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

EuroMix

European Test and Risk Assessment Strategies for Mixtures

Project number 633172

Collaborative project
H2020-SFS-2014-2

Deliverable D10.5 – Report

Report on stakeholder workshop 1

WP 10 – **Dissemination and stakeholder involvement**

Due month of deliverable: Month 26
Actual submission month: Month 26

Deliverable leader: MATIS

Document status: version 1 Creation date: 29/06/2017

Project co-funded by the European Commission within the H2020 Programme		
Dissemination Level		
PU	Public	x
PP	Restricted to other programme participants (including the Commission)	
RE	Restricted to a group specified by the consortium (including the Commission)	
CO	Confidential, only for members of the consortium (including the Commission)	

Deliverable D10.5

Report on stakeholder workshop 1

July 2017

Deliverable D10.5

Report on stakeholder workshop 1

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Table of Contents

Summary

Every day, we are exposed to multiple chemicals by several routes of exposure. These chemicals may exert toxic effects and therefore risk assessment by evaluation of exposure and toxicity is necessary to monitor and control possible adverse effects on human health. The EU funded project EuroMix (GA number 633172) will develop and disseminate a new, efficient and validated strategy for testing the toxicity of chemical mixtures, which should deliver refined information for future safety assessment of mixtures of chemicals. This includes exposure assessment via multiple exposure routes, e.g. food intake, inhalation and dermal contact. For more information refer to www.euromixproject.eu.

In the frame of the EuroMix project, after two years of work, a stakeholder consultation was held in Brussels (BE) on May 18th 2017. The title of the stakeholder workshop was '*Towards Harmonisation of Implementation of Test Strategies for Chemical Mixtures in Europe*'. It was organised to inform stakeholders on the progress made in the EuroMix project on the test strategy and the tools that will be released for future testing and risk assessment of chemical mixtures. It also aimed to obtain feedback regarding the needs of stakeholders as well as which further steps could be taken to ensure that the project is relevant to them.

In particular the strategic objectives of the workshop were the following:

- To contribute to harmonisation of implementation of test strategies for chemical mixtures in Europe
- To involve stakeholders in the harmonisation process
- To introduce EuroMix concepts and key tools that can facilitate the harmonisation
- To ensure relevance and accessibility of the EuroMix data and model platform infrastructure and thereby provide relevant links to international data harmonisation

Chairs of the workshop were Annemiek van Bolhuis, Director of Public Health and Health Services at RIVM National Institute for Public Health and the Environment in the Netherlands and Elisabet Berggren, Director of the European Commission Joint Research Centre (JRC). The workshop was organised in four sessions (i) Harmonisation of test strategies for chemical mixtures, (ii) EuroMix concepts and tools to facilitate harmonisation, (iii) Statements and reflections of stakeholders, and (iv) Future tools for harmonisation. Each session ended with panel discussions. The entire programme of the workshop is presented in Appendix 1. This report contains questions raised by the audience for clarification and the answers provided by the speakers after each presentation as well as the questions and answers from the panel discussions held at the end of each session. Additionally, the outcome of an electronic evaluation survey send to the participants after the completion of the workshop is presented.

In total, 72 participants attended the workshop, 50 stakeholders and 22 representatives from the EuroMix beneficiaries. Stakeholder groups included government/authorities (33%), academia (14%), industry (148%), European commission (13%), international organisations (7%) and NGOs (6%) with representation from European Member States and associated countries as well as the USA, Canada, Brazil and Japan.

The presentations given at this workshop are presented in Appendix 2 of this report.

Session 1 – Harmonisation of test strategies for chemical mixtures

Rapporteur *Stefanie Rotter*

1) *Jacob van Klaveren (RIVM): Welcome and workshop objectives*

No clarification questions

2) *Stephanie Bopp (JRC): Assessment of chemical mixtures –policy context, current practices and future directions*

Clarification question

Q: **Stephanie Melching-Kolmuss (BASF SE)** -What do the numbers presented in the graphs on the current practices represent?

A: Stephanie Bopp -They represent the numbers of answers, which were in total 85 replies, however, only 48 have practical experience in conducting cumulative risk assessment.

3) *Roland Solecki (BfR): Overview on legislation and scientific approaches for risk assessment of mixtures as EuroMix contribution*

No clarification questions

4) *Alan Boobis (ICL): Risk assessment of chemical mixtures: Implication for International harmonisation*

Clarification question

Q: **Unidentified WS participant** - What is done in the 3rd and 4th workshop and when are they scheduled?

A: Alan Boobis -They are planned for the end of 2017 and the end of the project (beginning 2019). The next workshops will focus more on the actual contribution of EuroMix:

- How the EuroMix toolbox can support exposure and hazard assessment and scientific progress to achieve harmonisation
- Proposal of a EuroMix approach for chemical grouping
- What is needed for implementation?

5) *Eeva Leinala (OECD): The Overview of the OECD Project on assessment of combined exposures to multiple chemicals*

No clarification question

Session 1: Panel discussions involving all the speakers in the session

Q: **Dick Sijm, Office for Risk Assessment and Research Netherlands** – It has been stated that there is a lack of methods for cumulative risk assessment and EuroMix is seeking for methodologies to conduct an appropriate cumulative risk assessment, I have two questions/remarks related to this.

i) I missed the point of mitigation and existing approaches addressing this. Guidance is available for biocidal products and in the US an environmental guidance allowing to assess risks of unintentional mixtures is available.

A: Alan Boobis – In the EFSA review it has been stated that the summation of all (similar and dissimilar acting) compounds leads to an overestimation of the risk, which is not intended. However, at worst this means that the estimation is over protective.

A: Jacob van Klaveren –Regarding possible refinement; kinetics are not taken into account in the current approach. Many substances e.g. pesticides are breaking down in the body, the average pesticide stays around 3 days in the body. Regarding mitigation concept: in pesticide risk management practice a substitution mechanism exist. If a new pesticide substance is less toxic compared to pesticides already on the market, discussions will be held on when to replace the most toxic pesticides. Persistent pesticides like DDT have been replaced by others that break down faster. However, the benefit and precautionary principle should be addressed as well.

ii) What can we learn from each other? What developments have been achieved? Can we test whole mixtures, without information on the chemical components?

A: Alan Boobis – Firstly, for each risk assessment the concern should be figured out. Whole mixture assessment is most reliable, but effect level is also useful i.e. how can we identify the chemicals in the mixture that are the culprits

Q: **Mattias Öberg, Karolinska Institutet/Swetox** – Is epidemiological data considered and used within EuroMix?

A: Jacob van Klaveren – The EU project EDC MixRisk addressing mixtures of endocrine disruptive chemicals is nicely linking epidemiological data mechanistic data. Furthermore, the EU has recently granted a 75M€ project on collecting epidemiological data, including data on mixtures in the so called HBM4EUproject. This project plans to collect the epidemiological data in the IPChem database hosted at JRC. The EuroMix project is cooperating with the other projects (EDCMixRisk, EUToxRISK21 and HBM4EU). The EuroMix project will also consider a linkage between the EuroMix data and model platform and the IPChem database.

A: Stephanie Bopp – There is an ongoing initiative that the EU projects mentioned (i.e. EuroMIx, EDCMixRisk, EUToxRISK21 and HBM4EU) will jointly work on that. A workshop focussing on epidemiological data is planned for 2018. Furthermore, JRC starts to review and work on case studies on vulnerable sub-populations, other substance groups, grouping approaches, mixtures across regulatory sectors. JRC is considering case studies on biomonitoring data. The IPCheM platform will collect biomonitoring data and this can be used to link to disease.

A: Alan Boobis –EuroMix also has a WP on human cohort study. It is important to work on this issue across more EU projects to ensure synergy and optimise the work

Q: **Giovanna Semino, Bayer SAS** – The experience has shown that is hard to have a harmonised approach, applicable in daily work. Because work is conducted at different levels, for example on the level of European Authorities (EFSA) and the zonal level (Member States). Did you discuss within EuroMix to have a more harmonised approach between the Member States? What are the scientific tools to support this harmonisation?

A: Jacob van Klaveren – EuroMix will start working with user groups that may try out the EuroMix tools providing that they recognise that these tools are still under development. One user group might be the regulators from different parts of Europe, the need for zonal harmonisation might be addressed in such a user group. EuroMix has scheduled a second stakeholder workshop at the end of the project to address several practical issues, including experiences of user groups.

A: Alan Boobis – There are different rationales for a harmonisation on a geographical level. The EuroMix contribution will be evidence-based decisions that can be taken. EuroMix should and will show the consequences of the decision taken, but policy makers must take the decisions. We will provide information and recommendations, this is currently done in the absence of data.

A: Roland Solecki – It is planned to publish the reviews on regulatory requirements and existing approaches, which will inform the public and will be the basis for further discussions and indicate where harmonisation is possible. The guidance developed by EFSA and OECD are also very important for further harmonisation.

Q: **Annemiek van Bolhuis, RIVM** – What is the critical success factor for EuroMix?

A: Jacob van Klaveren – To provide the tools and to make the data and models available to users so that risk assessment of combined exposure will become transparent.

A: Alan Boobis – Utilisation of tools beyond the end of the project by relevant stakeholders e.g. authorities and policy makers. Furthermore, the implementation of tools in regulatory work is important.

Q: **Heli Miriam Hollnagel, Dow Europe GmbH** – Does EuroMix contain/conduct a reality check for example with regard to drinking water or consumption? What would happen if we use the same tools for pesticides on a natural diet? Are the tools realistic for the exposure in daily life?

A: Alan Boobis – EuroMix will not check on the natural diet. EuroMix will conduct in vitro and in vivo tests. Developed models will be used to predict concentrations in tissues/organs, the predicted values will be compared to measured concentration in human population for evaluation of the models. EuroMix will be based on modelling, check if animal tests are realistic and using modelling of human population compared with biomonitoring of humans

Session 2 – EuroMix concepts and tools to facilitate harmonisation

Rapporteur *Sophie Jensen*

6) Johanna Zilliacus (KI): EuroMix tools and integration

Clarification question

Q: **Heli Miriam Hollnagel, Dow Europe GmbH** – Exposure & mixture ratios vary are they based on realistic environmental exposure?

A: Johanna Zilliacus – Alfonso Lampen will answer this in his presentation i.e. addressed in a slide called “Test concept: second step” in Alfonso´s presentation (for details see presentations from the workshop on the EuroMix website).

7) Angelo Moretto (UMIL): Criteria for grouping: challenges and approaches to uncertainties

No clarification questions

8) Alfonso Lampen (BfR): The in vitro toolbox to investigate mixtures: liver steatosis as an example

No clarification questions

Session 2: Panel discussions involving all the speakers in the session

Q: **Evisabel Craig, US EPA** – What is the rationale for selecting the chemicals for liver steatosis?

A: Alfonso Lampen – Actually there are two points here i) Exposure driven & ii) Mode of action (MoA). EuroMix needs to combine both of these criteria. Furthermore, a good set of compounds representing similar and dissimilar MoAs is required to test the idea. This is what we now have to investigate further.

Q: **Stephanie Melching-Kollmuss, BASF SE** – Regarding *in vitro* liver steatosis and lipid accumulation in the liver, are you identifying all molecular initiating events (MIE) in the system? Is lipid accumulation always related to liver steatosis?

A: Alfonso Lampen – The Adverse Outcome Pathways (AOP) for liver steatosis is described by the activation by different levels => The MIE event can by analysed and targeted genes that we know we can test. We have observed changes in gene expression in 6 genes which gives a clear result that liver steatosis can be the outcome. We are combining different methods => different results that indicate that this compound might cause liver steatosis. This approach reflects what is really happening. *In vivo* studies have already identified these genes, so part of the project is the proof of principle that the mode of action *in vitro* can be linked to *in vivo* effect and this investigation will start this year.

Q: **Mattias Öberg, Karolinska Institutet/Swetox** – How will you add endocrine disruption? The suggested approach seems to address health domains rather than AOP.

A: Angelo Moretto – We are addressing one end point in animals by combining estrogen and anti-androgen compounds. The idea is to see if the final outcome of combined exposures to compounds that share only part of the AOP can be described by dose additivity and in which conditions. Endocrine disruption is a mode of action, not an effect.

Q: **Giovanna Semino, Bayer SAS** – AOP for liver steatosis have been evaluated already and are well documented. How will you deal with the difficulties to predict malformation? Are you confident that you will be able to come up with validated AOP for all MoA? How will you perform the *in vivo* experiments? Will you select the doses based on *in vitro* results?

A: Angelo Moretto – It is not in the objective of EuroMix to identify the AOPs. Instead it is to use this as a tool to define the probabilities that we are on the right track and what we can get out of it. EuroMix is just testing for what we already have.

A: Alfonso Lampen – We are just testing if the AOPs are really working and proofing principle and from there we can start the validation process. If we can proof the principle, then we know we are on the right track.

A: Johanna Zilliacus –Criteria and grouping are based on the AOPs and are likely to be used in the future– do we have confidence in them? This is what we are currently discussing and is what needs to be addressed and is part of this project. More validation needs to be done.

A: Angelo Moretto – We want to highlight the problem of uncertainty we have in the grouping so we need an approach upfront that is pragmatic.

Session 3 – Statements and reflections of stakeholders

Rapporteur: *Helene Deruwe*

9) *Jean-Lou Dorne (EFSA): Harmonisation of human and ecological risk assessment of chemical mixtures at EFSA*

No clarification questions

10) *Martin Dermine (PanEurope): Scientific and public concerns on exposure to mixtures of pesticides*

Clarification from Jacob van Klaveren in response to Martins presentation regarding his remark on the mixture assessment factor, which has been suggested by RIVM for environmental risk assessment. This factor is based on the experience of the EU funded project "Solutions" as well as national projects, it is not only theoretical.

11) *Stephanie Melching-Kollmuss (BASF SE) – Developing science-based approaches for cumulative risk assessment*

No clarification questions

12) *Liesbeth Jacxsens – EuroMix stakeholders' survey towards testing and risk assessment of chemical mixtures*

No clarification questions

<u>Session 3: Panel discussions involving all the speakers in the session in addition to Eleni Ioannou Kakouri from Consumer Organisation Cyprus & Tilo Weber from Eurogroup for Animals</u>

Q: **Elisabet Berggren, Joint Research Centre** – There is some discussion about safety factors in risk assessment. When it comes to chemical mixtures, these factors can be under- or overestimated. How protected do we have to be?

Q: **Suzanne Pierlot, Anses** – Comment to Martin's presentation as a response to his claim that too little work is done for cumulative risk assessment: It is a pity that this is stated like this, as substantive work is being done on that subject in several Member States, even if the progress is not immediately visible.

A: Martin Dermine, PAN Europe – Correction to his claim: PAN Europe is aware that huge amount of work is being done, but they regret that none of it is being implemented. With regard to safety factors: according to PAN Europe's opinion, one should be as protective as possible.

A: Liesbeth Jacxsens, UGent – Within EuroMix, risk-benefit analyses will be executed to see how far you need to go with these safety factors for protection. There is a lot of focus on the risk factors of eating fruit and vegetables, but fruit and vegetables are also very healthy. The European consumer is already eating below the recommendations of the World Health Organisation (WHO) for fruit and vegetables.

A: Eleni Ioannou Kakouri, Consumer Organisation Cyprus – Risk-benefit for fruit and vegetables: there may be some residues in these products but also many beneficial components which could counteract the possible intake of the residues. One should therefore also rely on the recommendations of doctors and dieticians who advise a balanced diet, including sufficient fruit

and vegetables. To increase the consumption of these commodities, the potential bad effects from chemicals should be put in a balanced perspective.

A: Tilo Weber, Eurogroup for Animals – Additional comment on what had been said concerning animal testing: Animal testing should decrease, contrary to what had been said before in Martin´s presentation. Animal testing is not always predictive for the human risk and nowadays alternative test might even provide better predictions. There are alternative testing strategies out there, and in-vivo testing should only apply if relevant.

A: Martin Dermine, PAN Europe – Response to the comment from Tilo Weber: alternative testing is very interesting and promising, but is currently not available yet for cumulative risk assessment testing. Therefore, animal testing should not be reduced too fast, this needs to be done step by step.

A: Jean-Lou Dorne, EFSA – There are some areas where there are problems, such as contaminants caused by nature. A lot of them can be considered as carcinogens, and industry doesn't produce those compounds, but they are quite problematic for human health. The common view however is that, because something is natural, it is not toxic. This can be dangerous and the real world is not black and white.

Q: **Andy Hart, Fera** – A question related to the presentation of Stephanie Melching-Kollmuss concerning ECPA's interest in developing criteria for reducing the size of the CAGs. EuroMix recognises the need for a pragmatic approach, and this could be a reasonable solution to the problem. The cumulative risk assessment with whatever rules and criteria you would apply needs to be an appropriately conservative assessment of risk. Because of all the uncertainties affecting cumulative risk assessment, there is a realisation that, as the number of CAGs are reduced, eventually too many chemicals will be thrown out and the risk will be underestimated. Because of all the uncertainties, it is very hard to know where that point is. That is why the EuroMix team plans to calibrate those decisions and rules against larger assessments that include all the relevant compounds included in proportion to their likelihood of belonging and probability that they contribute to the risk. By doing that EuroMix will be able to check exactly what set of decision rules would correspond to appropriately precise measure of the actual cumulative risk. What approach does ECPA have to check that the results of their rules will be appropriately precise and conservative? Does it make sense to have a particular target number in mind? Ten was proposed during the presentation, but there is no certainty whether this number will be over or under conservative, or about right. This needs to be tested.

A: Stephanie Melching-Kollmuss, BASF SE – Agreed that the number of 10 is probably as arbitrarily used as the interspecies factor. In principle, there is understanding for the approach, coming from hazard, starting from all the compounds, phenomenologically, for those cases where one doesn't know more. What they did is reducing the aspects of the number of the CAGs and reducing the number of compounds in the CAGs, which is stricter hazard characterisation. With regard to looking for criteria, BASF, in coordination with Bayer and their mutual pathologists, starts from the proposed groupings for the liver. It was a start which now needs to be refined. They decided to start from the available in vivo studies, because they don't have the capacity to do in vitro.

A: Andy Hart, Fera – Main caveat is that every set of rules needs to be tested to demonstrate that they are appropriately conservative, not over- or under-conservative.

A: Alan Boobis, ICL – Clarification: There needs to be a distinction between the operation of EuroMix to establish a rule of principle and the implementation of the approach it involves. EuroMix works towards an experimental strategy to determine the appropriate approach.

Q: **Heli Miriam Hollnagel, Dow Europe** – There is not only the need to harmonise between ecological and human health risk assessment, but also between toxicologists and exposure assessors. Toxicologists might often test scenarios which are far from relevant for reality. How often are minor exposure and toxicology considered?

A: Jacob van Klaveren, RIVM – The EuroMix project is planning to establish user groups in the second part of EuroMix to test the developed tools, to gain experience with it and to frame relevant examples. Then the user will see how exposure will be integrated with hazard assessment and how refinement from EuroMix testing can be used in reality. EuroMix is not responsible for the risk assessment itself, only for developing the tools and make them available to calculate risk of combined exposure in the future in a more refined way than currently ongoing.

A: Jean-Lou Dorne, EFSA – It is a difficult exercise to make everyone agree as toxicologists from the biomedical area are placed together with ecologists from the ecological area, and modelers and exposure assessors. The approach for the exposure and hazard assessment is different in many areas. Furthermore, we should not decide on exposure or hazard only, but our decisions should be based on risk integrating both exposure and hazard. EuroMix provides tools and options to use in practice.

A: Natalie von Goetz, ETH Zurich – Additional comment: Within EuroMix a method has been developed to prioritize mixtures based on exposure, so that the mixture selection for in vitro testing is not only based on common toxicology, but also on co-exposure.

Session 4 – Future tools for harmonisation

Rapporteur: *Johanna Zilliacus*

13) Natalie von Goetz (ETHZ): Aggregate exposure from food and non-food sources

Clarification question

Q: **Unidentified participant**: Clarify if for some chemicals no data was available or if the measured concentrations were below Limit of detection (LOD).

A: Natalie von Goetz **–** If no data is available we normally extrapolate data. In this case the values were below LOD. It is important to discuss how to handle data that is below LOD.

14) Hilko v.d. Voet (Wageningen University & Research): Open data and model platform

Clarification question

Q: **Stephanie Melching-Kollmuss, BASF SE**: What is the timeline for the EuroMix platform?

A: Hilko v.d. Voet **–** the final and validated tools will be ready by the end of the project.

A: Jacob van Klaveren – Some parts of the tools/modules will become already available during the project lifetime and it is foreseen that user groups can test the modules in EuroMix platform before the project end. User groups will need to recognize that tools are still under development and have to sign confidentiality agreements to have access to ongoing modelling work.

15) *Helen Clayton (DG Environment): Perspective of European Commission Services on tools for risk assessment of chemical mixtures*

Clarification question

Q: **Stephanie Melching-Kollmuss, BASF SE**: What is the rational for selecting chemicals for the watch list (chemicals in surface water to be monitored temporarily to determine their risk)?

A: Helen Clayton – It is based on substances ranked highly in risk assessments from JRC and is based both on hazard and exposure

Session 4: Panel discussions involving all the speakers in the session

Q: **Philippe Verger, WHO**: Regarding how to manage concentration data below LOD, EFSA has a guidance on how to handle left sensored data and JECFA is preparing a guidance based on the EFSA document. He suggested that the terminology pessimistic and optimistic models should not be used. Lower bound and upper bound are better terms for using 0 value or LOD value when measurement is below LOD.

A: Natalie von Goetz – MCRA is using the terminology pessimistic and optimistic models. Agrees that lower bound and upper bound are better terms. EFSA guidance does not give guidance for cases when all measurements are below LOD (apart from suggesting to use lower and upper bounds), since for these cases regression methods cannot be used. More discussion on this issue is needed.

A: Hilko v.d. Voet – Pessimistic and optimistic models is used in EFSA guidance on probabilistic modelling. It includes additional aspects than lower bound and upper bound. New models for how to handle values below LOD are being developed.

Q: **Dick Sijm, Office for Risk Assessment and Research, NL**: Model outcome might be different in the future, how will that be handled?

A: Hilko v.d. Voet – Version controls will be used for models to know which one has been used. Version control is also needed for the input datasets.

Q: **Paul Price, US EPA**: Glad that the programme R is used, will the programme code will be publicly available to allow the stakeholders to recreate the models?

A: Hilko v.d. Voet – The EuroMix toolbox models are not in R, but can connect to R codes. The web-based toolbox is open to users, the focus is on the openly available web platform. If codes have to be made available it will be additional work, which is not foreseen in the EuroMix project.

A: Natalie von Goetz – The code for PACEM is in R and could maybe be available.

A: Jacob van Klaveren – The aim of the project is to harmonise approaches. By doing this, openly available reference and user manuals will be available. However, we don't feel the responsibility

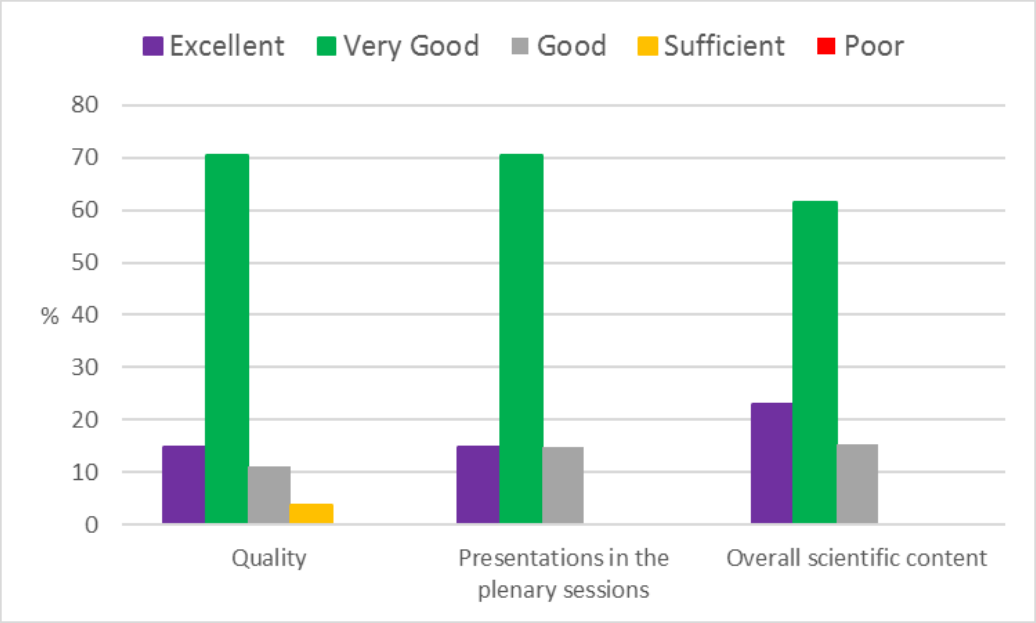
to become a software company distributing stand-alone codes including all the work associated with technical instructions.

General comment from **Yasunobu Aoki, National Institute for Environmental Studies, Japan**: It is important with opportunities for exchange of methods and tools between Europe and globally such as Japan.

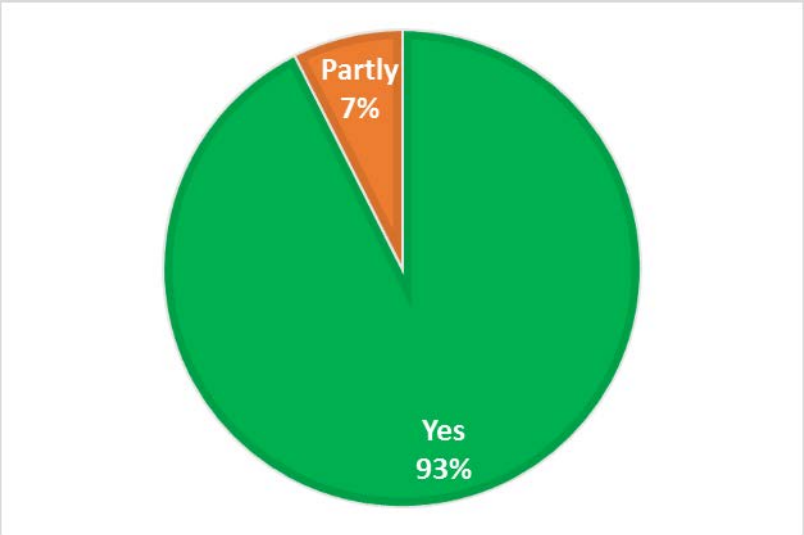
Feedback from the participants

On May 24th 2017, all meeting participants received an invitation to fill in a questionnaire to evaluate the workshop. A total of 27 answers were received from the 72 attendants of the workshop. The survey was send to all 72 workshop participants. However, it is worth pointing out that 22 of the participants were from EuroMix partners and since many of them were actively involved in the workshop (e.g. as speakers or organisers) it is unlikely that they participated in the evaluation survey due to conflicts of interests. For data integrity reasons we are not able to track the identity of the respondents of the survey, thus this deduction cannot be confirmed.

