroMix will include such comparisons in its research programme. This will lead to the development of

a framework for cumulative risk assessment that is flexible and feasible, enabling a balance between precision and pragmatism, according to the problem formulation.

Once CAGs have been created, it will be necessary to develop relative potency factors. The utility of in silico and in vitro approaches for this purpose is also being investigated by EuroMix. Possible in silico approaches include use of the appropriate TTC value for the structural class of compound and distribution of the (predicted) point of departure within those for the CAG. In vitro, qualitative concentration-response data for KEs or the MIE, with appropriate in vitro to in vivo extrapolation, could be used.

Final discussion and conclusion

Currently, there is no overarching approach to cumulative risk assessment (CRA), either within the EU (across regulatory sectors) or internationally. Approaches to CRA vary across regulatory sectors and geographies vary, sometimes markedly. In some areas, CRA is currently not a significant consideration, whereas in others there is appreciable concern. However, even in the latter case, approaches utilised in different regions show appreciable differences. The most common approach to date for developing cumulative assessment groups is use of common structure and/or co-occurrence and/or designed function (e.g. pesticidal mode of action). EuroMix is exploring implications of different exposure and toxicology cut-offs for human health protection, both experimentally and by simulation.

Work is underway both within and beyond the EU to explore harmonisation of approaches to cumulative risk assessment within and across chemical sectors. Case studies will be invaluable here.

The next workshop will explore in more detail how the results of EuroMix can help further the international harmonisation of cumulative risk assessment.

EuroMix

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

Program

The objective of the second workshop is to explore the necessary steps to implement a harmonised scientific approach to the risk assessment of combined exposures to chemicals in the diet in relevant legislation. The focus of the meeting should be on those policies impacting not only public health but also on international trade of food commodities.

08:30-17:15, 17 May 2017 Thon Hotel EU, Rue de la Loi 75, 1040 Bruxelles, Belgium

08:00-08:30	Welcome coffee and registration	
SESSION 1: Current and impending legislation		
Rapporteurs	Stefanie Rotter and Alan Boobis	
08:30-08:45	Introduction and objectives of meeting ***Alan R Boobis, Imperial College London***	
08:45-09:45	What legislation would have to be addressed? ***Roland Solecki, BfR, Germany***	20 min + 40 min discussion
09:45-10:30	Ongoing work on harmonisation ***Andrew Worth, JRC, Italy***	20 min + 25 min discussion
10:30-11:00	Refreshment break	
11.00-13.00	Perspectives of risk managers on: - need for cumulative risk assessment - difficulties in implementing management of combined exposures to chemicals - precautionary principle in current and future approaches - what do risk managers need from science	Input from DG SANTE on pesticide risk management contaminant risk management and additive risk management, DG Environment on environmental contamination, Codex Alimentarius on chemicals in food and US-EPA on mixture risk management
12:30-13:30	Lunch	

SESSION 2: Potential contribution from EuroMix		
14:00-14:45	What can be offered by exposure and hazard assessment and scientific progress to achieve harmonisation - Introduction (tiered assessment, examples of how uncertainties are covered in the current approach and in a future approach, how hazard data can be used…) ***Jacob van Klaveren, RIVM, The Netherlands***	30 min + 15 min discussion
14.45-15:30	AOP wise testing and how to reduce uncertainties in grouping pesticides and/or chemicals in cumulative assessment groups and how to use computational tools to identify which chemicals should be grouped ***Angelo Moretto, University of Milan, Italy***	30 min + 15 min discussion
15:30-16:00	Refreshment break	
SESSION 3: Implementation of EuroMix advances		
16:00-17:00	General discussion with the focus on harmonisation and MRL setting - timeline for implementation - possible risk management strategies when there is a potential concern and how the risk assessor could contribute - other issues relevant for harmonisation such as precautionary principle and costs for testing	
17:00-17:15	Conclusions and next steps	