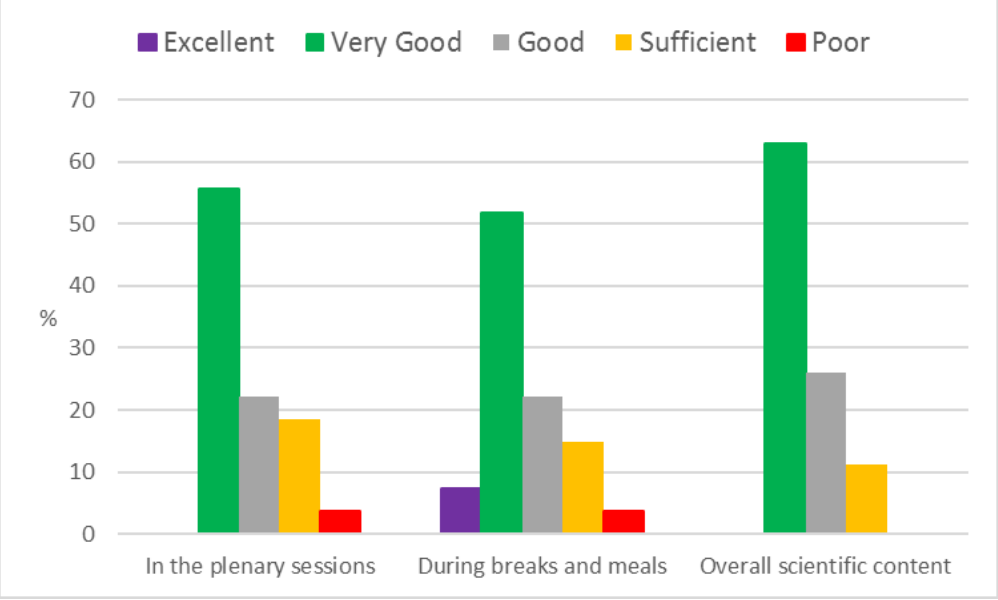
1. How would you rate the overall quality of the workshop and the quality of the scientific presentations and discussions?



2. Were the intended aims of the workshop met?



3. How would you rate the available time for discussions, both formal and informal as well as overall scientific content of the discussions?



4. How would you rate the practical/organisational information sent to you before the workshop?

	Poor (%)	Sufficient (%)	Good (%)	Very good (%)	Excellent (%)
Quality	0	11	15	48	26
Comprehensiveness	0	4	15	46	35
Timeliness	0	15	4	37	44

Conclusion

The feedback provided by the WS participants clearly shows that the majority was very positive towards the overall quality of the workshop and the quality of the scientific presentations and discussions. Similarly, they were happy with the time allocated in the program for discussions. Furthermore, 93% said that the intended aims of the workshop were met. The participants were not fully satisfied with the practical/organisational information sent before the workshop, hence clearly there is room for improvement regarding that issue. Unfortunately, the response rate on the evaluation survey was only 38%. However, the result of the survey is completely in line with the verbal feedback and emails received from the participants at the end of the workshop. Another, final general stakeholder workshop will be held by the EuroMix project towards the end of the project (M46) and the feedback received from the first stakeholder workshop will be used to improve the organisation, planning and implementation of the final stakeholder workshop.

Appendices

Appendix 1 – Workshop programme
Appendix 2 – Pdf files of PowerPoint presentations

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

EuroMix Stakeholder Workshop

Towards Harmonisation of Implementation of Test Strategies for Chemical Mixtures in Europe

Workshop Programme

Overall Chairs: ***Annemiek van Bolhuis & Elisabet Berggren***

Overall Rapporteur: ***Helga Gunnlaugsdóttir***

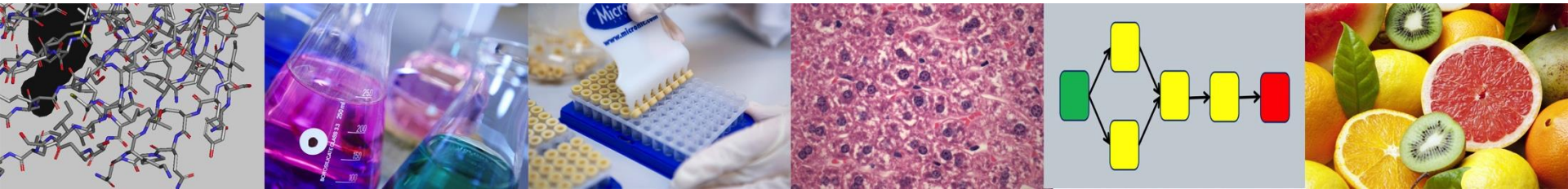
08:30-17:00 18th May 2017, Thon Hotel EU, Rue de la Loi 75, 1040 Brussels, Belgium

8:30-9:00	***Welcome coffee and registration***	
SESSION 1: Harmonisation of test strategies for chemical mixtures		
Rapporteur:	*Dr. Stefanie Rotter*	
9:00-9:15	Welcome and workshop objectives	*Prof. Jacob van Klaveren, RIVM*
9:15-9:40	Assessment of chemical mixtures – policy context, current practices and future directions	*Dr. Stephanie Bopp, JRC*
9:40-10:00	Overview on legislation and scientific approaches for risk assessment of mixtures as EuroMix contribution	*Dr. Roland Solecki, BfR*
10:00-10:20	Risk assessment of chemical mixtures: Implications for international harmonisation	*Prof. Alan Boobis, ICL*
10:20-10:40	Overview of the OECD Project on Assessment of Combined Exposures to Multiple Chemicals	*Dr. Eeva Leinala, OECD*
10:40-10:55	Session 1: Panel discussions	
10:55-11:15	***Refreshment Break***	
SESSION 2: EuroMix concepts and tools to facilitate harmonisation		
Rapporteur:	*Dr. Sophie Jensen*	
11:15-11.35	EuroMix - key tools and integration	*Dr. Johanna Zilliacus, KI*
11.35-11.55	Criteria for grouping: challenges and approaches to uncertainties	*Prof. Angelo Moretto, UMIL*
11:55-12.15	The *in vitro* tool box to investigate mixtures: liver steatosis as an example	*Prof. Alfonso Lampen, BfR*
12:15-12:30	Session 2: Panel discussions	

12:30-13:30	***Lunch***	
SESSION 3: Statements and reflections of stakeholders		
Rapporteur:	*Helene Deruwe*	
13:30-13:45	Harmonisation of human and ecological risk assessment of chemical mixtures at EFSA	*Dr. Jean-Lou Dorne, EFSA*
13:45-14:00	Scientific and public concerns on exposure to mixtures of pesticides	*Dr. Martin Dermine, PanEurope*
14:00-14:15	Developing science-based approaches for cumulative risk assessment	*Dr. Stephanie Melching-Kollmuss, BASF*
14:15-14:30	Euromix stakeholders' survey towards testing and risk assessment of chemical mixtures	*Dr. Liesbeth Jacxsens, Ugent*
14:30-14:45	Session 3: Panel discussions	
14:45-15:10	***Refreshment Break***	
SESSION 4: Future tools for harmonisation		
Rapporteur:	*Dr. Johanna Zilliacus*	
15:10-15:30	Aggregate exposure from food and non-food sources	*Dr. Natalie von Goetz, ETHZ*
15:30-15:50	Open data and model platform	*Dr. Hilko v.d. Voet, Wageningen University & Research*
15:50-16:10	Perspectives of European Commission Services on tools for risk assessment of chemical mixtures	*Dr. Helen Clayton, DG Environment, European Commission*
16:10-16:25	Session 4: Panel discussions	
16:25-16:50	Take home message & Conclusions	*Ms. Annemiek van Bolhuis*
16:50-17:00	Closing of WS	*Dr. Helga Gunnlaugsdóttir*

EuroMix

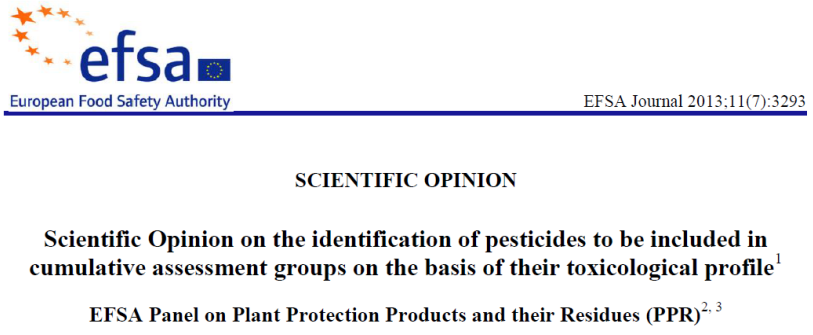
Welcome and workshop objectives
Jacob van Klaveren



What's the problem (call text)

FOCUS ON HUMAN RISK

1. EU direction to group pesticides affecting the same target organ, broad cumulative assessment groups for pesticides
2. Differences between US-EPA and Europe (harmonization)
3. Hardly any information on mixture effects of other chemicals
4. Societal need to reduce animal tests
5. How to test mixture effects (mechanism based strategy)
6. Aggregated exposure
7. Open platform to be maintained beyond the project's lifetime


efsa
European Food Safety Authority
EFSA Journal 2013;11(7):3293

SCIENTIFIC OPINION

Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile[1]

EFSA Panel on Plant Protection Products and their Residues (PPR)[2, 3]

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

About the EuroMix consortium

22 European institutes involved

1. 10 institutes with lab facilities
2. computational science and modelers
3. risk assessment experts
4. national food authorities

8M € EU funding and additional national funding. 4 years project.

4 Third parties for international harmonization

1. World Health Organization (WHO)
2. US-EPA
3. Health Canada
4. University of Brasilia

Kick-off meeting 20-21 May 2015

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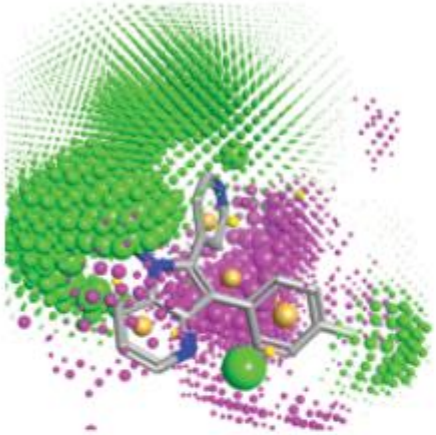
Concept test strategy

Focus on human risk assessment

QSAR



priorities

TTC approach

Possibility of co-exposure

bioassay tool box

In vivo confirmation

Very large number of chemicals → Large number of chemicals and mixture experiment → Selected number of chemicals

High uncertainty → Refine and retain → Reduced uncertainty

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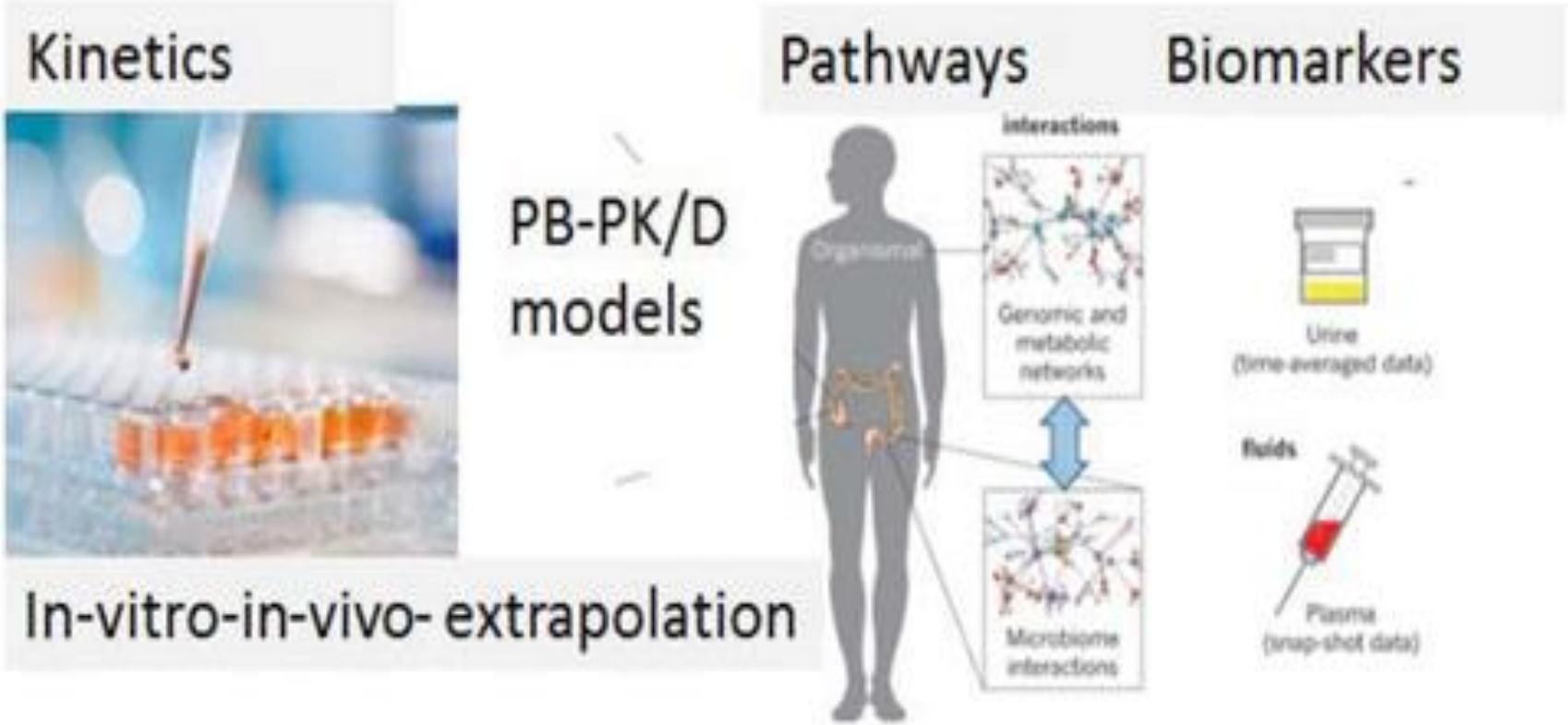
Concept extrapolation to humans



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Specific objectives

- Establishment of in-silico approaches, such as (Quantitative) Structure-Activity Relationships, for grouping of chemicals;
- Setting up methodology for prioritisation of chemicals and mixtures to be tested by using approaches such as TTC values, the Hazard Index and probabilistic modelling to determine the likelihood of *co-exposure*;
- Development of a bioassay toolbox using well-established bioassays in cell lines and primary cells
- Verification of the above mentioned *in-silico* methods and the *in-vitro* bioassay toolbox against *in-vivo* animal tests and biomarkers

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Specific objectives

- Performing realistic exposure assessment using aggregated and cumulative exposure models, to harmonize these approaches and to provide free access to data and models;

- Creation of a web-based platform of models and data openly accessible to all stakeholders that will remain available beyond the project's lifetime;

- To discuss how the tiered mechanism-based test strategy and exposure assessment methodology of mixtures can contribute to a harmonised approach between Europe, WHO/IPCS (Codex Alimentarius), and US-EPA;

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Scientific management

1. Kick-off meeting
   - What is on the agenda of the international organization
   - Coherence between the WPs

2. Scientific consortium meetings (3x)
   - Presentations and discussion on the concepts
   - Discussion on the integration

3. General Assembly meetings (3x)
   - Milestones and deliverables (stop/go decisions)
   - Cooperation with others

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Cooperation with others

1. Other EU Projects: EDCMixRisk, EUToxRISK21, and HBM4EU
2. European Commission Joint Research Centre
3. EFSA (two members in SAB)
4. Cooperation at the Member State level

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Exploitation and dissemination

1. In period 1-12M, the focus was on proof-of-principles and trying out

2. Building a EuroMIx identity

3. Ownership of data and tools and access to it, are well described in the Consortium Agreement

4. Huge interest to become associated partner of the EuroMix

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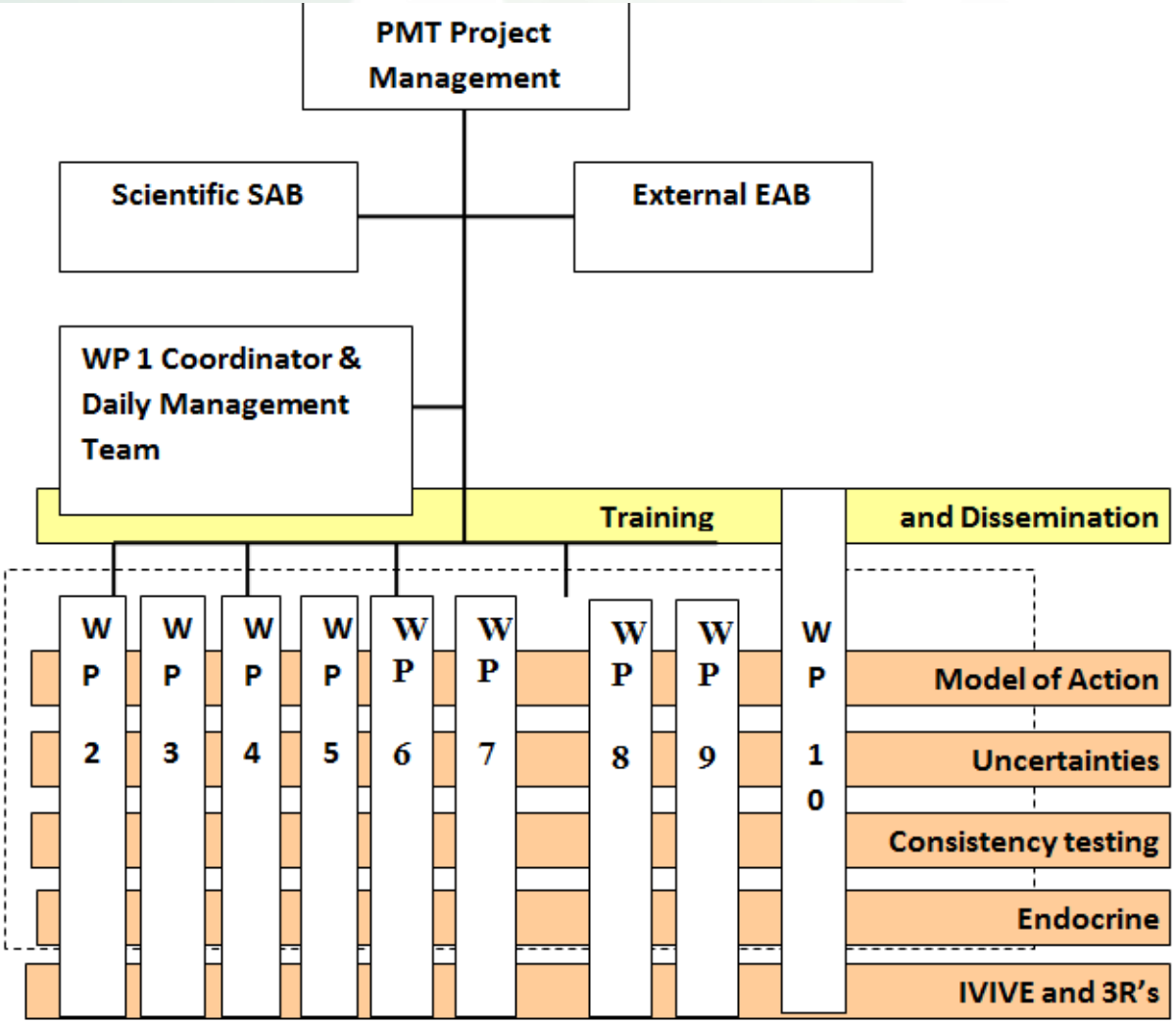
EuroMix advisory boards



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Stakeholder workshop objectives

1. To contribute to harmonisation of test strategies for chemical mixtures (in Europe and beyond)

2. How in silico and bio-assay testing can be used in Adverse Outcome Pathways and how it might help the harmonisation process, the risk assessment and the grouping principles

3. To involve stakeholders in the EuroMix concept

4. To address multiple exposure routes and to discuss how the EuroMix data and model platform infrastructure can be used in Europe and beyond

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The EuroMix consortium as a whole

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The European Commission's science and knowledge service

Joint Research Centre

Assessment of chemical mixtures

Policy context, current practices and future directions

Stephanie Bopp
stephanie.bopp@ec.europa.eu

The views expressed are those of the speaker and not an official position of the European Commission

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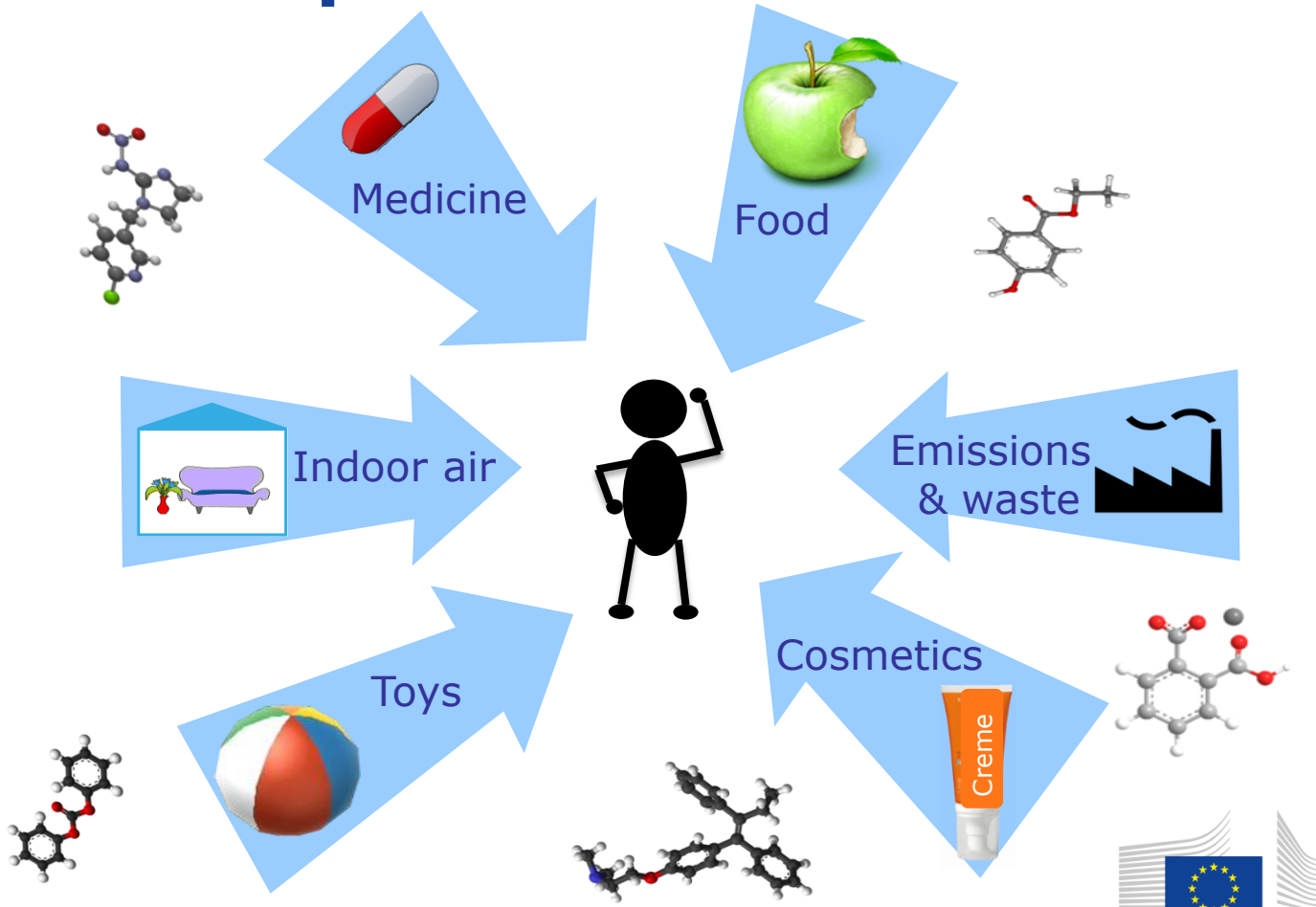
Why is it important?



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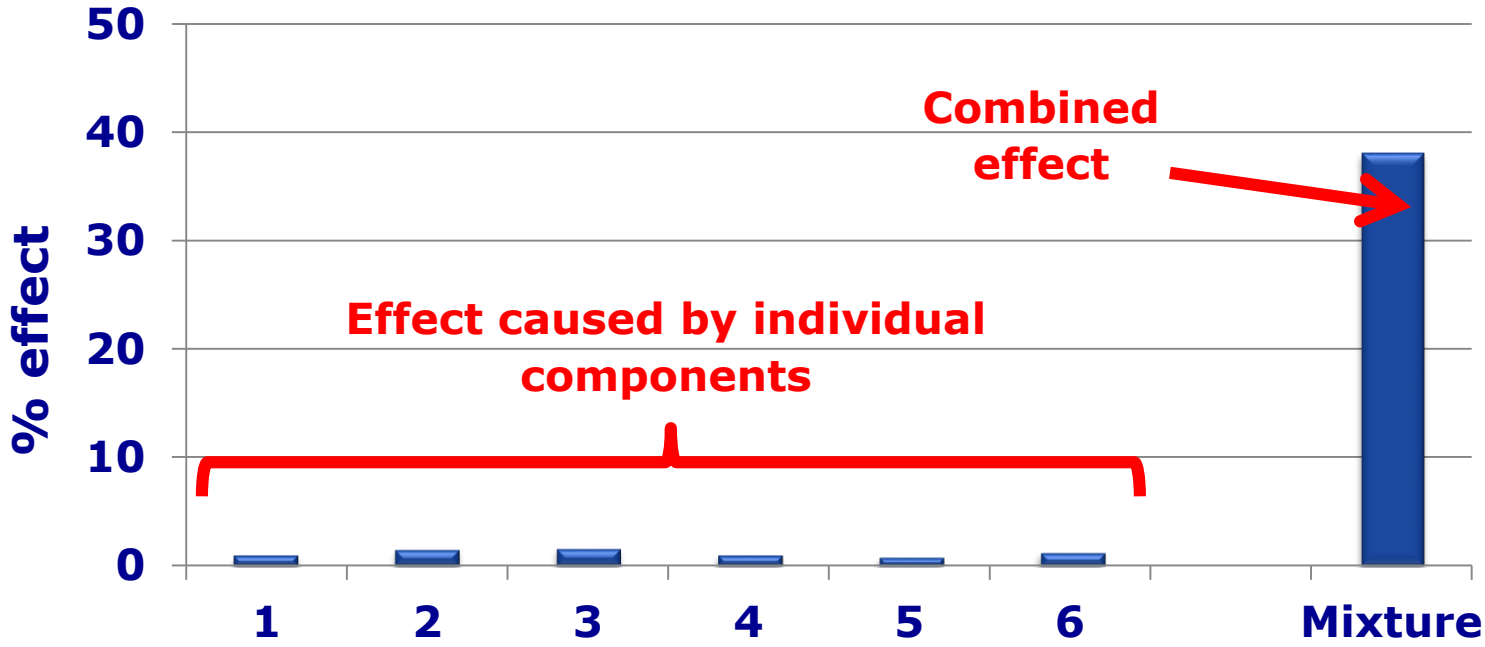
Why is it important?



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Terminology

Intentional mixtures

Unintentional mixtures

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Terminology

Aggregate exposure

Chemical X Chemical X

one substance
originating from different sources

Combined exposure

Chemical X Chemical Y Chemical Z
Chemical n Chemical …

multiple substances
from one or different sources

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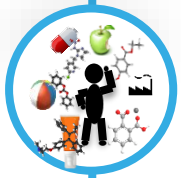
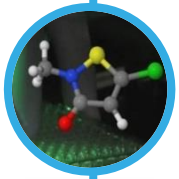
Outline

Policy context / Commission Communication 2012



Exposure Assessment



Hazard Assessment

Current practices

- Expert survey
- Case study review

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Past EC activities




- Kortenkamp et al. 2009 State of the Art Report on mixture toxicity
- SCHER/SCENIHR/SCCS 2011 Opinion on toxicity assessment of chemical mixtures
- Commission Communication on the combined effects of chemicals (COM(2012)252 final)

Conclusions Commission Communication 2012

- **Human Health**

  for **dissimilarly** acting compounds ➔ **protected by individual chemical RA**

  for **similarly** acting compounds ➔ **potential combined effects**

- **Environmental Health**

  for **dissimilarly** and **similarly** acting compounds ➔ **potential combined effects**

- "…no mechanism for a systematic, comprehensive and integrated assessment of mixture effects…"

Regulatory Requirements

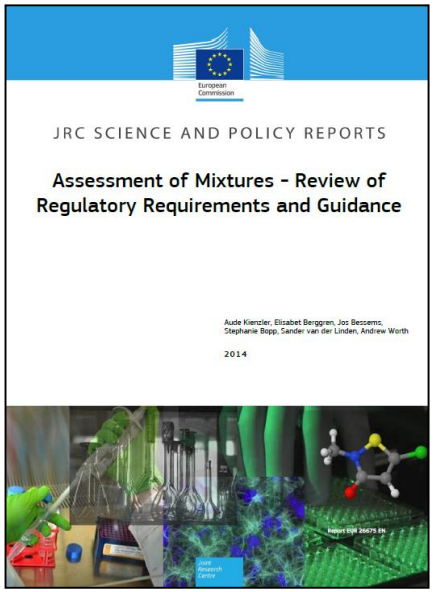
Intentional:

- CLP
- REACH
- pesticides
- biocides
- medicines
- cosmetics
- food /feed additives

Unintentional/environmental:

- Food contaminants
- Food contact materials
- Waste streams
- WFD
- Marine Strategy
- Groundwater
- Drinking Water
- PPP MRL
- Soil
- Air
- EIA
- IPPC
- Toys

→ Presentation Roland Solecki



Kienzler et al (2014) JRC Science and Policy Report, EUR 26675 EN

- Mixtures addressed
- Mixtures partly addressed
- Mixtures not addressed

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Follow-up actions Commission Communication 2012

- Establish an ad-hoc working group of European Commission services and agencies/authorities to strengthen coordination

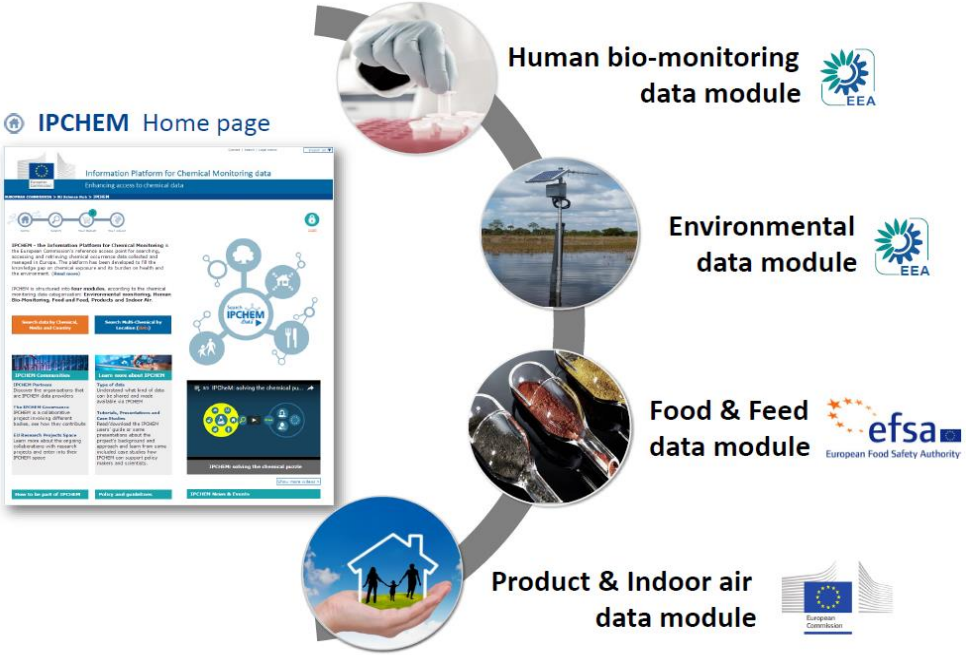
- Develop technical guidelines to promote a consistent approach to the assessment of priority mixtures

→ Ongoing work by JRC
→ EFSA developing Guidance for harmonised human and ecological RA of chemical mixtures (presentation Jean-Lou Dorne)

Follow-up actions Commission Communication 2012

- **Understanding actual exposure of humans and environment**
- Mode of Action (MoA) of chemicals
- Grouping of chemicals
- Predicting interactions (antagonisms, synergisms)
- Identify substances that are drivers of mixture toxicity

IPCHEM: the reference platform for chemical monitoring data in Europe



Collaborations:

European Agencies

EU Research projects and Research Consortia

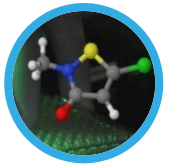
National Authorities

https://ipchem.jrc.ec.europa.eu

→ Presentation Helen Clayton

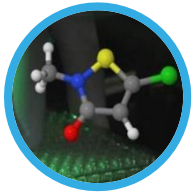
European Commission

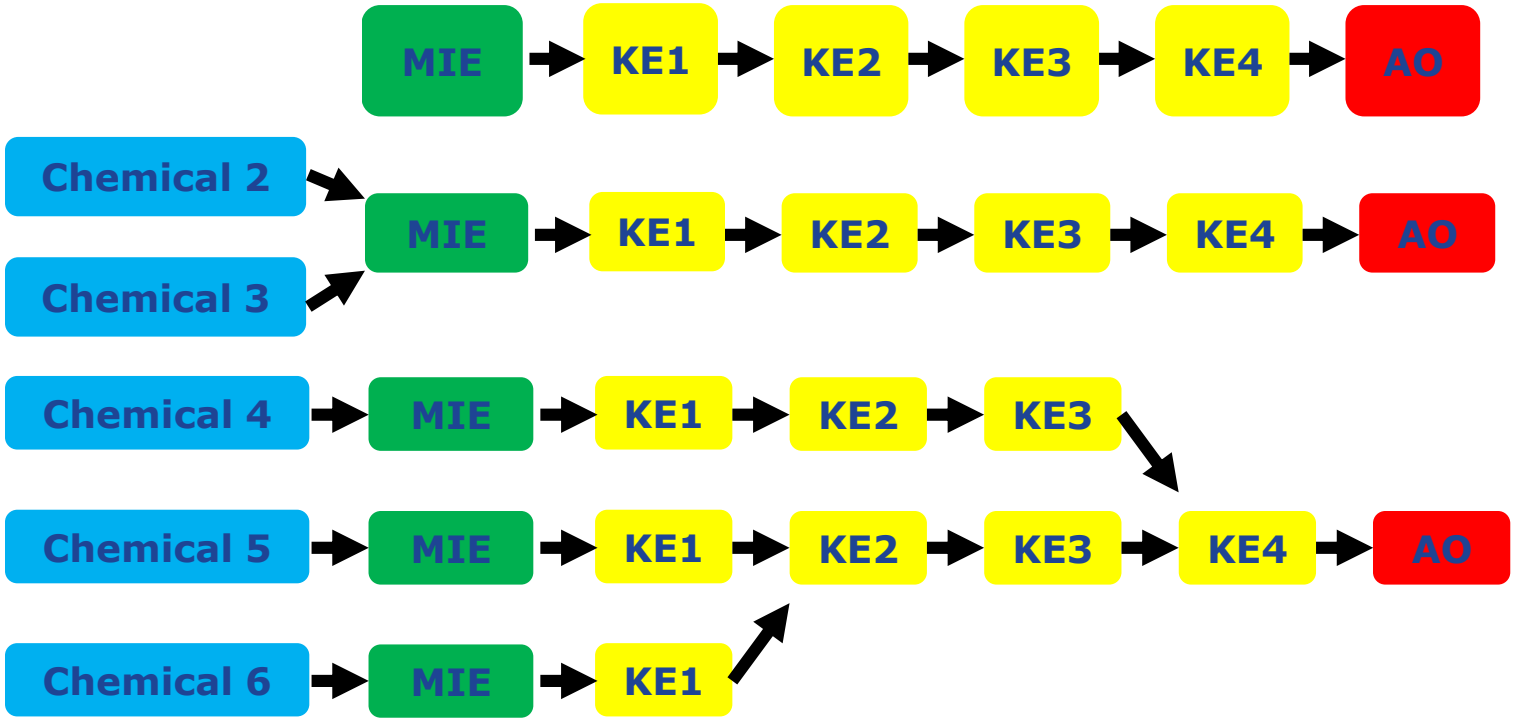
Follow-up actions Commission Communication 2012



- Mode of Action (MoA) of chemicals
- Grouping of chemicals
- Predicting interactions (antagonisms, synergisms)
- Identify substances that are drivers of mixture toxicity

Mode of Action of Chemicals and Grouping





Bopp et al (2015) JRC Technical Report, EUR 27471 EN

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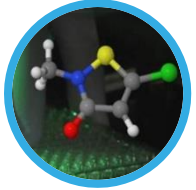
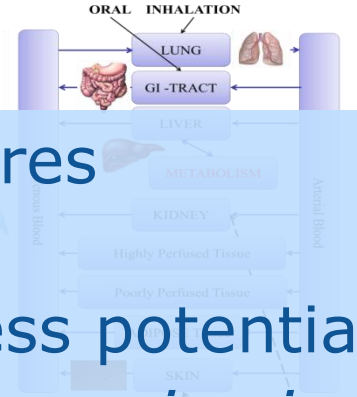
Review- Use of novel tools



in vitro testing

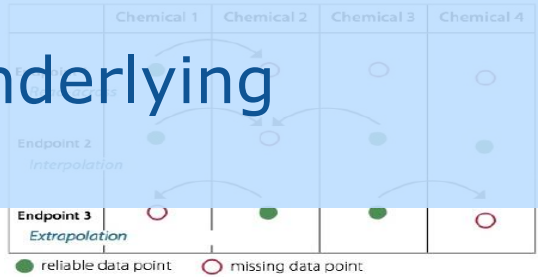
PBK



- impossible to test all possible mixtures experimentally
- smart strategies are needed to assess potential hazards using new tools, relying less on *in vivo* testing
- Allow better understanding of the underlying mechanisms

Proteomics
Metabolomics

Quantitative Structure Activity Relationship



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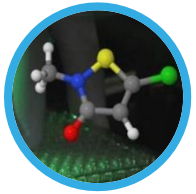
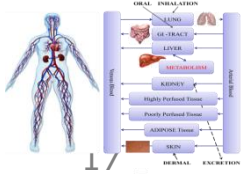
Mode of Action of Chemicals and Grouping



Toxicokinetics

QSAR

Chemical 1	MIE	KE1	KE2	KE3	KE4	AO
Chemical 2	MIE	KE1	KE2	KE3	KE4	AO
Chemical 3						
Chemical 4	MIE	KE1	KE2	KE3		
Chemical 5	MIE	KE1	KE2	KE3	KE4	AO
Chemical 6	MIE	KE1				



Bopp et al (2015) JRC Technical Report, EUR 27471 EN

→ Presentation Angelo Moretto and Alfonso Lampen

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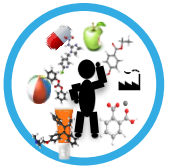
Follow-up actions Commission Communication 2012



- Promote consistent approach at global level

OECD

World Health Organization

→ Presentation Eeva Leinala on OECD project

→ Presentation Alan Boobis on harmonisation

EuroMix

European Commission

Follow-up actions Commission Communication 2012

- …may be supported by Horizon2020 projects

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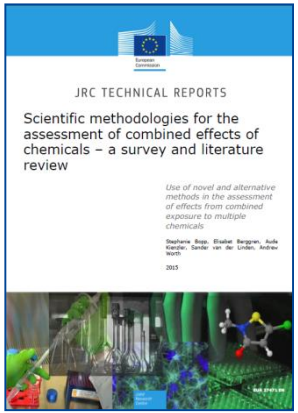
Current practices

- JRC expert survey



EUR 27471 EN
doi:10.2788/093511

- Case study review

EUR 27968
doi:10.2788/272583

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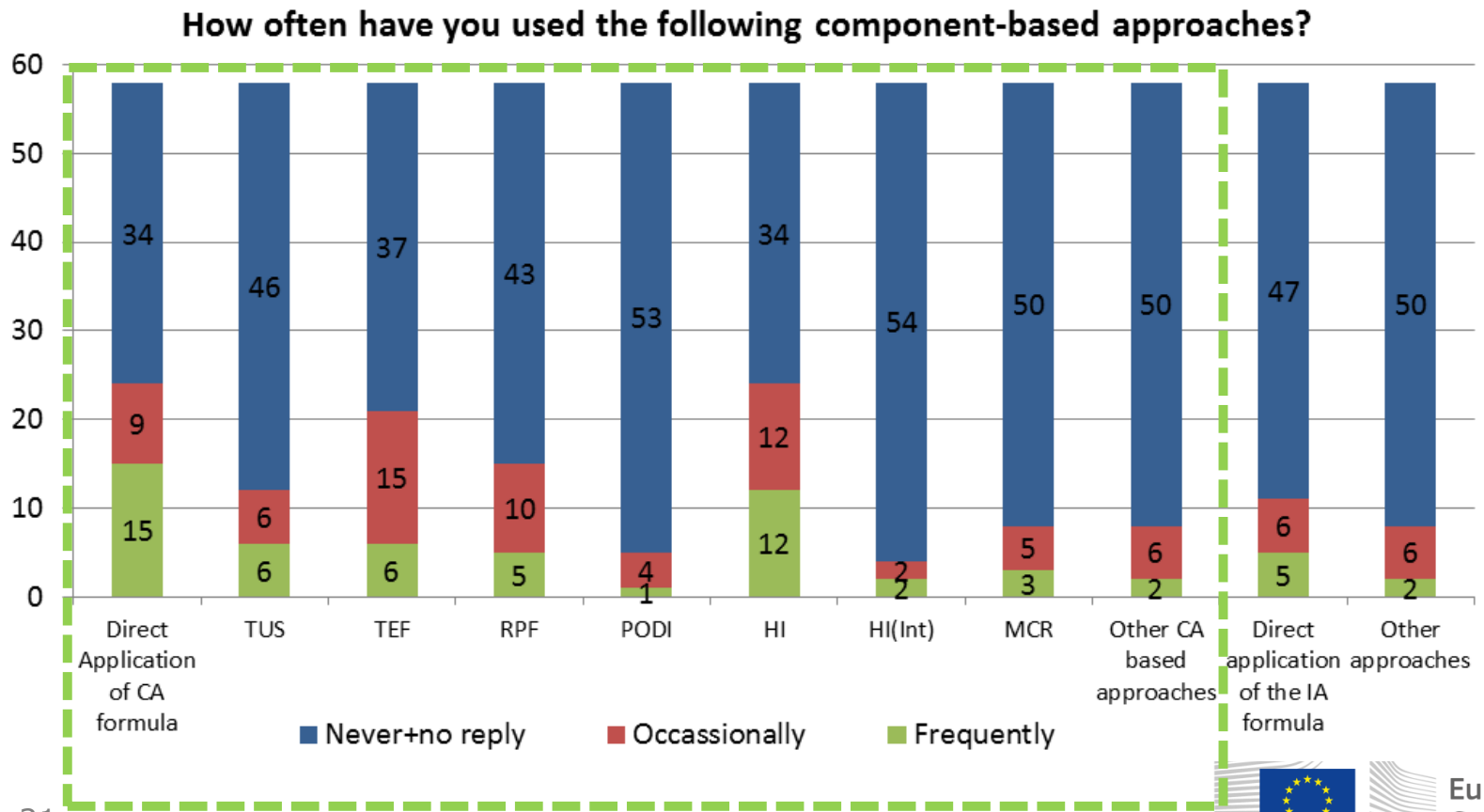
Current practices - Methodologies



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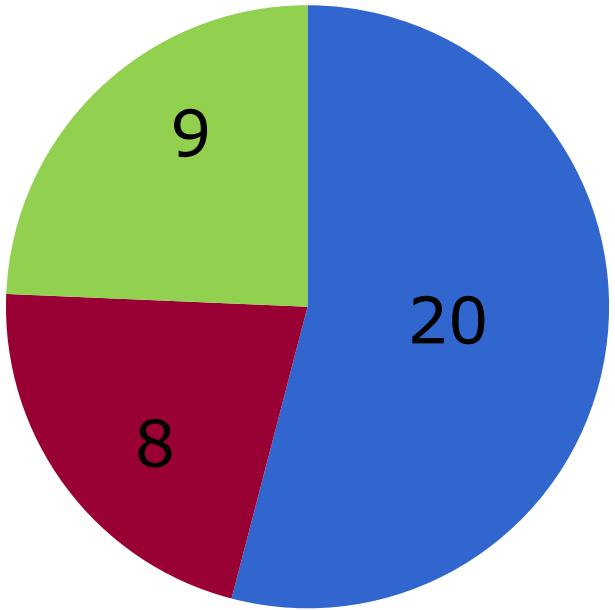
Current practices - Frameworks



- WHO/IPCS 2009, Meek et al 2011
- Proposal by the three non-food Scientific Committees of the European Commission from 2012
- Proposal by CEFIC Mixtures Industry Ad-Hoc team (MIAT) 2012

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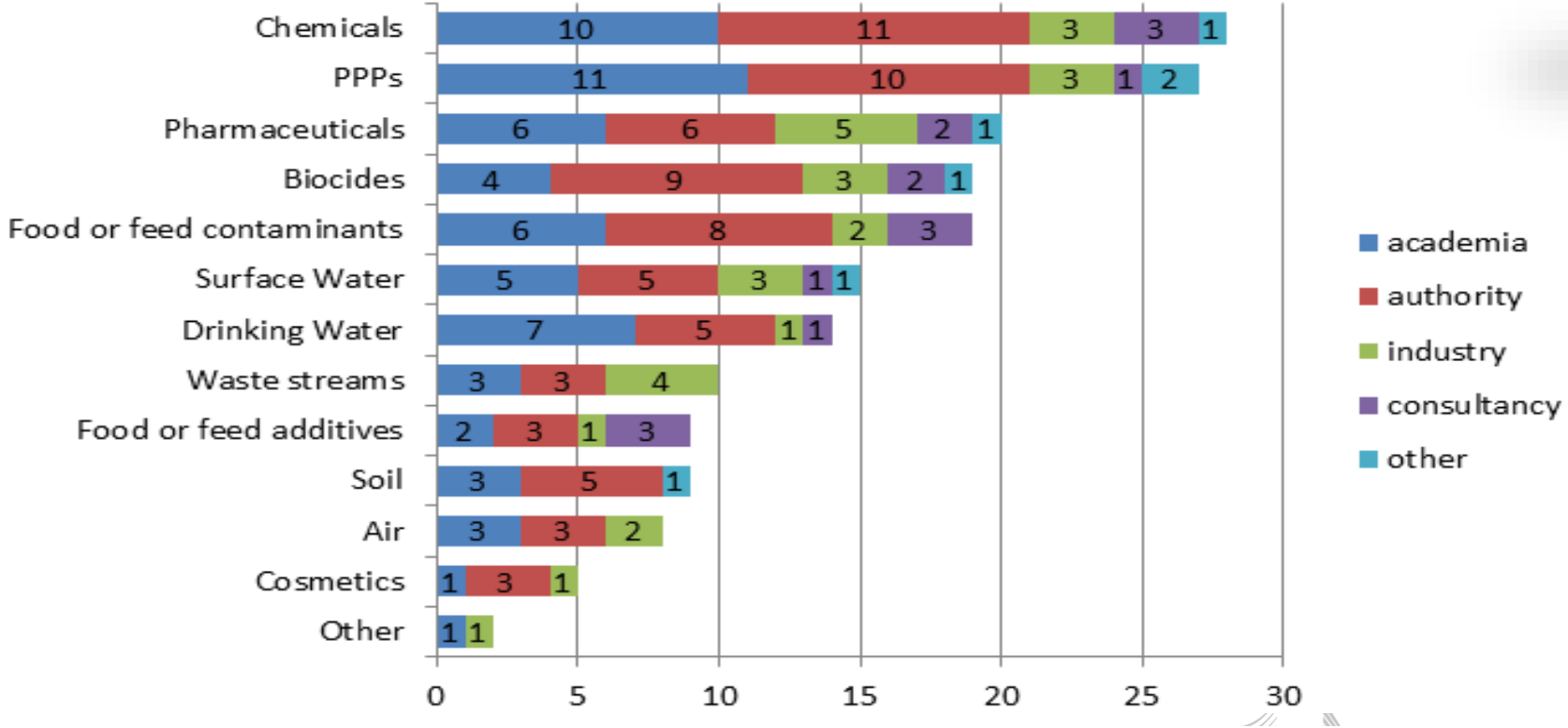
Current practices – Priority sectors



* "Chemicals" = industrial chemicals under REACH (MCS and UVCB)

Current practices – Priority sectors

	HRA	ERA
Pesticides	4	2
Phthalates	1	
PBDEs	1	
Parabens	1	
Pharmaceuticals		2
Food contact materials	1	
Dioxin-like compounds	1	
Cross-sectorial mixtures	6	2

- Selection of chemicals not fully representative
- Potential concern identified in some cases for vulnerable population groups
- Potential for over-and underestimations
- Mostly screening-level
- Lack of data: exposure/toxicity/ Mode of Action

Conclusions and future needs

- Most experience related to plant protection products
- Agreed models/methods and different frameworks available
- We need to learn from further case studies (e.g. on vulnerable sub-populations, other substance groups, grouping approaches, mixtures across regulatory sectors)
- Need for harmonised approach for combined exposure assessments across sectors

Stay in touch

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YouTube: ***EU Science Hub***

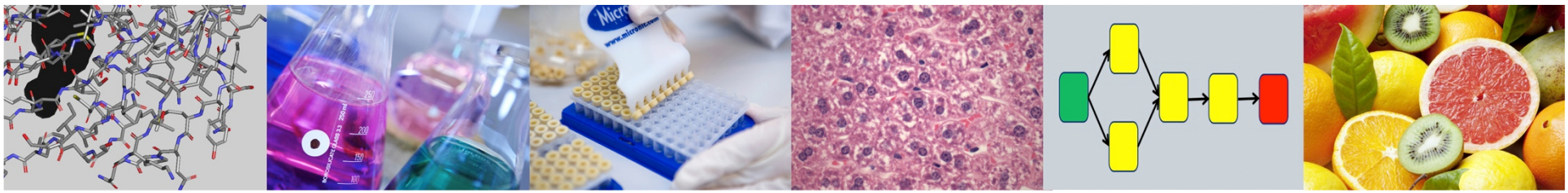
European Commission

Overview on legislation and scientific approaches for risk assessment of mixtures as EuroMix contribution

EuroMix Stakeholder Workshop, 18 May 2017, Brussels, Belgium

Roland Alfred Solecki

Rotter S., Beronius A., Boobis A., Hanberg A., van Klaveren J.D., Luijten M., Machera K., Nikolopoulou D., Zilliacus J.



Introduction

- Exposure to mixtures are the rule rather than the exception.
- Risk assessment needs to consider mixtures to ensure human and environmental health.
- In EU, no common approach has been proposed by the European authorities yet, except for the CLP and biocide legislation (ECHA) and drug interaction (EMA).

Topics of the talk:

1. **Review on EU legislations** regarding their requirements on mixtures
2. **Analysis of** legal requirements for mixtures in **EU countries**
3. **Analysis of** legal requirements for mixtures of **non-EU countries**
4. **Summary of existing frameworks** for human health risk assessment
5. **Outline** of the **new US EPA framework**
6. **Summary → Conclusion**

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1) Review on the EU legislation

Reviewed Regulations and Directives of the EU law		Principals of the regulations	Mixture assessment for human health required?	Guidance for implementation of CRA available?
Biocidal products	Reg. EU No. 528/2012	Procedure: appr. of substance & author. of products	**Yes**	**Yes** **ECHA, 2015a**
CLP	Reg. EC No. 1272/2008	Classification of substances & mixtures	**Yes**	**Yes** **ECHA, 2015b**
Plant Protection Products	Reg. EC No. 1107/2009 Reg. EU No. 283/2013 Reg. EU No. 284/2013	Procedure: appr. of substance & author. of products	**Yes**	**No**
MRL`s	Reg. EC No. 396/2005	Setting of maximum residue levels	**Yes**	**No**
Medicinal Prod. for Human & Veterinary Use	Direct. 2001/83/EC Direct. 2001/82/EC	Author. procedure of products	**Yes**	**Yes,** **drug interactions**
Cosmetics	Reg. EC No. 1223/2009	Author. procedure of products	**Yes**	**No**
REACH	Reg. EC No. 1907/2006	Registration, authorisation of chemicals	**No**	**No**
Food and Feed Additives	Reg. EC No. 1333/2008 Reg. EC No. 1831/2003	Author. procedure of products	**No**	**No**

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2a) Analysis EU legislation – actual state

- Many reviewed Regulations (CLP, PPP, BP, MRL, medicinal products, general food law) stipulate to consider cumulative and synergistic effects.
- Mixture toxicity is not clearly addressed in REACH, food and feed additives.
- Regulations are predominantly substance and product oriented and refer mainly to intentional mixtures with known compositions.
- Restrictions are made by statements like "*if appropriate methods are available*", or "*where relevant*" etc.

→ This creates inconsistencies → expert knowledge is required.

- Risk assessment is based mainly on intentional uses in one regulatory sector as if they were present in isolation.
- Risk profiles of chemicals from different regulatory sectors are overlapping.
- As the development of guidance is still pending, current legal requirements regarding the assessment of cumulative risks are often conditional.

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2b) Analysis EU legislation – identified problems

- Most of the reviewed European Regulations stipulate to consider potential combined effects from exposures to multiple chemicals.
- No clear legal mandates to assess the combined effects implemented in Regulations, as long as harmonised and accepted methods are lacking.
- No framework for a systematic and integrated assessment of mixture effects taking into account different routes of exposure and different product types.

MRL Regulation requires developing new methodologies for CRA.

→ **Method development is the first necessary step to implement clear legal mandates and establish guidelines for a sound risk assessment.**

EFSA requested the Scientific Committee to **develop an overarching guidance document** on the harmonisation of risk assessment methodologies **for human health and ecological risk assessment** of chemical mixtures within and across regulatory sectors (EFSA 2016).

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2c) Analysis EU legislation - challenges

Challenges are the lack of…

- General and accepted scientific methods and overarching principles for Cumulative Risk Assessment,
- Harmonized approaches and resulting guidelines for the assessment of mixture effects,
- Accessible and well structured toxicity data, e.g.:
  - 1) *in vivo* data from experimental testing of mixtures,
  - 2) *in vitro* and *in silico* data on hazardous mixtures.
- Compiled exposure data:
  - 1) on frequently co-occurring chemicals,
  - 2) for a realistic assessment of the exposure.

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3) Analysis non-EU legislation

Examples from Australia, Brazil, Canada, Japan, Korea & USA

- All countries have legal acts to authorize chemical substances before use
  - Risk assessment for authorization is required
  - specific products are regulated in specific legal acts
- GHS requires a hazard-based assessment of synergistic effects in mixtures, but is not implemented in all OECD countries
- Brazil, Japan and Korea do not have legal requirements to consider mixtures
- **USA** requires a cumulative risk assessment in legal acts on intentional mixtures and routinely implements cumulative risk assessment for pesticides
  - US EPA developed a tiered system for the evaluation of mixtures
- **Canada:** requires assessing impact of combined exposure to multiple chemicals
  - No clear legally binding guidelines → supports approaches from US EPA
- **Australia:** considers the synergistic effects of mixtures

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4) Existing frameworks for human health RA

- Several authorities and organisations have proposed approaches for health risk assessment of chemical mixtures
  → commonly decision trees or tiered frameworks.
- Some approaches are general in their intended application and some are proposed for assessment of specific exposure scenarios or groups of chemicals within one regulatory sector.
- EFSA is reviewing relevant overarching approaches within and across regulatory sectors in the current mandate of the SC (EFSA 2016).
- US EPA has adopted a recent framework for CRA as a tiered approach based on the level of details available on human health effects and exposure data (US EPA 2016).

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4) Existing frameworks for human health RA

- In EuroMix existing frameworks were summarised, to provide a structured overview and comparisons of the general principles and methods applied in different frameworks.
- 12 frameworks identified from literature searches have been developed by different organisations under different jurisdictions and regulatory settings.
- The purpose, scope, considerations for problem formulation and principles applied vary to some extent between these frameworks, but they also show many similarities.

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4) Existing frameworks for human health RA

1	**US EPA, 2000**	Supplementary Guidance for Conducting Health RAt of Chemical Mixtures
2	**US EPA, 2002b**	Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity
3	**ATSDR, 2004**	Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures
4	**SSC of the Norwegian Scientific Com. for Food Safety 2008**	Combined toxic effects of multiple chemical exposures
5	**EFSA PPR, 2008**	Opinion of the Scientific Panel on Plant Protection Products and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005.
6	**UK Interdepartmental Group on Health Risks from Chem., 2009**	Chemical Mixtures: A framework for assessing risks to human health
7	**WHO/IPCS (Meek et al., 2011)**	Framework for the RA of combined exposure to multiple chemicals
8	**SCHER/SCENIHR/SCCS, 2012**	Toxicity and assessment of chemical mixtures
9	**European Chemical Industry Council (Price et al., 2012)**	A decision tree for assessing effects from exposures to multiple substances
10	**BfR (Stein et al., 2014)**	Human health risk assessment from combined exposure in the framework of plant protection products and biocidal products
11	**ECHA, 2015a**	Guidance on the Biocidal Products Regulation. Vol. III Human Health- Part B Risk Assessment”
12	**US EPA, 2016**	Pesticide Cumulative Risk Assessment: Framework for Screening analysis purpose..

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

4) Existing frameworks for human health RA

1	**US EPA, 2000**	Supplementary Guidance for Conducting Health RAt of Chemical Mixtures
2	**US EPA, 2002b**	Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity
3	**ATSDR, 2004**	Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures
4	**SSC of the Norwegian Scientific Com. for Food Safety 2008**	Combined toxic effects of multiple chemical exposures
5	**EFSA PPR, 2008**	Opinion of the Scientific Panel on Plant Protection Products and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with ++ New OECD framework published soon pesticides in the frame of Regulation (EC) 396/2005.
6	**UK Interdepartmental Group on Health**	Chemical Mixtures: A framework for assessing risks to human health ++ Modifications of EFSA frameworks in an overarching EFSA Guidance
7	**WHO/IPCS (Meek et al., 2011)**	Framework for the RA of combined exposure to multiple chemicals
8	**SCHER/SCENIHR/SCCS, 2012**	Toxicity and assessment of chemical mixtures
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12	**US EPA, 2016**	Pesticide Cumulative Risk Assessment: Framework for Screening analysis purpose..

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5) The new US EPA approach

- In 2016, US EPA has published a guidance document "*Pesticide cumulative risk assessment: Framework for screening analysis purpose*"
- The framework:
  - provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach:
    1. starting with evaluation of available toxicological information and, if necessary,
    2. follow up with a risk-based screening approach.
  - supplements the existing guidance documents for establishing common mechanism groups and conducting cumulative risk assessments.
- US EPA will determine if available toxicological data for a group of chemicals may be used to suggest a candidate common mechanism group (CMG).
- An established CMG may be used to conduct a screening-level toxicology and exposure analysis to provide an initial screen for multiple pesticide exposure.
- A screening-level analysis of chemicals that have potential cumulative risks, allows a more efficient prioritization of cumulative risk assessments.

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5) The new US EPA approach

INITIAL REVIEW *(US EPA 1999)*
of toxicological profile, chemical structure, MOA/AOP

OPTION 1
No common mechanism;
No further CRA work necessary.

- thiocarbamates
- dithiocarbamates

OPTION 2
Evidence of common toxicological profile:
Candidate CMG; Proceed to screening level toxicology & exposure analysis

?

to be applied…

OPTION 3
Sufficient MOA/AOP information available for establishing key events & CMG

US EPA 2002a

- organophosphates
- N-methyl carbamates
- chloracetanilides
- triazines
- pyrethrins / pyrethroids

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Framework for CRA screening of pesticides (US EPA, 2016)

EuroMix

INITIAL REVIEW
of toxicological profile, chemical structure, MOA/AOP

OPTION 2
Evidence of common toxicological profile: Candidate CMG; Proceed to screening level toxicology & exposure analysis

Set a MOA/AOP hypothesis and estimate RPFs for the common toxic effect as in US EPA (2002a)

Screening level exposure & aggregate analysis (tiered approach)

Residential exposure analysis

Dietary exposure analysis

Compare cumulative risks to the level of concern (LOC; e.g. BMD_{10})

Cumulative risks < LOC
Cumulative screening is complete.

Cumulative risks > LOC
Additional toxicology and/or exposure data are necessary to further evaluate MOA/AOP.

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6) Summary → Conclusion

- The earlier reports from the US EPA (2000), ATSDR (2004), VKM (2008) and IGHRC (2009) describe step-by-step approaches, or decision trees.
  - Guidance how to progress through the mixture RA based on type of data.
- Approaches presented by the EFSA PPR (EFSA 2008), the WHO/IPCS (Meek et al. 2011) & BfR (Stein et al. 2014) are tiered frameworks, containing:
  - Simple deterministic (conservative/worst-case) assessments at lower tiers, &
  - Complex and quantitative probabilistic assessments at higher tiers.
- CEFIC (Price et al. 2012) and SCHER, SCENIHR, SCCS (2012) combined the tiered approach of WHO/IPCS approach with a stepwise decision tree.
- The US EPA guidance (2016) presents a tiered approach intended for screening of common mechanism groups (CMG) to determine if cumulative assessment should be applied. The guidance:
  - does not propose very refined risk assessment at higher tiers.
  - foresees refinement only if the CMG is carried forward.

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6) Summary → Conclusion

- Substantial differences and commonalities identified in EU and non EU countries.
- Implementation of legal mandates in each Regulation is considered necessary.
- No harmonized guideline available on how to conduct cumulative risk assessment.
- Development of a clear harmonized guidance on how to assess mixture toxicity in the respective Regulations are required in the EU, some documents are in progress.
- Different approaches for risk assessment in different Regulations should be based on the same terminology and harmonized principles.
- Risk assessment of different Regulations shall come to similar results.

- Several frameworks have been developed by different organisations under different regulatory settings with varying purpose and scopes.
- Foundations for the development of a common approach have been laid.
- More research is considered necessary, particularly on the implementation of new methodologies.

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6) Summary → Conclusion

- EuroMix aims to establish efficient and proven test strategies for human health risk assessment of chemical mixtures, including the required test methods and tools.
- In line with the existing concepts for CRA, the strategies to be developed within the EuroMix project will be mechanism-based.
- In the EuroMix project, in principle all chemical classes and all routes of combined exposure are considered.

- **The EuroMix toolbox will:**
  - include tiered approaches for exposure, hazard and risk assessment,
  - allow to choose different tiers for substances or other entities, according to the need as follows from a retain and refine approach.

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6) Summary → Conclusion

- A scientific paper reviewing cumulative risk assessment under current legislation, restricted to human health and chemicals in food is in preparation.
- It summarises current legislation, proposes future approaches for cumulative risk assessment and recommends an improvement of harmonised testing strategies.
- The expected contribution of EuroMix will be summarised.
  - Recommendations are expected for improvement of guidance and approaches focussing on pesticides in a data-rich situation, but do not aim for changes or amendments of the current legislation.

EuroMix can help to overcome the following issues in three areas:

1) Challenges related to grouping within on regulatory sector,

2) Aspects with regard to overarching mixtures,

3) Issues regarding harmonization.

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

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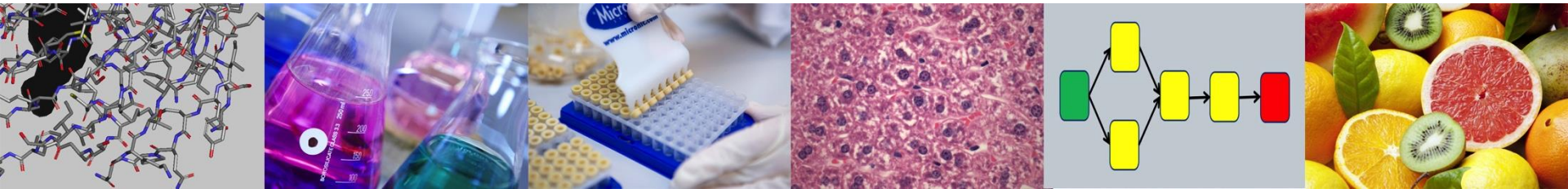
EuroMix participants

22 beneficiaries from 16 countries linked to international organisations including WHO, FAO and EFSA.
EuroMix is coordinated by RIVM.

Risk assessment of chemical mixtures: Implications for international harmonisation

EuroMix Stakeholder Workshop, 18 May 2017, Brussels, Belgium

Alan R Boobis
Imperial College London
(a.boobis@imperial.ac.uk)



EuroMix and international harmonisation

- One of the tasks of EuroMix is to organise a series of four international workshops, to explore options and potential limitations in the international acceptance of approaches to the assessment of combined exposures to chemicals
- This has obvious implications for those commodities where Maximum Residue Limits (MRLs) have to be established for residues, in that if very different approaches were to be used for combined risk assessment, the acceptability of MRLs could vary markedly

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

Key issues in international harmonisation

- Need to ensure consumer safety whilst not restricting international trade unnecessarily
- Assessments must be based on sound science (SPS agreement, etc)
- Scope of assessment?
  - Exposure sources, routes of exposure
  - Basis for grouping chemicals
  - Inclusion of non-chemical stressors?
- Practicalities of options available should the ‘risk cup’ be exceeded

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First Workshop on International Harmonisation

- First EuroMix Workshop on International Harmonisation on the Risk Assessment of Combined Exposures to Chemicals
  - 20-21 October 2016, Imperial College London, London W12 0HS
- Focus on the scientific issues involved and identify those topics of greatest priority for consideration at future workshops in this series
- 14 participants
  - Europe, North and South America, Australasia and North Africa
  - EFSA, JRC, OECD, FAO, US EPA, APVMA, RIVM, BfR, NIES (Japan)

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

Problem formulation

- Problem formulation by risk managers, in dialogue with risk assessors, is critical to fit-for-purpose assessments
  - In general, problem formulation is not well developed for the assessment of combined exposures to chemicals, leading to lack of transparency
  - Problem formulation should include the nature of the chemical sector, the regulatory context (legislative and policy considerations), the objective of the assessment, the timescale within which the assessment is required, the resources available, and the level of uncertainty that would be acceptable
  - This is particularly necessary if probabilistic approaches are used: which percentile (or percentiles) should be assessed within each tier
- A tiered approach should be used, to enable pragmatic decisions, but this will vary with the chemical sector
- Terminology for cumulative risk assessment should be harmonised to achieve a shared global understanding

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Definition of an exposure combination of concern

- What is the chemical domain of concern?
  - To what extent do “legislative/regulatory silos” influence this
- What is meant by co-exposure?
  - Is co-exposure likely within a relevant timeframe such that there is simultaneous internal (systemic) exposure or effect of the chemicals
  - Both toxicokinetics and toxicodynamics need to be taken into account
- Chemicals could be grouped based either on likelihood of co-exposure or biological characteristics
  - Choice will likely depend on problem formulation
  - Harmonisation should be possible, at least within a chemical sector

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Cumulative Assessment Groups (CAGs)

- There is a need to harmonise how chemicals are combined into assessment groups
- The rationale for an assessment group needs to be clearly defined, whatever its basis
- Agreement is needed on how information on modes of action/adverse outcome pathways should be taken into account in cumulative risk assessments
- While synergy is highly unlikely at exposures below the respective HBGVs, guidance should be developed to help consider the possibility synergy, as appropriate
- The use of data generated using non-animal methods is of considerable potential value, but will need careful integration into the entire weight-of-evidence

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Exposure assessment

- Refinements in exposure assessments are ongoing, with a shift in focus to probabilistic methods, and in particular to individual co-exposures
- Harmonisation of probabilistic exposure assessments will compliment efforts to harmonise how chemicals are combined into assessment groups.
  - The development of standardised templates for data input and an openly accessible computing platform for probabilistic exposure assessment, with links to other web services will help in harmonisation efforts

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Second Workshop on International Harmonisation

- 17 May 2017, Thon Hotel EU, Brussels, Belgium
- 19 participants
  - Europe, North and South America
  - DG SANTE, DG Environment, EFSA, JRC, OECD, WHO, Codex Alimentarius, US EPA, US FDA, RIVM, BfR
- Objectives:
- Understand current and upcoming legislative needs for cumulative risk assessment of chemicals (with a focus on assessment of chemicals (with a focus on the diet)
  - How this varies across chemical sectors (e.g. pesticides, additives) and the extent to which this might be harmonised
  - How this varies across geographical region 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

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Perspectives of Risk Managers

- 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?

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Perspectives of Risk Managers

- European (e.g. DG SANTE, DG Environment, EFSA), US (EPA, FDA), Codex and WHO on:
  - Pesticide risk management
  - Contaminant risk management
  - Additive risk management
  - Chemical mixture risk management, generally

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Potential contribution from EuroMix

- What can be offered by exposure and hazard assessment and scientific progress to achieve harmonisation
- Tiered assessment and EuroMix toolbox
- EuroMix approach to chemical grouping
  - AOP-wise testing
  - Assessment of uncertainty

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Conclusions

- Currently there is no overarching approach to cumulative risk assessment in Europe (or elsewhere) but work in now ongoing to explore this
- Approaches to cumulative risk assessment vary across sectors and with geography
- The most common approach for grouping chemicals is based on common structure and/or co-occurrence and/or designed function
- EuroMix will explore the implications of different exposure and toxicology choices in grouping chemicals

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National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

WAGENINGEN UR
For quality of life

folkehelseinstituttet

BfR
Bundesinstitut für Risikobewertung

anses
French agency for food, environmental and occupational health & safety

INERIS
controlling risks for sustainable development

UNIVERSITEIT GENT

freshfel
EUROPEAN FRESH PRODUCE ASSOCIATION

Karolinska Institutet

ГХК SGL

Imperial College London

NIJZ Nacionalni inštitut za javno zdravje

NATIONAL INSTITUTE OF PUBLIC HEALTH SZÚ

HSE
Health & Safety Executive

BENAKI PHYTOPATHOLOGICAL INSTITUTE

INRA
SCIENCE & IMPACT

UNIVERSITAT ROVIRA i VIRGILI

UNIVERSITÀ DEGLI STUDI DI MILANO

DTU Food
National Food Institute
DTU

ETH zürich

fera

matís

OVERVIEW OF THE OECD PROJECT ON ASSESSMENT OF COMBINED EXPOSURES TO MULTIPLE CHEMICALS

EuroMix Stakeholder Workshop - Brussels
18 May, 2017

Eeva Leinala
Principal Administrator
Hazard Assessment Programme and Risk Reduction Programme
Environment, Health, Safety Division
OECD

BETTER POLICIES FOR BETTER LIVES

OECD ENVIRONMENT, HEALTH AND SAFETY (EHS) PROGRAMME

35 Member countries, many partner countries and other stakeholders work together to develop and co-ordinate activities on chemical safety and biosafety on an international basis. One of the core aspects of the work relates to the Mutual Acceptance of Data.

The main objectives of the Programme are to:

•Assist OECD Member countries' efforts to protect human health and the environment through improving chemical safety and biosafety

•Make chemical control policies more transparent and efficient and save resources for government and industry; and

•Prevent unnecessary distortions in the trade of chemicals, chemical products and products of modern biotechnology.

http://www.oecd.org/chemicalsafety/

Methodologies for Hazard Assessment

- Development of harmonised novel methodologies for assessing the hazards of chemicals
  - ensure consistency
  - generate confidence and support for integrating novel tools and approaches into regulatory decision-making
  - increase the mutual acceptance of hazard assessments in order to avoid duplication of efforts

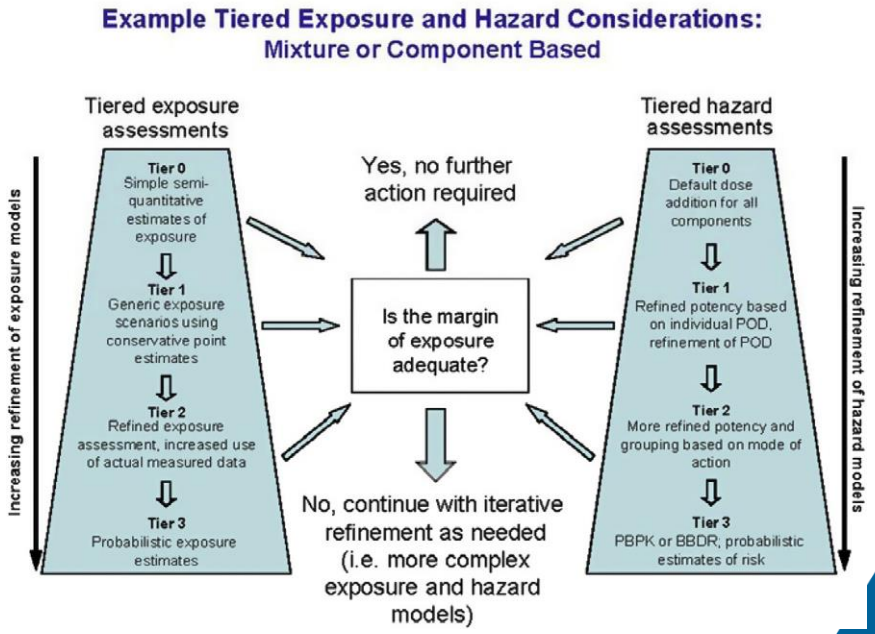
- Types of Output:
  - Case studies on using novel methods for regulatory decision-making
  - Integrated approaches to testing and assessment
  - QSAR Toolbox

http://www.oecd.org/chemicalsafety/risk-assessment/

Combined Exposures to Multiple Chemicals

- Human and ecological receptors are continuously co-exposed to multiple chemicals; however, chemicals have traditionally been regulated on a chemical-by-chemical basis.

- Project aims to discuss technical aspects to perform a hazard and exposure assessment for a combined exposure risk assessment and provide further guidance



Meek et al., 2011

Combined Exposures to Multiple Chemicals

- Objective:
  - Knowledge exchange on topics related to the assessment of risk from the combined exposure to multiple chemicals with the overall goal of moving towards technical convergence on scientific considerations between member countries.

- Organization:
  - Working Party on Hazard Assessment and Working Party on Exposure Assessment
  - Expert group consisting of representatives from Australia, Denmark, European Chemicals Agency, European Commission, Canada, France, Germany, Japan, Netherlands, Sweden, United States, NGOs and industry
  - Working Group on Pesticides will collaborate by reviewing draft documents

- Deliverables:
  - Guidance document focusing on considerations for assessment of risk from the combined exposure to multiple chemicals

- Timelines:
  - 2017

Four Main Topical Areas

- Development of problem formulation guidance on prioritization/triggers/scope for assessment of combined exposures
- Considerations regarding hazard characterization to inform assessment of combined exposures
- Considerations regarding co-exposure characterization to inform assessment of combined exposures
- Considerations regarding risk assessment of combined exposures using various approaches and articulating uncertainties in findings

Area 1 – Problem Formulation & Scoping

- Determining when to conduct an assessment of combined exposures to multiple chemicals
  - Evidence regarding co-occurrence/co-exposure
  - Evidence regarding common hazard

- Ways to scope an assessment
  - Endpoint-based assessments
  - Chemical-class assessments
  - Source-based assessments.
  - Formulation-based assessments
  - Population-based assessments
  - Disease-based assessments

Area 1 – Problem Formulation & Scoping

- Defining boundaries
  - Sources/uses for inclusion
  - Initial hazard boundaries
  - Regulatory program considerations in defining the scope

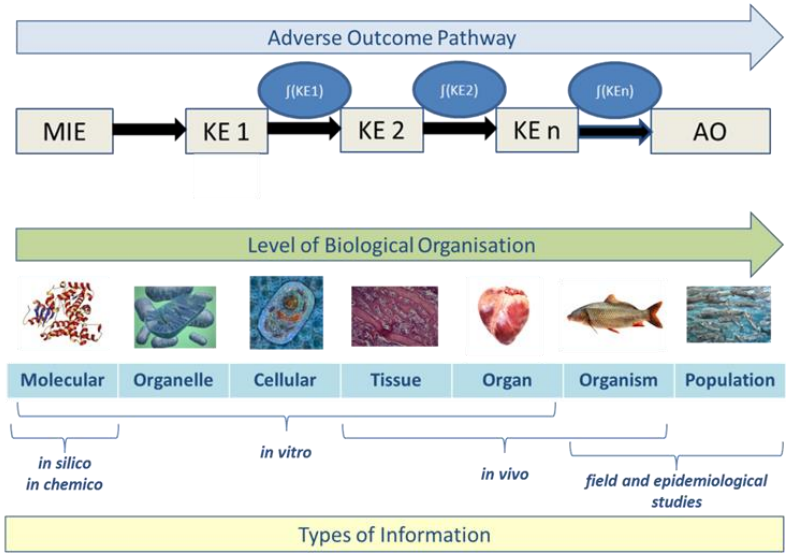
- Flexibility in scope as assessment progresses
- Data poor and data rich situations
- Pre-determining the 'tier' of the assessment at the scoping stage

Area 2 – Hazard Characterization

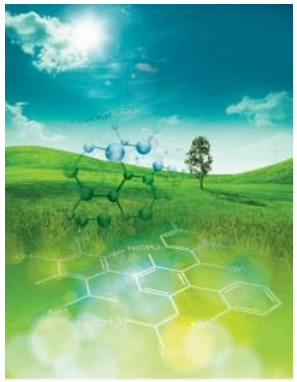
Area 2:

Considerations for hazard characterization to inform assessment of combined exposures

- Combining chemicals into hazard categories
  - Structural similarity
  - Biological response of interest
    - Same effect/target organ
    - Same adverse outcome pathway /mode of action
- Incorporating and integrating different data types
  - *in silico*, *in vitro*, *in vivo* methods
- Potency considerations
- Further development of tiers of hazard assessment and the data needs for moving through these tiers



Area 3 – Co-Exposure Characterization



- Factors affecting co-exposure
  - Sources, use patterns and lifecycle
  - Pathways and routes of exposure
  - Frequency and duration of exposure
  - Exposure target
  - Physico-chemical and fate properties

- Data types as evidence for co-exposure
- Data needs for moving through different tiers of exposure assessment

Area 4 – Risk Characterization

Considerations regarding risk assessment of combined exposures using various approaches and capturing and communicating uncertainties in findings

- Aims of risk characterisation of combined exposure
- Methodologies and Mathematical Approaches Applied for Risk Characterisation
- Tiered approaches to assessment
- Options for integrating the assessment of risks to human health effects and to the environment
- Uncertainty

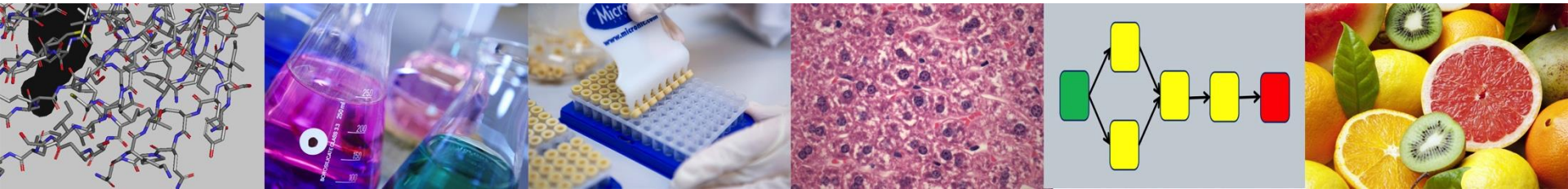
Further Information on OECD Chemical Safety Activities

- Website
  - http://www.oecd.org/chemicalsafety/
- EHS Programme Brochure
  - http://www.oecd.org/env/ehs/Environment-Health-Safety-Brochure.pdf
- EHS Newsletters (sign up to receive automatically)
  - http://www.oecd.org/chemicalsafety/environment-health-safety-news.htm

EuroMix – key tools and integration

EuroMix Stakeholder Workshop, 18 May 2017, Brussels, Belgium

Johanna Zilliacus, Institute of Environmental Medicine IMM, Karolinska Institutet

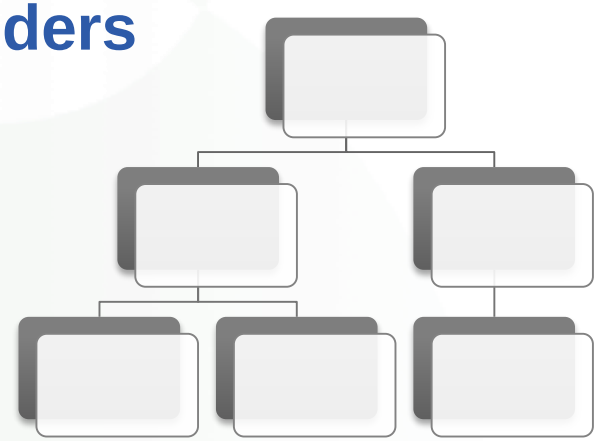


Web-based EuroMix tool and strategy

Aim is to develop

- web-based EuroMix tool for risk assessment of chemical mixtures
- strategy and guidance for risk assessment of chemical mixtures

Useful and acceptable for stakeholders



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EuroMix tool and strategy

Hazard

- Adverse outcome pathway (AOP) networks
- Grouping of chemicals
- Hazard data
- Kinetics

Exposure

- Probabilistic and other models
- Exposure data
- Identification of mixtures

Risk

- Margin of exposure and other approaches

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

Case studies

Three adverse outcomes

- Liver steatosis
- Craniofacial skeletal malformation
- Reproduction impairment mediated by estrogenic/anti-androgenic effect

Three groups of chemicals

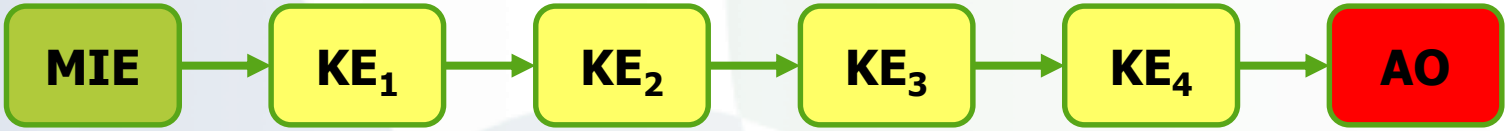
- Pesticides
- Food additives
- Contaminants

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

Adverse outcome pathways (AOPs) in mixture toxicology and risk assessment

EuroMix

- Structure knowledge on toxicity
- Identify assays for key events
- Group chemicals with similar toxicity
- Test assumptions on similar and dissimilar mode of action and interactions
- Test assumptions on relative potency factors
- Support development of risk assessment based on in vitro assays



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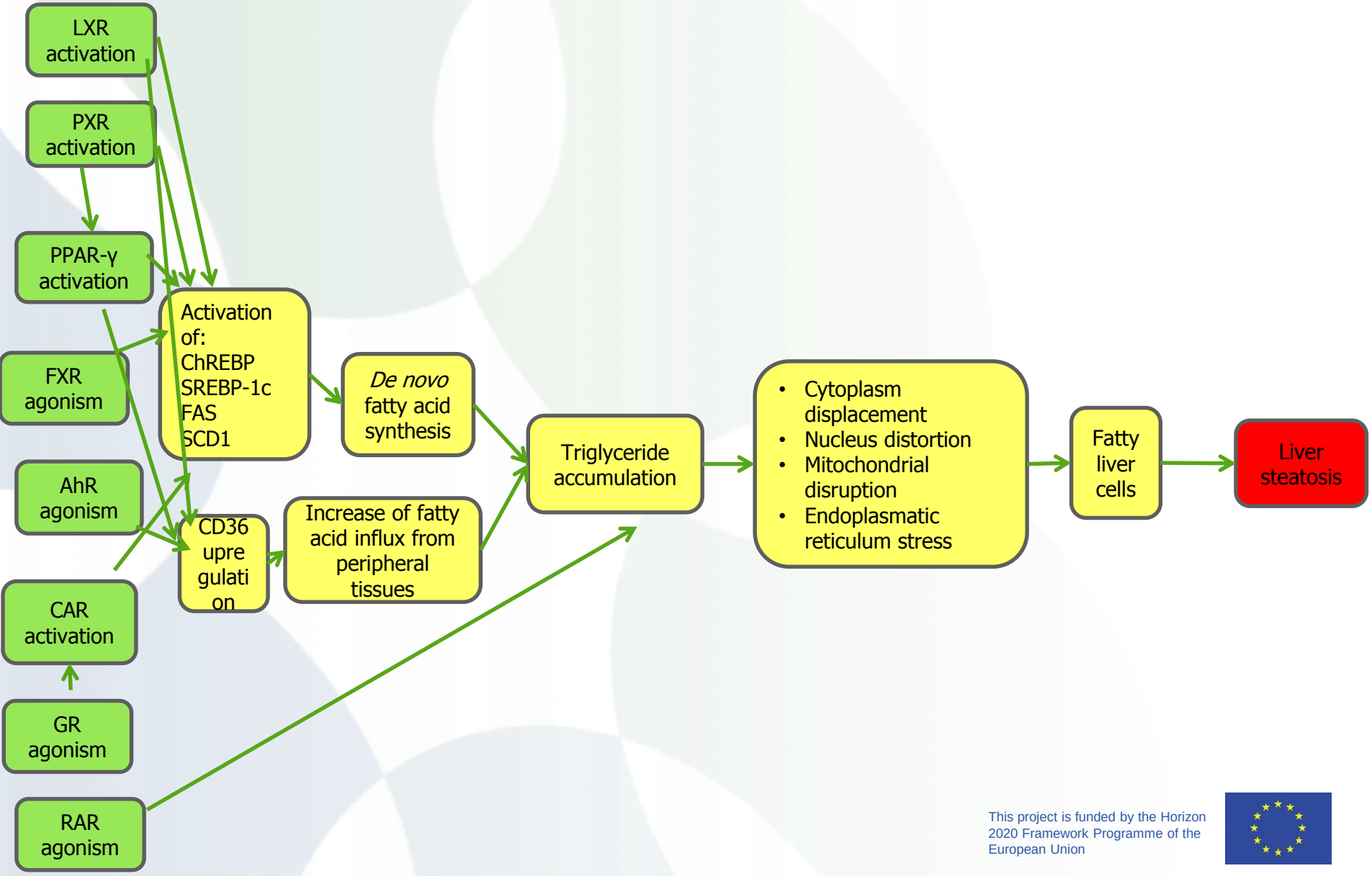
AOP network for liver steatosis



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Grouping of chemicals

- Which chemicals should be assessed together
  - Principles and criteria for grouping
  - Data needs for grouping
  - Uncertainties
- Which models for combining chemicals should be used
  - Dose addition
  - Response addition (independent action)

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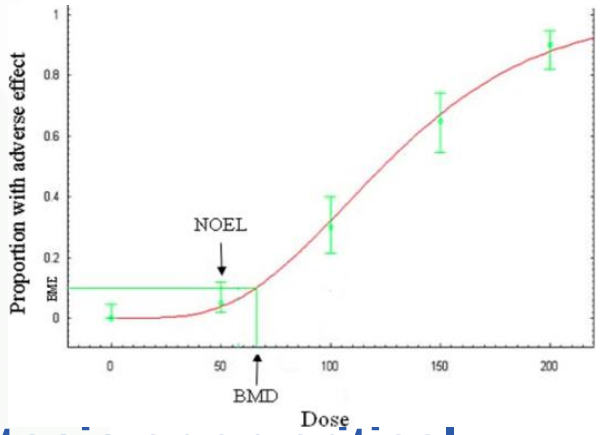
Hazard data

Toxicity of chemicals in the mixture

- In vivo data
- In vitro data
- In silico data
- No data



- Toxicity data on specific effect, e.g. liver steatosis or on critical effect
- Extrapolation from in vitro to in vivo data (IVIVE)
- QSAR to predict adverse outcome or key event (for grouping)
- Missing hazard data, use of TTC values (Cramer classes) or values derived from other chemicals in the group
- Benchmark dose modelling using PROAST software

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EuroMix toxicity database

- Inventory of chemicals
- Toxicity data
  - Liver toxicity
  - Developmental toxicity
  - Endocrine system
- Study design
- Measured endpoints
- NOAEL/LOAEL on specific effect and critical effect
- Use for case studies on grouping and assessment
-

Chemical category	Number of substances
Plant protection products	501
Biocidal products	34
Non-Intentionally Added Substances (NIAS) and Food Contact Materials migrants (FCM)	66
Mycotoxins	20
Alkaloids	40
Environmental pollutants	308
Others	224

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QSAR models to predict toxicity

- Predict adverse outcomes or specific key events
- Grouping of chemicals

- Test chemicals using QSAR models
- Criteria for grouping based on QSAR results
- Strength and weaknesses of models
- Prediction and uncertainty

QSAR models for liver toxicity
DEREK Hepatotoxicity Alert Score
MULTICASE Consensus Highest
Pizzo Alert Score
PADEL Predict Hepatotoxic
Toolbox rep.dose HESS alerts; Hepatox
Fera C4.5 model CDK descriptors
COSMOS Nuclear Receptor model
COSMOS LXR-binding Tanagra
OCHEM AhR activity
OCHEM PPARg activity

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Test assumptions of similar and dissimilar toxicity and interactions

EuroMix

Testing in EuroMix

- In silico, in vitro, In vivo

Three AOP networks

- Liver steatosis
- Craniofacial skeletal malformation
- Reproduction impairment mediated by estrogenic/anti-androgenic effect

In different combination:

- Two chemicals (A, B) with assumed similar toxicity
- One chemical (C) with assumed dissimilar toxicity

Compare result to dose additivity

- Any interactions (synergistic or antagonistic effects)
- Are dissimilar chemicals behaving as similar?

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Relative potency factors from different key events

Testing in EuroMix

Three AOP networks

Testing of single chemicals

Compare relative potency of chemicals tested at different key events

Can relative potency be derived from in vitro assays

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Exposure assessment

MCRA tool

- Probabilistic exposure modelling based on individual data on consumption and chemical concentrations
- Exposure assessment based on point estimates

- Dose addition model for chemicals with similar toxicity: Exposure to mixture is scaled based on each chemicals toxicity (relative potency factors)
- Develop and integrate models for response addition (independent action) for chemicals with dissimilar toxicity

- Missing exposure data for chemicals
- Derive exposure distribution based on other chemicals

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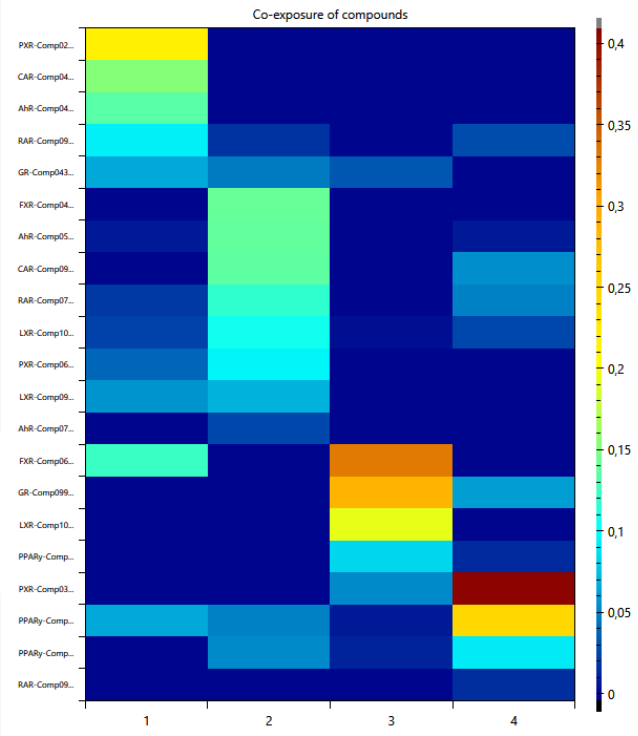
Identification of mixtures

Identify the mixtures of chemicals that a population is exposed to

- Based on patterns of food consumption, concentrations of chemicals in the food and the toxicity of the chemicals
- Module in the EuroMix tool box
- Use information for prioritisation of testing, refinement



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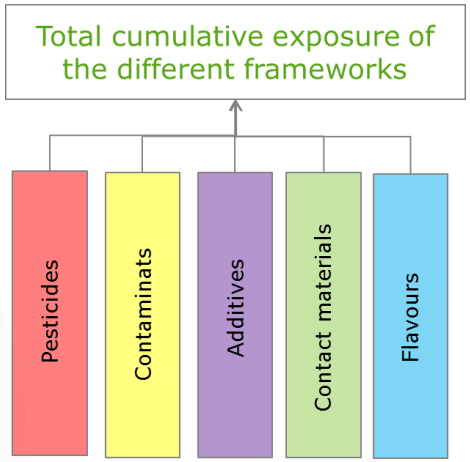
Risk assessment case studies for different groups of chemicals

- Pesticides
- Food additives
- Contaminants



Different regulatory frameworks

Different data availability: toxicity and exposure

Perform assessment for at least 1 of the 3 adverse outcomes

Steps:

- Group chemicals
- Identify or extrapolate hazard data
- Identify or extrapolate exposure data
- Assessment using point estimates or probabilistic assessment
- Combine assessment from different regulatory frameworks

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EuroMix strategy and guidance for risk assessment of chemical mixtures

- Problem formulation
- Grouping of chemicals
- Dose addition and response addition models
- Hazard data, relative potency factors and index chemical
- Benchmark dose modelling
- Extrapolation of missing hazard data
- In vitro to in vivo extrapolations
- Exposure assessment: Probabilistic and point estimate models
- Extrapolation of missing exposure data
- Identification of mixtures for prioritisation
- Uncertainty

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

Acknowledgements

Anna Beronius, KI
Amélie Crépet, ANSES
Annika Hanberg, KI
Andy Hart, Fera
Alfonso Lampen, BfR
Mirjam Luijten, RIVM
Angelo Moretto, UMIL
Ad Peijnenburg, WUR
Emiel Rorije, RIVM
Corinne Sprong, RIVM
Hilko van der Voet, WUR
Jacob van Klaveren, RIVM

And all other colleagues in EuroMix

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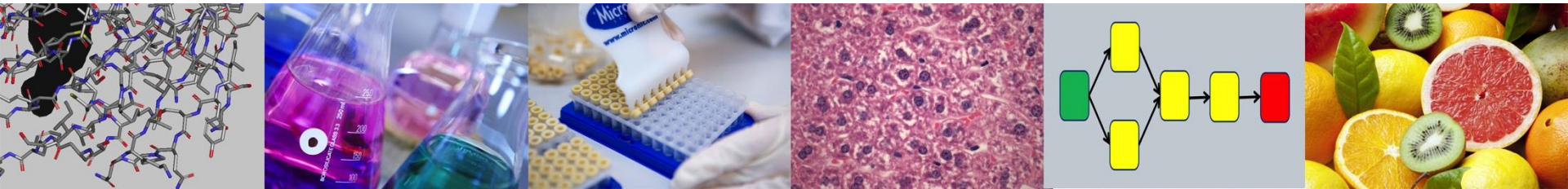
Criteria for grouping: challenges and approaches to uncertainties

EuroMix Stakeholder Workshop, 18 May 2017, Brussels, Belgium

Angelo Moretto
Dept. of Biomedical and Clinical Sciences
University of Milano, Italy



OUTLINE

- Generalities
- AOP approach
- Issues with grouping: data-rich vs data-poor compounds
- Quantifying uncertainties
- Exposure vs toxicology
- Conclusions

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Why do we want to group compounds?

Impossible to assess all compounds together

Not reasonable to assess compounds that

- **Do not interact**
- **Do not “SUM” their effect**

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Available evidence is that interaction either does not occur or it is of low relevance at doses that are at or below the No-Observable-Adverse-Effect-Level (NOAEL)

(EFSA, 2008; Boobis et al., 2011; ECETOC, 2012)

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Default assumption when dealing with combined exposures

- Exposure to each individual compound is below its limit (however defined)
- Dose additivity applies, unless proven otherwise

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What do we mean by “Common Toxicity”? (can the AOP approach help?)

Which criteria do we adopt for grouping?

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Adverse Outcome Pathway (AOP)

MIE – Molecular Initiating Event
KE – Key Event
AO – Adverse Outcome

an AOP is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect

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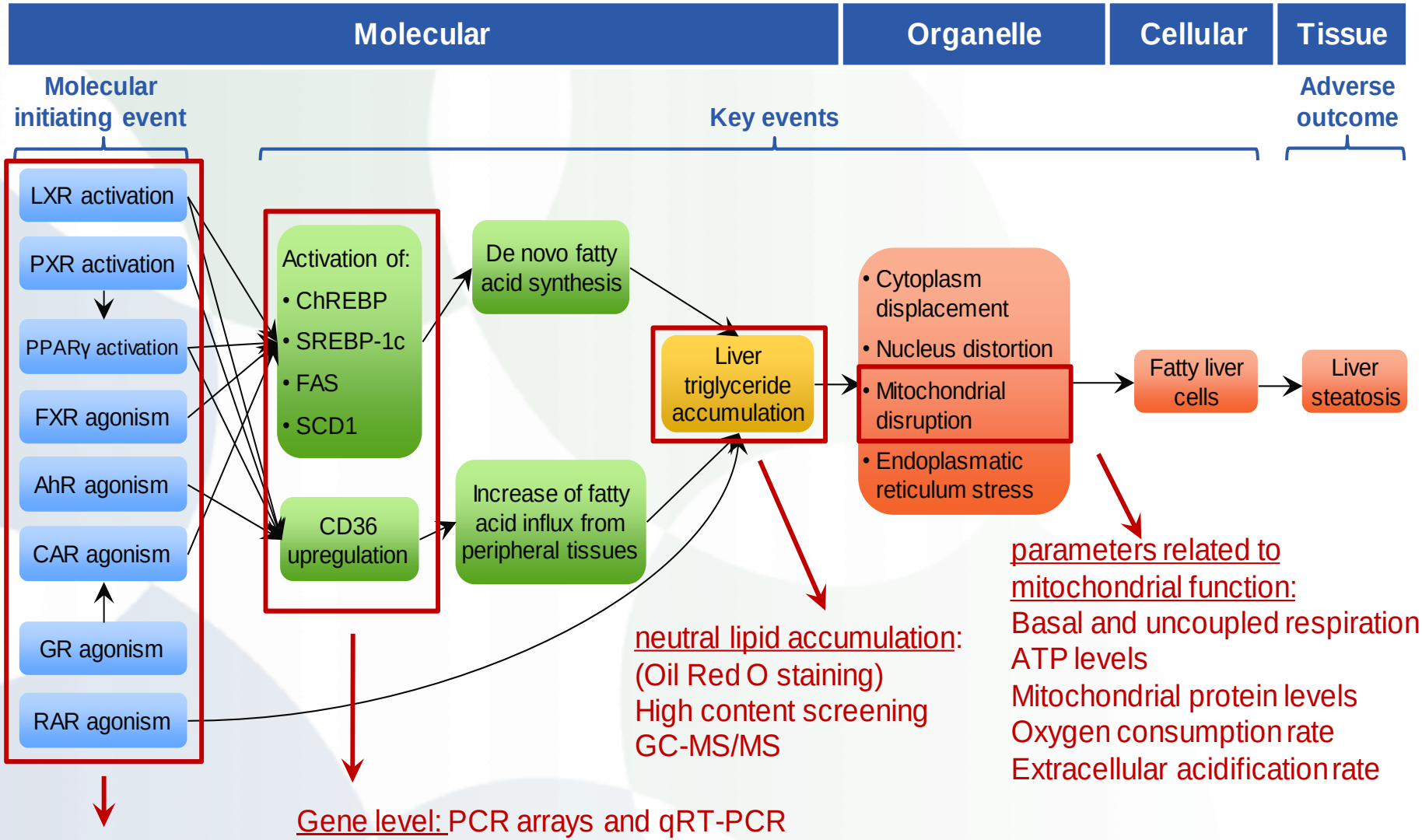

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Question being asked within EuroMix

Do effects on different MIEs/KEs “cumulate” at environmentally relevant doses(exposures)?

Approach:

(in vivo and in vitro) testing of mixtures of compounds that cause the same AO but with different MIEs and (partly) different KEs.

Use doses close the NOAEL

- to avoid interactions
- To allow for “below threshold” interaction with the molecular target(s)

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MIXTURE TESTING

IN VITRO: more experiments feasible

- test compounds with different AOPs (though converging to a common AO)
- test dose-addition

IN VIVO: fewer experiments available

- test compounds with same AOP (cmpd: A and B)
- test compounds with different MIE/KE (cmpd: C)
- combine A+B, A+C, B+C, A+B+C

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What do we mean by “Common Toxicity”? (can the AOP approach help?)

Which criteria do we adopt for grouping?

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- **When we have a lot of data (data rich, usually regulated, compounds)**

- **When we have few (do not have) data (data poor compounds, usually contaminants)**

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Data rich compounds: the example of pesticides

The EFSA APPROACH

Target organ (CAG level 1);
Phenotypic effect (CAG level 2);
Common MoA/AoP (CAG3),
with increasing details (CAG4)

Compounds included in a CAG regardless whether the AO is the critical AO

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EFSA Approach: the example of liver effects (1 among 15 organ systems)

- **CAG1 (common target organ): >200 compounds**
- **CAG2s (common phenotypic effect)**
  - **CAG 2A: hypertrophy**
  - **CAG 2B: fatty changes**
  - **CAG 2C: cell degeneration/cell death**
  - **CAG 2D: inflammation**
  - **CAG 2E: foci of cellular alteration**
  - **CAG 2F: neoplasm**
  - **CAG 2G: lesion of biliary epithelium**
  - **CAG 2H: porphyria**
  - **CAG 2I: cholestasis**
  - **CAG 2J: karyocytomegaly**
  - **CAG 2K: inclusions**

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Partial analysis of Liver CAG2s belonging to multiple CAGs that might be linked:

CAG2	Total	Unique CAG
A: hypertrophy	189	90 (48%)
B: fatty changes	106	22 (21%)
C: cell degeneration/cell death	139	19 (14%)

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Data-poor compounds: non-animal tests(data)

- Probability of belonging to a CAG with QSAR/molecular docking
- Distribution of PoDs within a given CAG (estimation of potency)
- Probability of belonging to CAG with *in vitro* data (AOP-based)
- (more uncertainties to be quantified: e.g. missing exposure data, non-detects, deviation from dose-additivity etc…..)

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Each point has a degree of uncertainty that needs to be addressed and quantified to the extent scientifically achievable (EFSA, CODEX).

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Ideal approach:

RETAIN and REFINE

but

NEED TO BALANCE WITH RESOURCES NEEDED/AVAILABLE

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What is ‘RETAIN AND REFINE’

- Retain all relevant chemicals in the assessment;
- (Using default values or distributions for missing data);
- Quantify all the uncertainties affecting them;
- Take account of the probability that they contribute.

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What is the best approach?

We need science-based pragmatism ("Enough precision to make a decision")

- **How much REFINEMENT?**
- **When/What RETAIN/EXCLUDE?**

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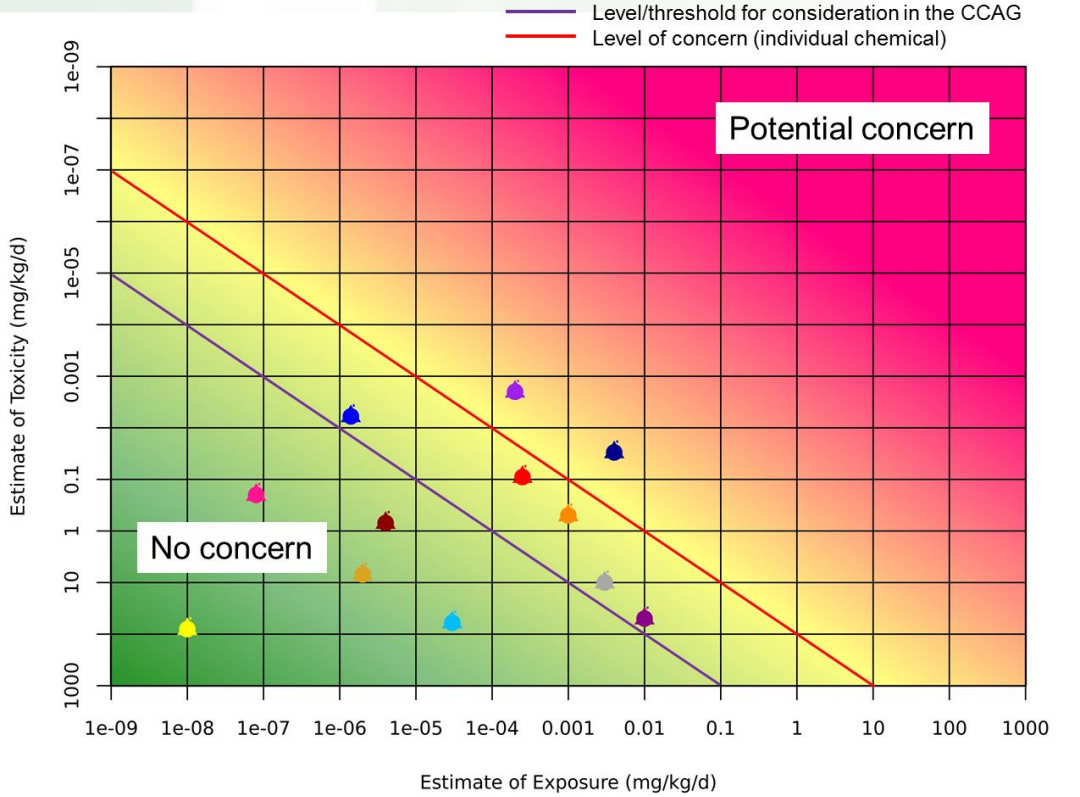
Chemicals in Common Chemical Assessment Group



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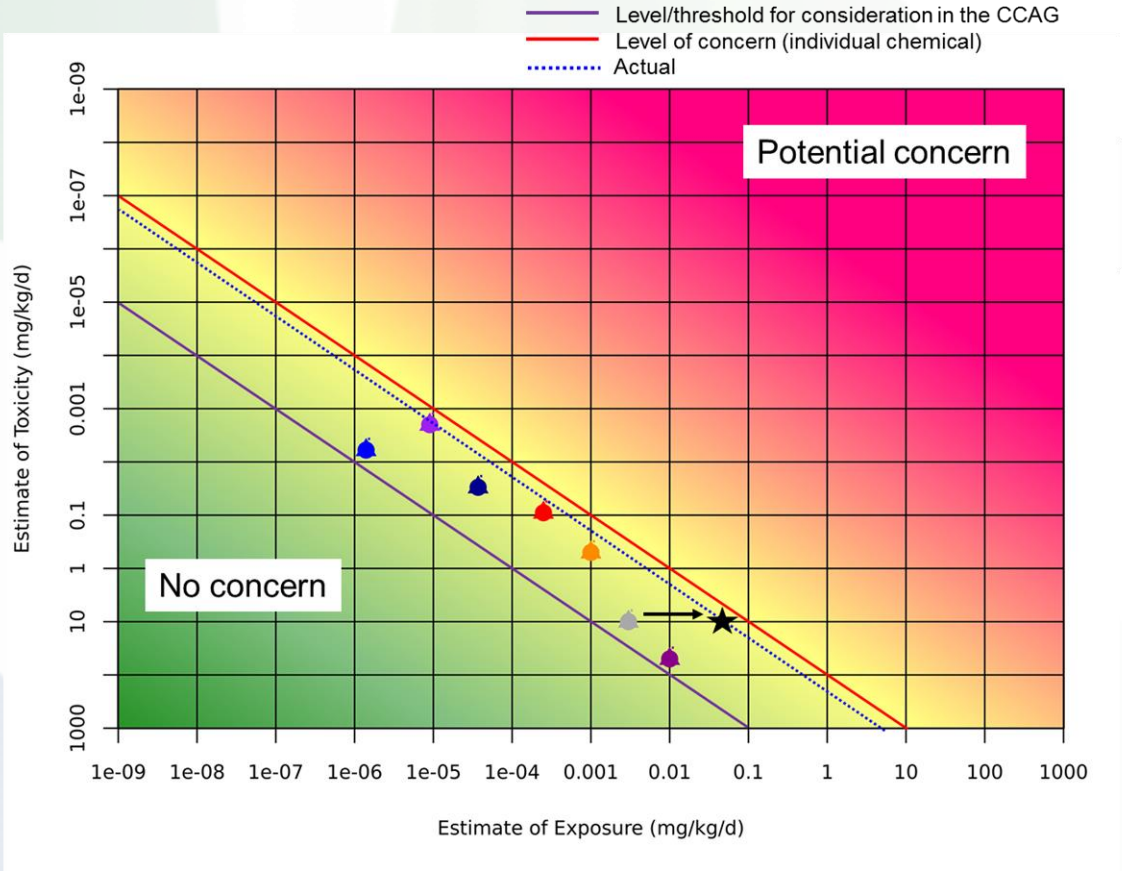
Chemicals in Common Chemical Assessment Group



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Exposure considerations for individual compounds:

“THRESHOLD FOR EXCLUSION/RETAINMENT”?

DATA-POOR COMPOUNDS

- “classical” TTC: threshold of saturation (MoE)?
- Comparison of probabilities of belonging to various CAGs and distribution of PoDs: threshold of ratios?

DATA-RICH COMPOUNDS

- The PoD for a CAG is NOT the critical PoD: thereshold of PoD ratio?
- Estimated MoE: threshold level?

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WHAT EUROMIX CAN OFFER

- Retain and refine;
- Run all uncertainties against proposed cut-off thresholds for exclusion;
- Compare results using proposed decision “exclusion” rules against the full “retain and refine” model;
- Assess which exclusion criteria can be accepted/acceptable (*appropriate balance* between precision and pragmatism);
- Propose a framework that is feasible.

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FINAL CONSIDERATIONS

Assessment of co-exposures is a difficult task.

It requires pragmatic solutions.

Discussion still ongoing on

- **how to refine grouping**
- **How much retain in the assessment**

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Thank you all

A very special thank you to Andy Hart

Special thanks to Ad, Alan, Annika, Emiel, Hilko, Jacob, Johanna, Johannes, Mark, Waldo

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Back-up slides

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Issues with data-poor compounds

- How to combine QSAR models that address the AO or specific Kes (or even MIEs)?
- How to incorporate in vitro data that identify different KEs and KERs?
  - How many of the KE and KER do we need to quantify?
  - Do we always need to identify and characterise the MIE?
- How do we model PoD distribution within a “small” CAG?

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Dealing with uncertainty

- EFSA and Codex specify that uncertainties in risk assessment must be addressed and quantified to the extent scientifically achievable
- For cumulative assessment, the uncertainties include:
  - The normal uncertainties for single-compound assessment
  - Additional uncertainty for data-poor compounds
  - Uncertainty about CAG membership, at each level
  - Uncertainty about assumptions, e.g. whether and how closely dose addition applies
  - How to combine the same effect caused by different Level 3 or 4 CAGs

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Dealing with uncertainty

- "Pragmatic" solutions might include:
  - Assume all the normal assumptions are precisely correct
  - Exclude chemicals which are unlikely to belong to a CAG
  - Exclude chemicals with missing data

- But:
  - The combined effect of the uncertainties is unknown
  - Excluding chemicals makes the assessment unconservative, to an unknown degree

- Only defensible for regulatory assessment if we can demonstrate an appropriate degree of conservatism
  - This requires comparison with a 'full' model

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Dealing with uncertainty

- EuroMix is exploring the feasibility and practicality of the RETAIN AND REFINE approach, including:
  - Developing methods to quantify uncertainty about missing data – e.g. TTC and QSAR for missing toxicity data
  - Developing methods to quantify uncertainty about CAG membership – based on QSAR (Level 2) and AOPs (L3-4)
  - Exploring how to combine different CAGs for the same effect
  - Providing default distributions to avoid users having to enter large quantities of data

- Initial progress is promising
- Aim to include completed methods in the EuroMix toolbox

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EUROMIX & OTHERS APPROACH

- Exposure-driven
- "Enough precision to make a decision"

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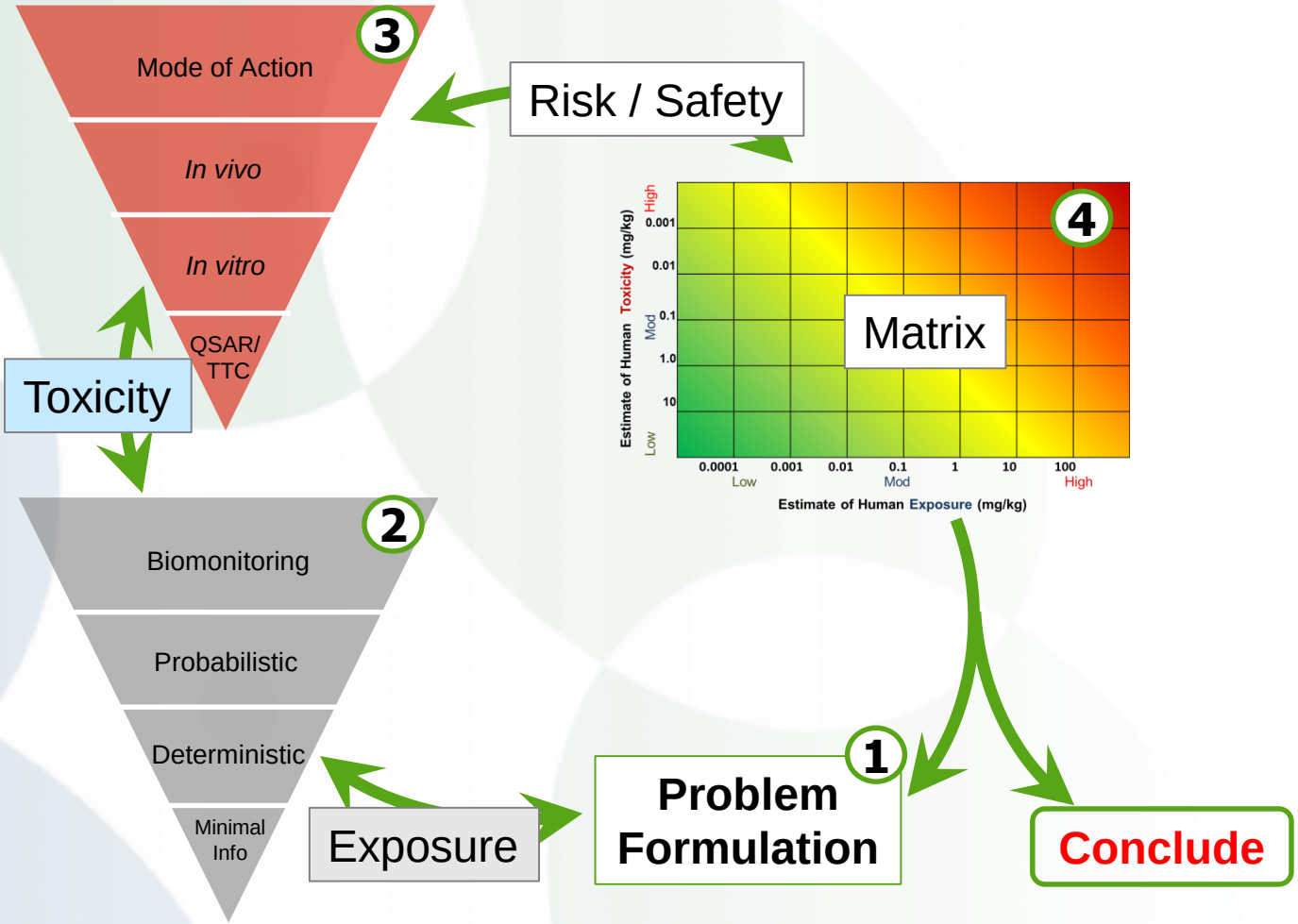
EuroMix



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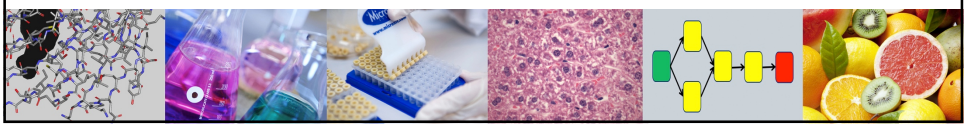
EuroMix

The in vitro bioassay tool box to investigate mixtures: liver steatosis as an example

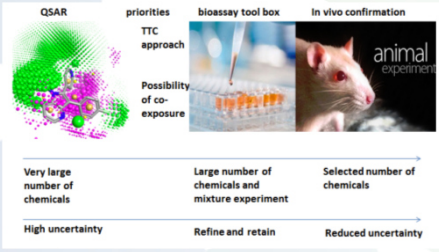
Prof. Dr. Dr. Alfonso Lampen
German Federal Institut for Risk Assessment (BfR)

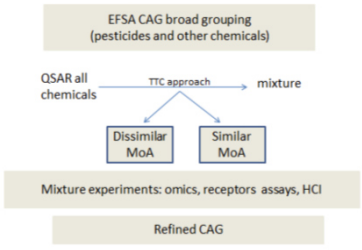


Objectives

EuroMix

- identify optimal *in-vitro* models for liver toxicity, developmental toxicity, endocrine effects
- define a bioassay tool box – to refine cumulative assessment groups (CAGs)
- test combined effects of chemicals having similar and dissimilar mode of action (MoA)
- identify optimal *in-vitro* test battery for grouping chemicals and for predicting mixture effects





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EuroMix: endpoints and CAGs

EFSA: grouping of chemicals into Cumulative Assessment Groups (CAGs)

- aligning EFSA methodology with specific endpoints in EuroMix:

EuroMix	EFSA CAG
liver toxicity	Liver – Fatty changes
developmental toxicity	Reproductive and developmental toxicity - Malformation
endocrine effects	Reproductive and developmental toxicity

- linking mode of action to endpoints as well as *in-vitro* data to *in-vivo* outcome
  → concept of Adverse Outcome Pathways (AOP)

liver toxicity ⟶ AOP for liver steatosis

developmental toxicity ⟶ AOP for cranio-facial malformation

endocrine effects ⟶ AOP for androgenic/estrogenic disruption

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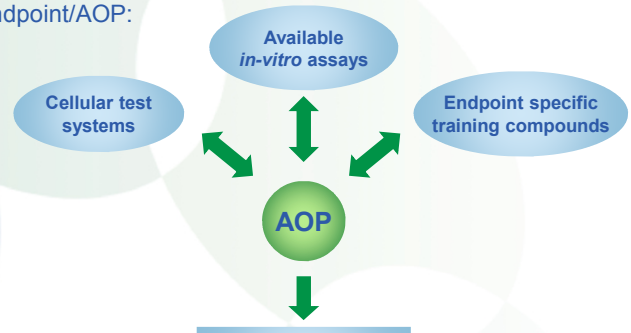
Identification of optimal *in- vitro* approaches

For each endpoint/AOP:



Liver: 13 assays
Developmental: 4 Assay
Endocrine: 4 Assays

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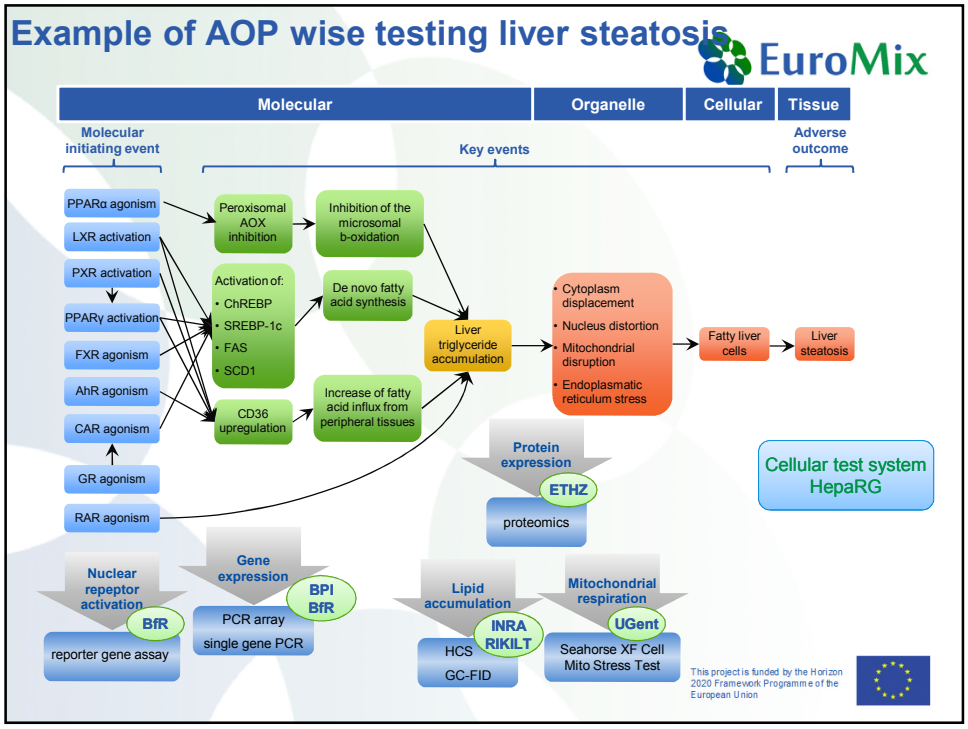
Example of AOP wise testing liver steatosis
EuroMix
Molecular
Organelle
Cellular
Tissue
Molecular initiating event
Key events
Adverse outcome
PPARα agonism
LXR activation
PXR activation
PPARγ activation
FXR agonism
AhR agonism
CAR agonism
GR agonism
RAR agonism
Peroxisomal AOX inhibition
Inhibition of the microsomal b-oxidation
Activation of:
• ChREBP
• SREBP-1c
• FAS
• SCD1
De novo fatty acid synthesis
CD36 upregulation
Increase of fatty acid influx from peripheral tissues
Liver triglyceride accumulation
• Cytoplasm displacement
• Nucleus distortion
• Mitochondrial disruption
• Endoplasmatic reticulum stress
Fatty liver cells
Liver steatosis
Protein expression
ETHZ
proteomics
Cellular test system HepaRG
Nuclear repeptor activation
BfR
reporter gene assay
Gene expression
BPI BfR
PCR array
single gene PCR
Lipid accumulation
INRA RIKILT
HCS
GC-FID
Mitochondrial respiration
UGent
Seahorse XF Cell Mito Stress Test
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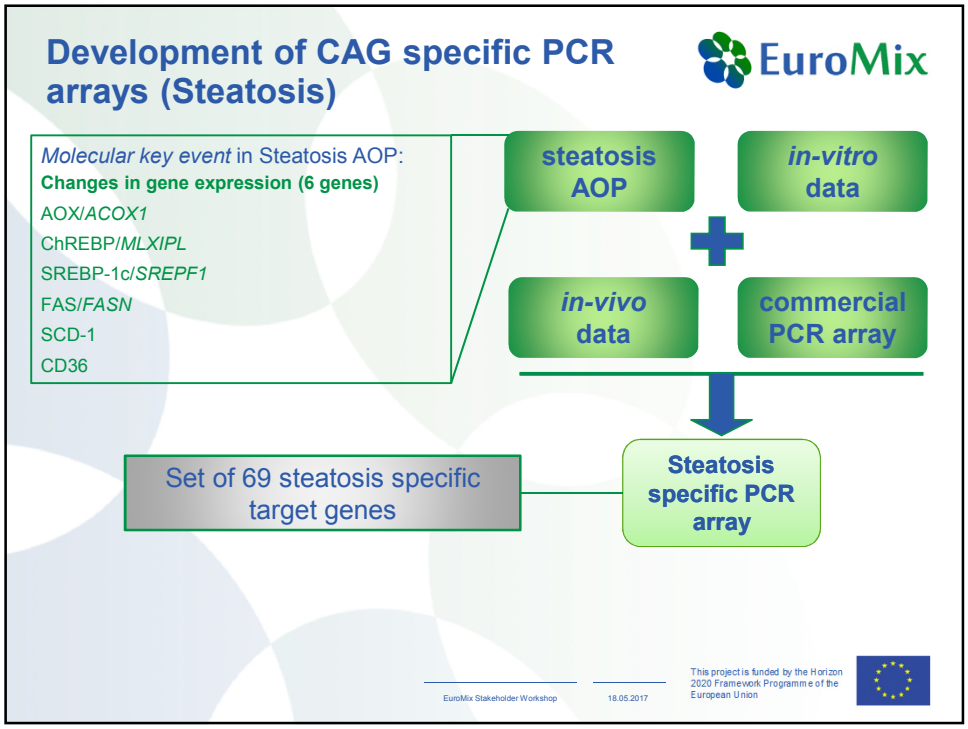
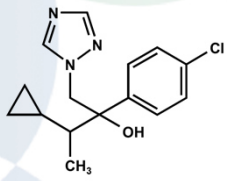

Development of CAG specific PCR arrays (Steatosis)
EuroMix
Molecular key event in Steatosis AOP:
Changes in gene expression (6 genes)
AOX/ACOX1
ChREBP/MLXIPL
SREBP-1c/SREPF1
FAS/FASN
SCD-1
CD36
steatosis AOP
in-vitro data
in-vivo data
commercial PCR array
Set of 69 steatosis specific target genes
Steatosis specific PCR array
EuroMix Stakeholder Workshop
18.05.2017
This project is funded by the Horizon 2020 Framework Programme of the European Union

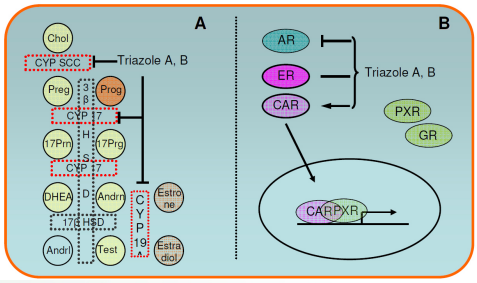
Test concept: first step

EuroMix

training compounds → Proof of Principle: AOP → AOP

Cyproconazole





- Widely used fungicide
- Mode of action: Inhibition of the ergosterole synthetase (CYP51)
- Known target organs (chronic exposure): liver; endocrine system

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Test concept: second step

EuroMix

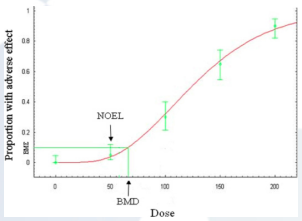
training compounds → Proof of Principle: AOP → AOP

Proof of Principle: similar/dissimilar MoA

test compounds

single compounds ⟷ combinations

- dose response curves
- Relativ Potency Factors (RPF)



- equipotent mixtures
- dose additivity?
- interactions?

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

Selection of compounds for mixture experiments

EuroMix

Aim: Identify mixtures for *in-vitro* and *in-vivo* testing

List of relevant mixtures (WP2/WP5) based on hazard and exposure

Select 3 compounds (A, B, C)
- A , B: similar MoA
- C: dissimilar MoA to A and B

Tentative information about MoA:
ToxCast Database
Literature

***In-vitro* mixture testing**
binary, ternary combinations

***In-vivo* mixture testing**
binary, ternary combinations

PB-PK modelling

confirmation

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

WP5 mixtures (…from exposure data)

EuroMix

Table 2: CAG: Steatosis, Chronic, RPFs, Adults (Subpopulation, with MCR)

French : 156 individuals		Netherlands : 109 individuals		UK : 280 individuals		Greece: 84 individuals		Czech Republic: 1666 individuals	
Variance : 66.2%		Variance: 64.8%		Variance : 70.7%		Variance: 66.2%		Variance: 59.6%	
Name	SNMU weight	Name	SNMU weight	Name	SNMU weight	Name	SNMU weight	Name	SNMU weight
Carbendazim and benomyl (RD)	21%	Carbendazim and benomyl (RD)	24%	Carbendazim and benomyl (RD)	19%	Ethoprophos	24%	Carbendazim and benomyl (RD)	21%
Thiacloprid	16%	**Cypermethrin (RD)**	18%	**Thiacloprid**	15%	Carbendazim and benomyl (RD)	22%	**Deltamethrin (RD)**	10%
Imazalil	10%	**Iprodione**	15%	**Imazalil**	14%	**Cypermethrin (RD)**	13%	**Imazalil**	9%
Cypermethrin (RD)	9%	**Deltamethrin (RD)**	8%	**Deltamethrin (RD)**	11%	Abamectin (RD)	12%	Difenoconazole	8%
Deltamethrin (RD)	9%	**Thiacloprid**	5%	**Cypermethrin (RD)**	11%	Thiametoxam (RD)	6%	Propiconazole	7%
Thiametoxam (RD)	6%	**Imazalil**	5%	Thiametoxam (RD)	8%	Metalaxyl and metalaxyl-M (RD)	5%	**Thiacloprid**	6%

Present in 7 countries
Present in 5-6 countries
Present in 3 countries
Present in 1 country

Tested in vitro

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

Conclusions

- the in vitro toolbox is working; it is possible to identify compounds causing liver steatosis
- testing of mixtures is ongoing;
- dose addition was measured for similar MoA but also for compounds originally expected dissimilar MoA such as thiacloprid (very weak nuclear receptor agonist, PXR and PPARγ) and fenpyroximate (PXR agonist)… further studies needed
- therefore, it is difficult to identify dissimilar acting compounds
  (ongoing tests)

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

EuroMix participants

22 beneficiaries from 16 countries linked to international organisations including WHO, FAO and EFSA.
EuroMix is coordinated by RIVM.

Harmonisation of Human and Ecological Risk Assessment of Chemical Mixtures at EFSA

Jean Lou Dorne
Scientific Committee and Emerging Risks Unit

Christer Hogstrand
Kings college London

EUROMIX 18 May 2017

efsa
European Food Safety Authority


Intentional Mixtures ?
Coincidential Mixtures ?
Be careful
with this one
(unpublished
observation)

TOR SUBJECTED TO PUBLIC CONSULTATION

25 October 2016

Cross-cutting science

print

Tweet

Share

Share

Chemical mixtures: help us define 'MixTox' before work starts

People, animals and the environment can be exposed to multiple chemicals from a variety of sources. EFSA is launching a ground-breaking initiative to propose methods for carrying out risk assessment for this complex issue. We are calling on stakeholders from science and civil society in Europe and beyond to help shape this work before it starts.

Building on recent international developments and previous work at EFSA on pesticides and contaminants, our scientists have started to develop new approaches for assessing risks to humans and the environment from exposure to multiple chemicals in the food chain: "chemical mixtures" and their "cocktail effects".

EFSA is already developing methods to assess combined toxicity for groups of

Subject area

Cross-cutting science

Scientific Committee

Scientific Committee

Related topics

Chemical mixtures

Related News

OpenFoodTox: EFSA's new one-click tool for information on chemical hazards

Cross-cutting science, DATA

published: 18 Jan 2017

Endocrine disruptors: EFSA asks

New Terms of Reference: February 2017

- EFSA requests SC to develop GD on Harmonised RA methodologies for HRA and ERA of combined exposure to multiple chemicals

- GD overarching for work EFSA panels/scientific advisory bodies dealing chemical RA within/across regulatory applications/sectors

- Review definitions/ methods/ tools for different RA contexts and develop harmonised framework(s) supported by a consistent terminology.

- GD start from first scientific principles for all relevant steps i.e. problem formulation, hazard identification and characterisation, exposure assessment, risk characterisation and uncertainty analysis.

New Terms of Reference II

- For each step, tiered approaches developed where feasible (purpose, data availability, resources) include decision points/ associated assumptions (e.g. dose addition and deviation including interactions)
- GD explicitly address component-based + whole mixture, application of uncertainty factors in mixture RA context
- Where harmonisation HRA/ERA not possible/relevant (e.g. state of science, regulatory framework) discuss

New Terms of Reference III

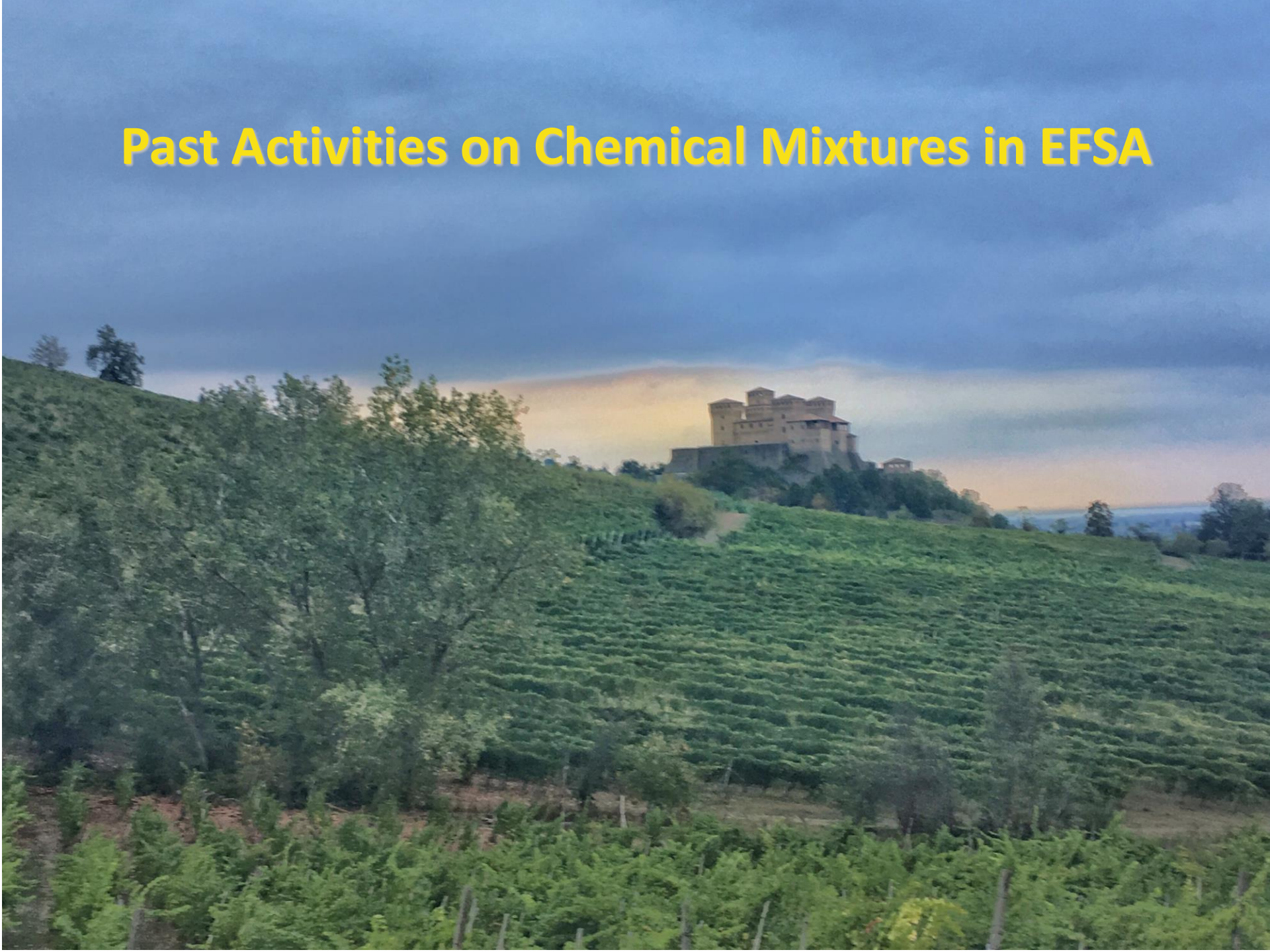
- GD start/build on European (e.g. EC, ECHA, EFSA) /international (e.g. US-EPA, WHO, OECD) terminology, methods/frameworks ensure inter-agency cooperation, consistency, no duplication
- Case studies annexed in GD explore feasibility/spectrum applications of proposed methods/approaches HRA and ERA
- In line with EFSA's TERA, draft GD will be subject to Public Consultation

TIMELINE

- **February 2016**: Nomination of WG by the Scientific Committee
- **June 2016**: First WG meeting
- **November 2016**: Launch Public Consultation of the ToR
- **January 2017:** Draft technical report on outcome of the Public Consultation
- **December 2017**: Two technical reports on tiered approaches for ecological and human risk assessment of combined exposure to multiple chemicals
- **June 2018**: Draft GD and Public Consultation
- **December 2018**: Adoption of the draft GD

- **Spring 2019:** International workshop

Past Activities on Chemical Mixtures in EFSA



MIXTURES @EFSA PPR: HUMAN AND ECO RA

- **HUMAN**

EFSA PPR (2008) Suitability of existing methodologies assessing cumulative and synergistic risks from pesticides to human health to set MRLs (Regulation (EC) 396/2005)

EFSA PPR (2009) Assessment of cumulative human health effects of Triazole fungicides.

EFSA (2013) Identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile.

- **ECO**

EFSA PPR (2012) Science behind the development of a risk assessment of Plant Protection Products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees).

dealing with mixture toxicity/synergistic effects

European Food Safety Authority

EFSA Journal 2013;11(7):3313

SCIENTIFIC REPORT OF EFSA

International Frameworks Dealing with Human Risk Assessment of Combined Exposure to Multiple Chemicals[1,]

European Food Safety Authority[2,3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The development of harmonised terminology and frameworks for the human risk assessment of combined exposure to multiple chemicals ("chemical mixtures") is an important area for EFSA and a number of activities have already been undertaken, i.e. in the fields of pesticides and contaminants. The first step prior to a risk assessment of combined exposure to multiple chemicals is problem formulation defining the relevant exposure, hazard and population to be considered. In practice, risk assessment of multiple chemicals is conducted using a tiered approach for exposure assessment, hazard assessment and risk characterisation. Higher tiers require increasing knowledge about the group of chemicals under assessment and the tiers can range from tier 0 (default values, data poor situation) to tier 3 (full probabilistic models). This scientific report reviews the terminology, methodologies and frameworks developed by national and international agencies for the human risk assessment of combined exposure to multiple chemicals and provides recommendations for future activities at EFSA in this area.

KEY WORDS

risk assessment, human health, combined exposure, multiple chemicals, chemical mixtures, frameworks, methodology

RECOMMENDATIONS: EXPOSURE ASSESSMENT

- **Occurrence Data collection for multiple priority chemicals in food samples**
  - ✓ Monitoring/total diet studies for priority chemicals id using either exposure, hazard-based criteria, susceptible populations, or legislation (MRLs)
  - ✓ Multi-agency collaboration to gather exposure data via other routes (inhalation…)
  - ✓ Investigation co-occurrence multiple substances in individual food samples and correlations of co-occurrence for acute/chronic exposure (mean/95thpercentiles)

- **Develop case /training sets comparing deterministic vs probabilistic methods**
  - ✓ Characterise dietary exposure for chemicals of priority: occurrence data and existing/other databases/tools (EFSA Databases, total diet studies, monitoring…).
  - ✓ Methods/guidelines adapted to co-occurrence of chemicals and need of exposure assessment (left-censored data, acute/chronic exposure, regulated versus contaminants)

- **Develop methods for aggregate exposure assessment**

RECOMMENDATIONS: HAZARD ASSESSMENT

Support harmonisation of methodologies with regards to hazard assessment

- **Scientific basis for whole mixture approach**
  - ✓ Methods needed: large fraction of un-id chemicals
  - ✓ Evidence (stat/chemical/tox) similar WM- use as surrogate for other WM.

- **Scientific basis for setting assessment groups**
  - ✓ Further exploration criteria settings Assessment groups (AGs) e.g.MOA both TK and TD aspects (interspecies differences/ human variability)
  - ✓ Appropriateness generalised methods set AGs using decision criteria/WoE approach different scenarios (common/unknown MOA, different MOA…)

- **Data Collection TK/TD using Systematic Review**
  - ✓ Critical assessment of additivity as most commonly observed.

SCIENTIFIC COLLOQUIUM SERIES

APPROVED: 25 March 2015

PUBLISHED: 31 March 2015

Summary Report

EFSA Scientific Colloquium 21

Harmonisation of human and ecological risk assessment of combined exposure to multiple chemicals

11-12 September 2014

Edinburgh, UK

European Food Safety Authority

Data Collection

EXTERNAL SCIENTIFIC REPORT

APPROVED: 8 December 2014 PUBLISHED: 31 March 2015

Data collection on toxicokinetic and toxicodynamic interactions of chemical mixtures for human risk assessment

LASER Analytica

Nadia Quignot, Camille Béchaux, Billy Amzal

Abstract

There is an increasing need to develop harmonised terminology, approaches and frameworks for the human risk assessment of combined exposure to multiple compounds. A number of activities have already been undertaken by EFSA, notably in the fields of pesticides and contaminants. This project aimed at providing quantitative information on combined effects of multiple compounds to support evidence-based hazard assessment. The first step was to record and collect, using extensive literature searches/systematic review methods, Pharmaco/Toxicokinetic (PK/TK) and Pharmaco-dynamic/Toxicodynamic (PD/TD) information on potential interactions between selected compounds. *In vivo* PD/TD and *in vitro* and *in vivo* PK/TK data were collected mostly for binary mixtures of pharmaceuticals (substrates of major routes of metabolism and known inhibitors/inducers) and major classes of regulated compounds and contaminants relevant to food safety. All data were then consolidated via meta-analyses to quantify magnitudes of interaction and their inter-individual variability for both TK and TD dimensions. Overall, this report illustrates application of systematic data collection for both human TK and TD aspects of multiple compounds to quantify magnitudes of metabolic and toxicological interactions respectively. Further analyses are recommended to integrate such magnitude of interaction and variability data in human hazard assessment of multiple compounds.

Key words: Combined effects, Interaction, Hazard assessment, Mixture, Pharmaco/Toxicodynamics, Pharmaco/Toxicokinetics

EXTERNAL SCIENTIFIC REPORT

APPROVED: 24 July 2015

PUBLISHED: 30 July 2015

Data collection on Combined Toxicity of Multiple Chemicals for Animal Health and Ecological Risk Assessment

LASER Analytica

Nadia Quignot, Audrey Grech, Billy Amzal

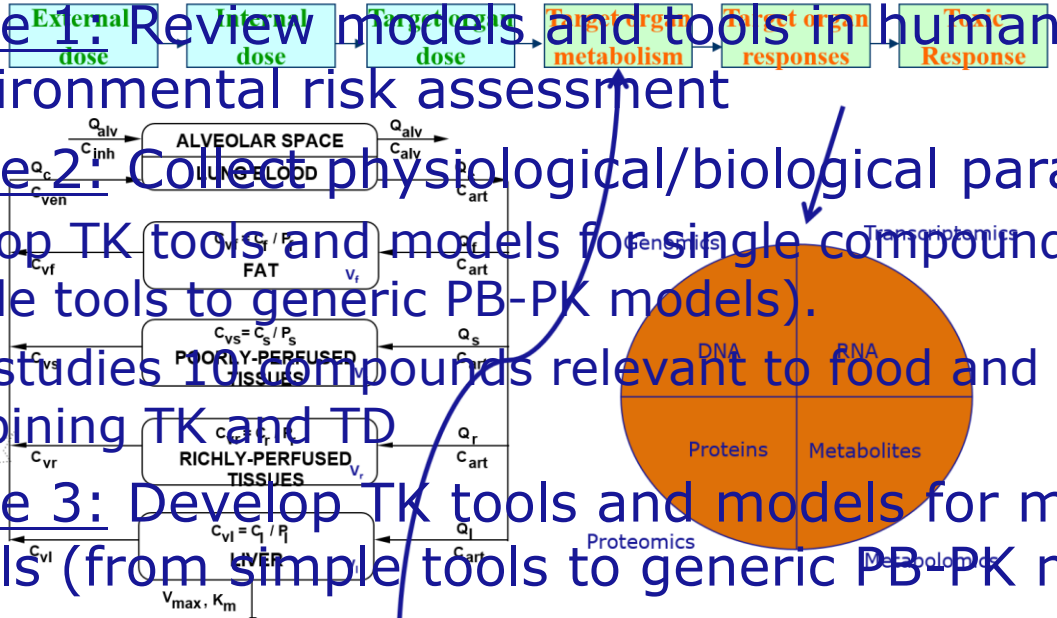
Abstract

There is an increasing need to develop harmonised frameworks and methods for the risk assessment of combined exposure to multiple chemicals. A number of activities have already been undertaken by EFSA, notably in the fields of pesticides and contaminants. This project aims at searching for, reviewing, collecting and synthesizing the published data on combined effects of multiple chemicals in more than 50 species of veterinary and ecological relevance, using extensive literature searches. The taxonomical hierarchy for the literature searches was very wide ranging from bacteria, fungi, invertebrates and vertebrates (amphibians, reptiles, birds, cats, cattle, deers, goats, horses, minks, pigs, sheep, fishes, spiders, ephemeroptera, hymenoptera, diptera, earthworms, Caenorhabditis elegans, molluscs, mites, crustacea, odonata, orthoptera, collembola, coleoptera, blattids, plants, cyanobacteria, proteobacteria, fungi). *In vivo* toxicity data were extracted from 199 publications representing 3,074 individual studies on pesticides, environmental contaminants, food-related products, hormones, metals, mycotoxins and pharmaceuticals. The magnitudes of interaction following acute and chronic exposure to multiple chemicals were consolidated via meta-analysis and expressed as mean effect ratios between single and multiple chemicals. Overall, this report illustrates how systematic published data collection and synthesis can support hazard characterisation of combined toxicity of multiple chemicals. Further work is proposed to compare the toxicity datasets for which statically significant interactions have been reported with chemical-specific reference points

TK AND MULTIPLE CHEMICALS : TOOLS AND MODELS

Procurement call on the integration of TK tools in chemical risk assessment applied to human health, animal health and the environment aiming to develop models for single and multiple chemicals

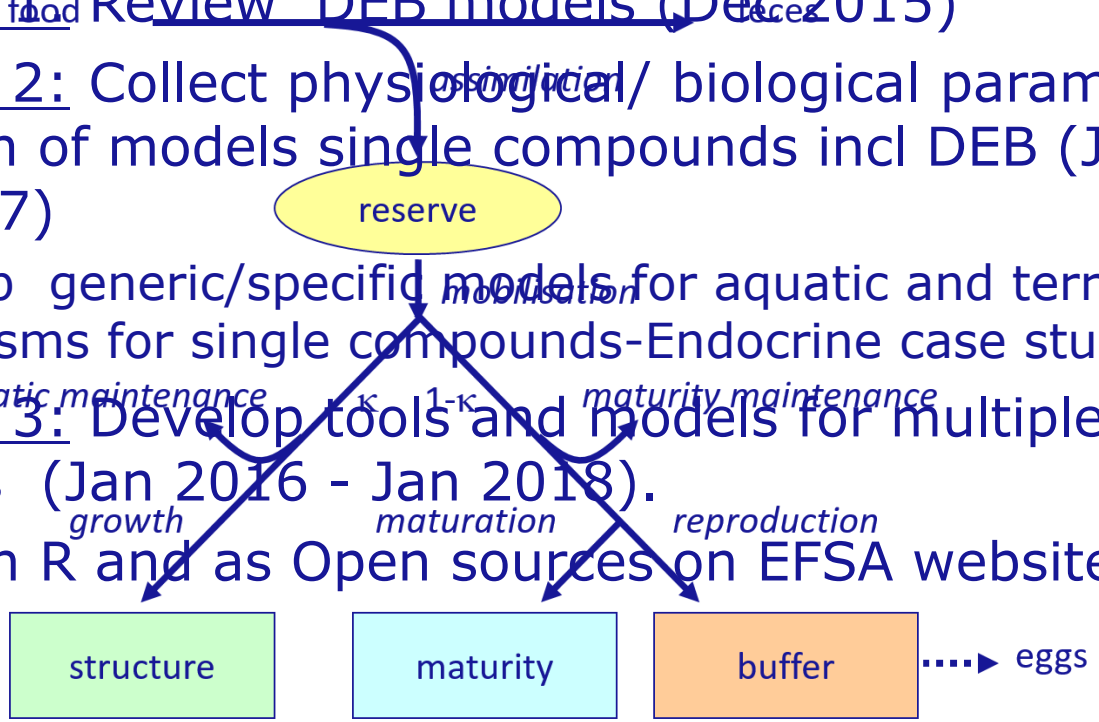
- Objective 1: Review models and tools in human, animal and environmental risk assessment
- Objective 2: Collect physiological/biological parameters
  - Develop TK tools and models for single compounds (from simple tools to generic PB-PK models).
  - Case studies 10 compounds relevant to food and feed safety combining TK and TD
- Objective 3: Develop TK tools and models for multiple chemicals (from simple tools to generic PB-PK models).
  - Case studies 10 compounds relevant to food/feed safety



DYNAMIC ENERGY BUDGET (DEB) MODELS

Procurement on modelling population dynamics of aquatic and terrestrial organisms using Dynamic Energy Budget Models aiming to develop models for the risk assessment of single and multiple chemicals

- Objective 1: Review DEB models (Dec 2015)
- Objective 2: Collect physiological/ biological parameters-calibration of models single compounds incl DEB (Jan 2016 - Apr 2017)
  - Develop generic/specific models for aquatic and terrestrial organisms for single compounds-Endocrine case study
- Objective 3: Develop tools and models for multiple chemicals (Jan 2016 - Jan 2018).
- All tools in R and as Open sources on EFSA website



INTEGRATED RA METHODOLOGIES FOR MIXTURES

Mycotoxins: from synthesis to effects on organisms

- Objective 1: Extensive literature searches and structured data collection on biochemical, genetic and environmental variables and impact on mycotoxin production

- Objective 2: Extensive literature searches and structured data collection on realistic occurrence of mycotoxin mixtures, TK and combined toxicity in animals and humans

- Objective 3: Integrated approach to RA mycotoxin mixtures using modelling

Combine environmental variables, TK, toxicity data for RA using whole food chain approach (from environment to internal dose including carry over in farm animals and toxicity) plus comparative approach to mycotoxin toxicity in vertebrates.

Where are we now ?

Harmonise between Human and Ecological RA ?

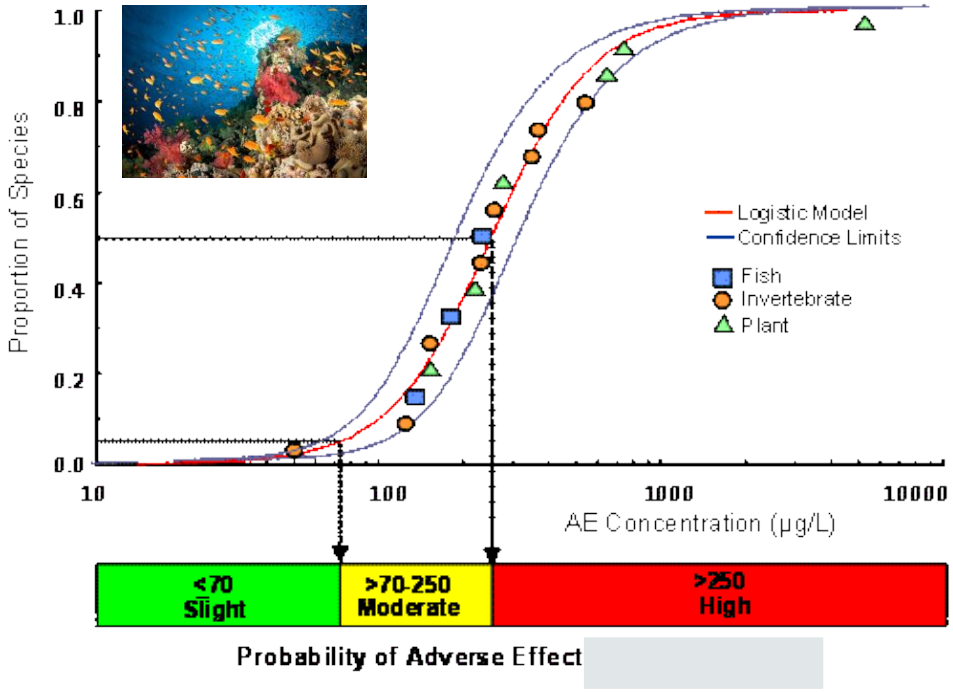
Similarities

- Concept: Risk assessment with 4 pillars
  - Problem formulation, Hazard characterisation
  - Exposure assessment
  - Risk characterisation
- Tiered approaches: default values →probabilistic approaches
- Similar Tools
  - Human TTC ←→ ecoTTC
  - QSAR
  - Doase addition, interaction

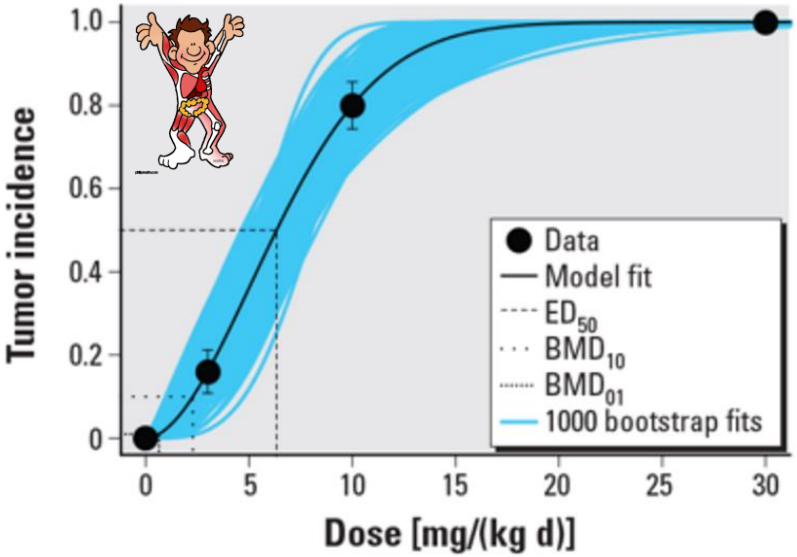
Differences

- Protection goals: Individual vs. Population/Ecosystem
- Biologically meaningful effects
  - Ecotox: survival, growth, reproduction
  - Human tox: Health related effect including neoplasms

Difference in protection goals between human and ecological RA



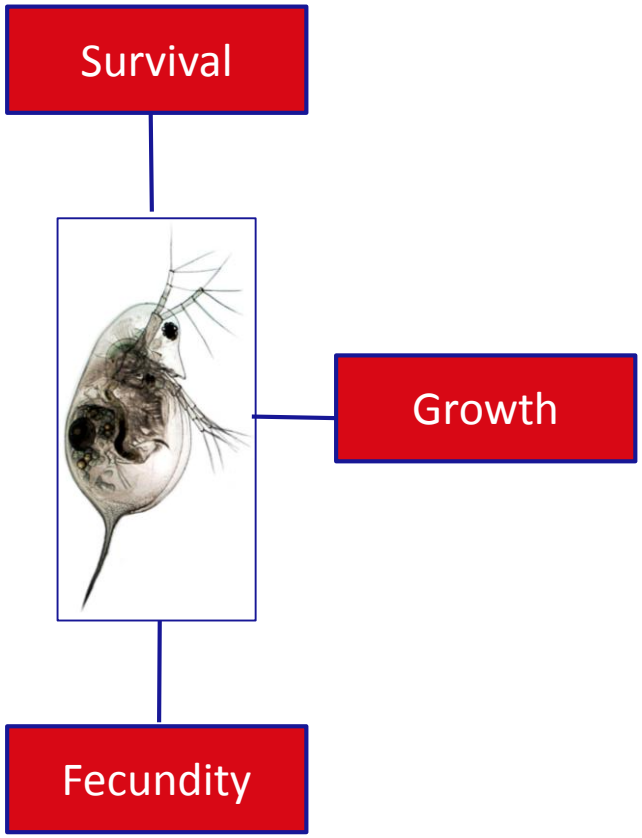
Environment Canada, 2013

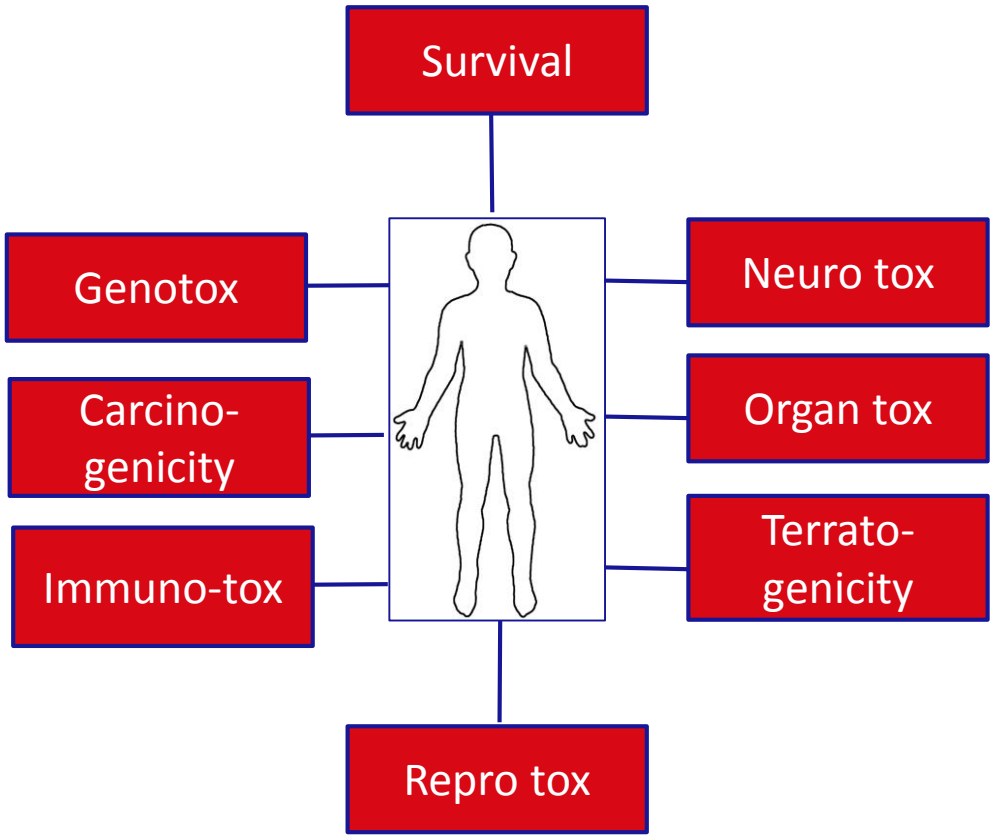


Chiu & Slob, 2015, EHP

…but in both areas, probabilistic methods can be applied to determine the Point of Departure

Differences in relevant effects between human and ecological risk assessment





Approach to Harmonise Human and RA of Chemical Mixtures

Anchor harmonisation to the four pillars of RA

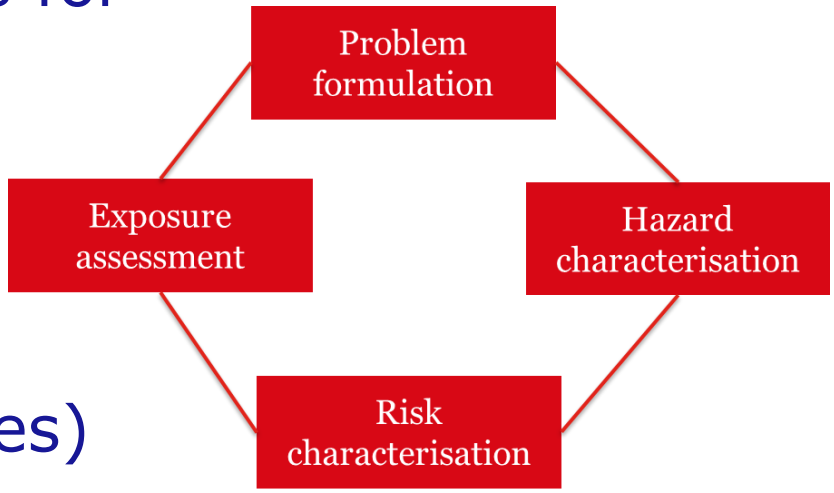
Identify the steps and options for each pillar:

Must do (list options)

Think of (list options)

Models available (list options)

Data requirements (list sources)



Map across (where possible) steps and options for HRA and ERA

Mapping of conceptually similar approaches between human and ecological risk assessments

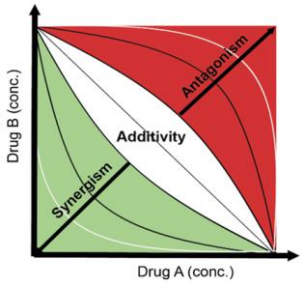
HUMAN RISK		ECO RISK
Data for the model → Mixture model		Mixture Model ← Data for the model
Data + supporting model → …….		…… ← ….data + supporting model
Human-tox data → Human-tox TTC	Hazard characterisation	eco-TTCs ← ecotoxicity data
Data + supporting model → …….		…… ← ….data + supporting model
Data + supporting model → …….		…… ← ….data + supporting model

Conceptually similar approaches can be aligned

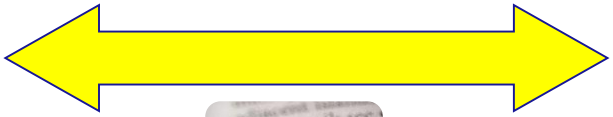
1. When both present → align, and describe briefly in Guidance
2. When e.g. ERA has a method and HRA not → Cross-sectoral learning option

Fact sheets and appendices describe tools and techniques at each level

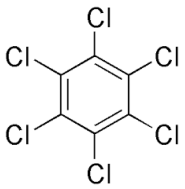
THANK YOU

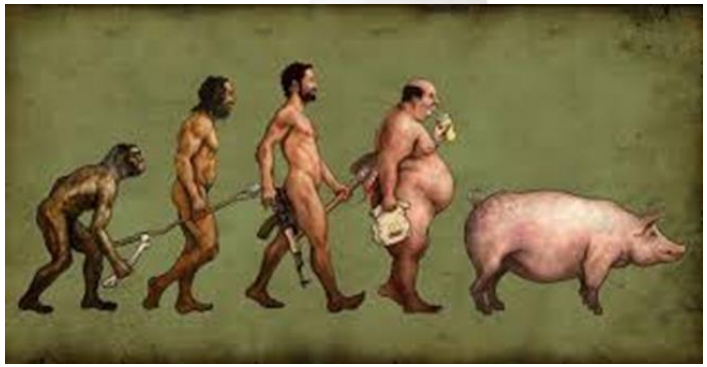


Ecological



Human





Scientific and public concerns on exposure to mixtures of pesticides

Martin Dermine, DVM, PhD

Euromix workshop, Brussels, 18 May 2017

Current pesticide risk assessment

- Best system in the world…but
- Single route of exposure
- Single chemical
- Acceptable daily intake :
  - Interspecific safety factor of 10 insufficient (Schneider 2005, Falk-Filipsson 2007)
  - Intraspecific factor of 10 insufficient (Dorne 2001).

Uncertainty factor of 100.

Highly theoretical !

Pesticide legislation (Reg. 1007/2008, 396/2005)

- No harmful effect on human health, no unacceptable effect on the environment

- Establishment of a risk assessment for cumulative and synergistic effects of combined exposure

Use of models in Risk Assessment

- Probabilities: not in line with reg. 1107/2009
- Highly theoretical: e.g. Monte Carlo model: all citizens not protected
- Models are currently failing to protect the environment

Use of models in Risk Assessment

- Predicted Environmental Concentration (PEC): FOCUS scenarios
- Measures Fungicide Concentration (surface water, sediments)
- Are PECs worst case scenarios?

  - No, its an underestimation:
    - Step 3: **15**% PECsw <MFCsw ---- **67**% PECsed<MFCsed
    - Step 4: **28**% PECsw <MFCsw ---- **76**% PECsed<MFCsed

Stehle S, Schulz R (2015). Pesticide Authorization in the EU – environment unprotected? *Environ Sci Pollut Res* **22**: 19632-19647

Use of models in Risk Assessment

- Apply precautionary principle to models
- Confront models to reality: monitoring data and regular adjustments
- Conduct lab experiments based on monitoring data to verify the safety of the models

Failures of the Risk Assessment

- Due to lack of knowledge
- Highly theoretical. E.g. endocrine disrupting chemicals having an xenoestrogenic effect below NOECs (Rajapakse 2002).
- Exposure is permanent and ubiquitous. E.g. tens of (banned) pesticides, PCBs and others in human breast milk (Schlumpf 2010)
- Epidemiological surveys show increased diseases prevalence for pesticides users and bystanders (Chubilleau 2011)

Adverse Outcome Pathways

- Interesting tool: fundamental research, industry tool
- In its infancy
- Future cut-off criteria to avoid animal testing?
- Not a method to refine risk assessment
- Should in no way reduce animal testing at present

Thank you!

Developing science-based approaches for cumulative risk assessment

Stephanie Melching-Kollmuss

18th May, 2017

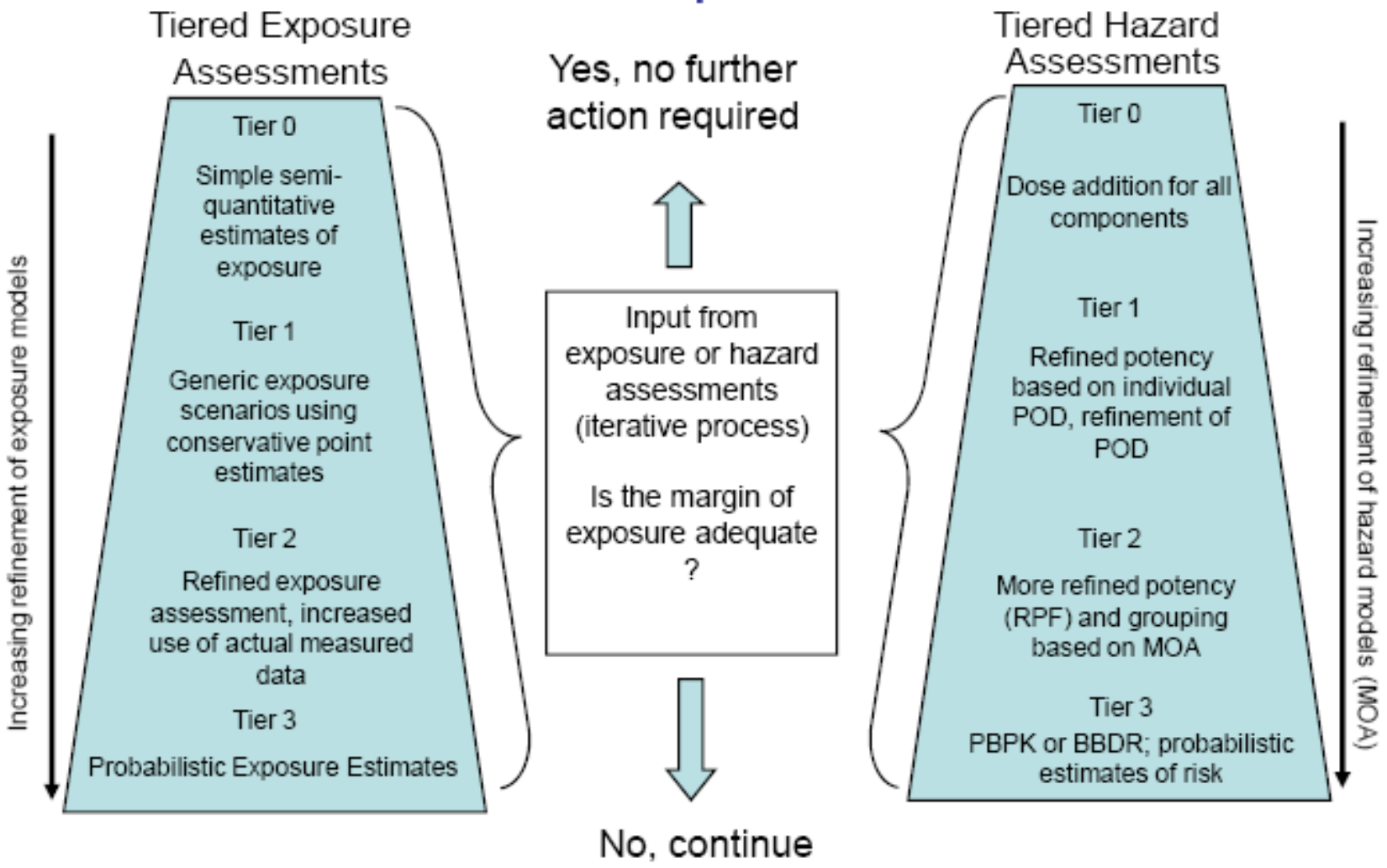
Cumulative Risk Assessment - general considerations

- **Pesticide residues are low (usually below MRLs and exposures are well below reference values) and represent a minor part of the real exposure to chemicals**
- **Need for a cumulative assessment, only if co-exposure is expected. Most relevant includes:**
  - Acute situations
  - Applied formulations
- **Conduct a cumulative assessment only for substances with assumed similar toxicity**
- **Chronic cumulative risk assessments are best performed in a post-approval context based on residue data from monitoring**

Cumulative Risk Assessment

Sample Tiered Exposure and Hazard Considerations

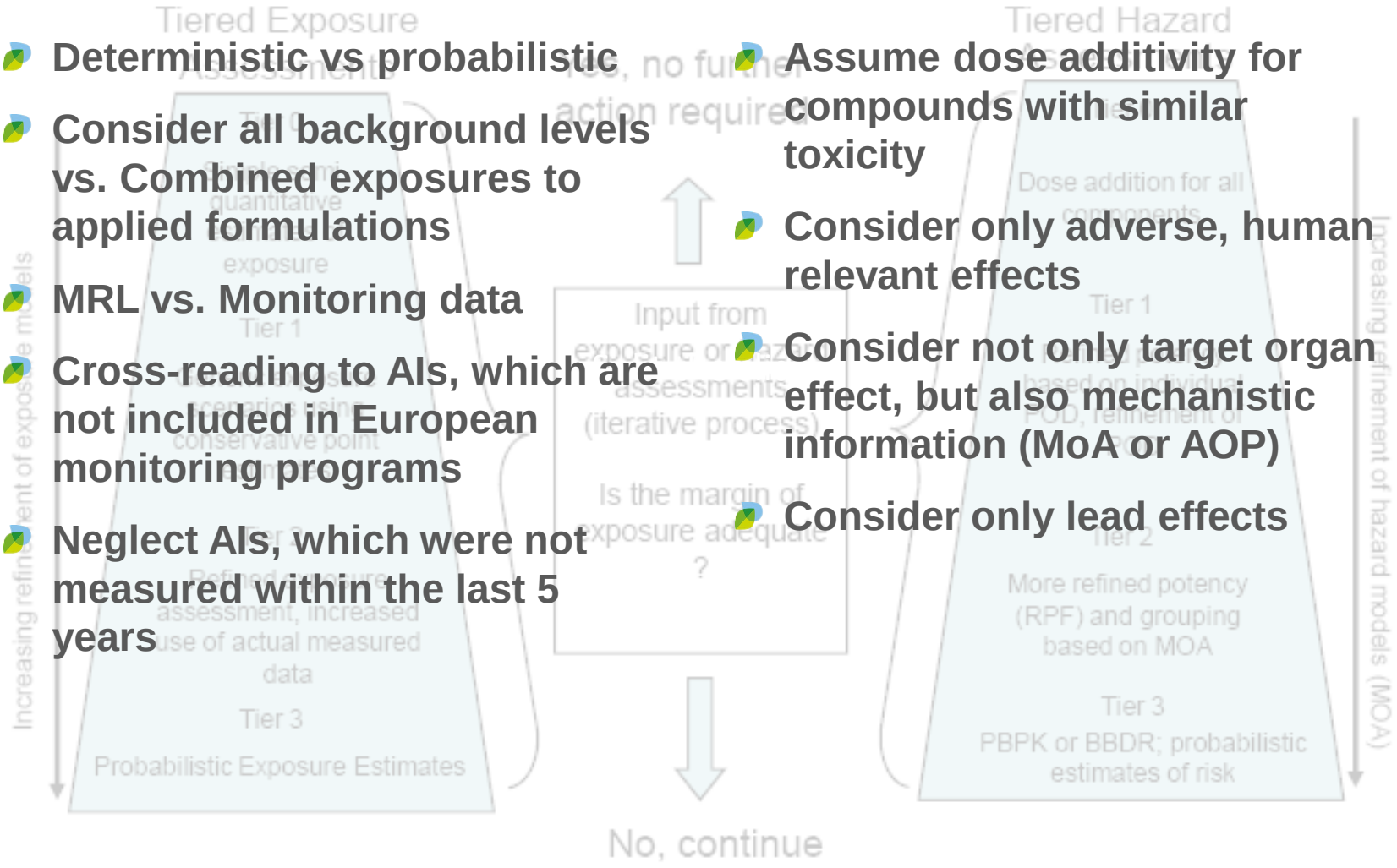
Mixture or Component Based



Cumulative Risk Assessment - more specific refinements

- Deterministic vs probabilistic
- Consider all background levels vs. Combined exposures to applied formulations
- MRL vs. Monitoring data
- Cross-reading to AIs, which are not included in European monitoring programs
- Neglect AIs, which were not measured within the last 5 years

- Assume dose additivity for compounds with similar toxicity
- Consider only adverse, human relevant effects
- Consider not only target organ effect, but also mechanistic information (MoA or AOP)
- Consider only lead effects



Grouping approach proposed by EFSA

- CAG level 1: Toxicological target organ
- CAG level 2: Common specific phenomenological effect
- CAG level 3: Common mode of action
- CAG level 4: Common mechanism of action

Rarely data available

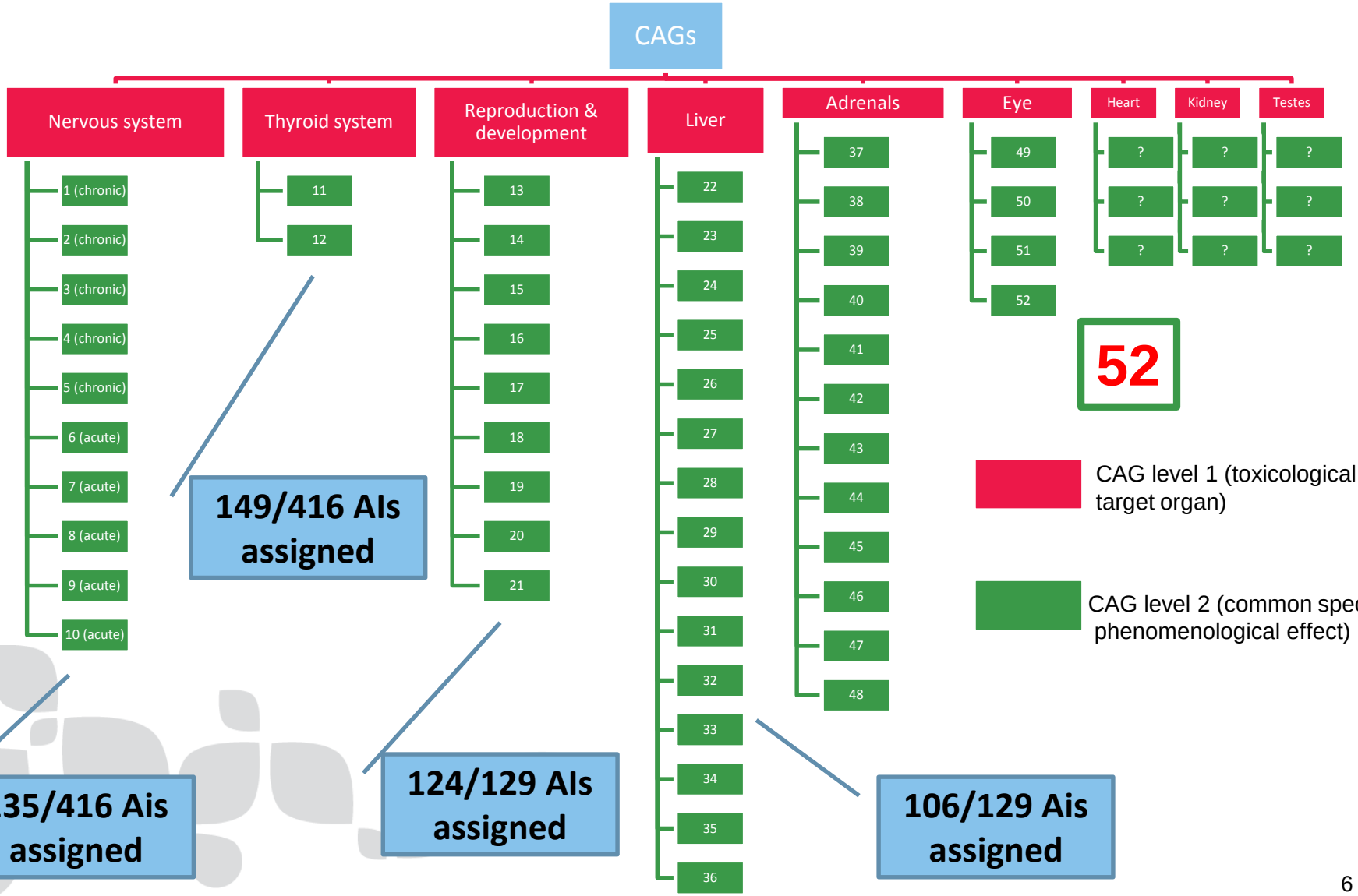
Chemicals with common target organ toxicity (any effects in any study, dose level or species)

Exclusion

Only based on specific data

Cumulative Assessment Groups - current no. of proposed CAGs

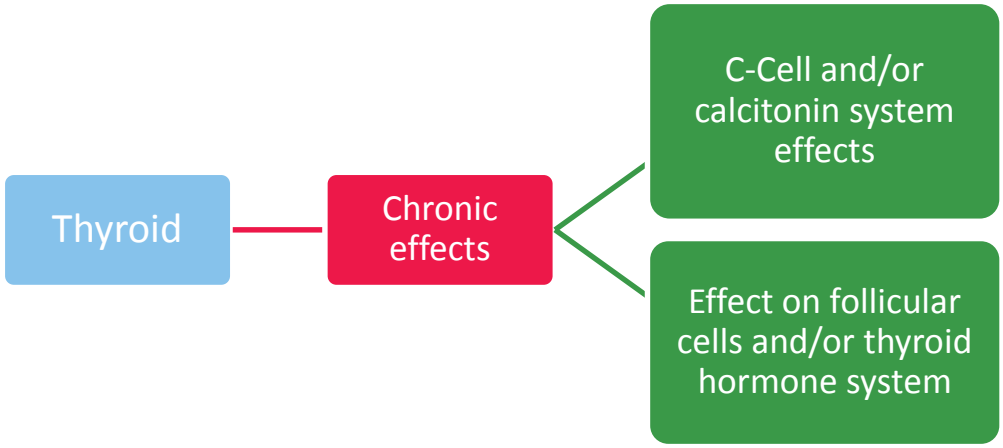
European Crop Protection



Research activity within ECPA

- **Decrease the number of CAGs to a more reasonable figure**
- **Decrease the number of AIs per CAG to more reasonable figures**
  - Hazard characterisation of the individual compounds
  - Propose more relevant criteria for grouping in CAGs

Thyroid group (Level 2B)

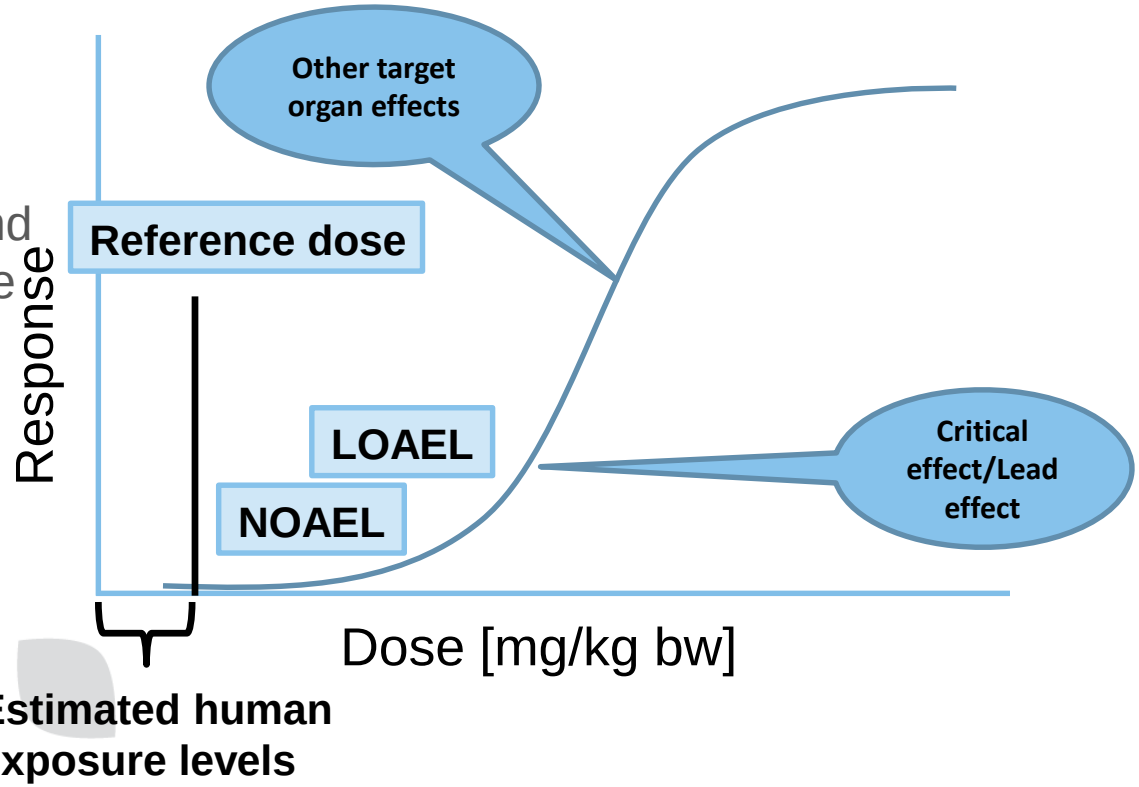


	Scientific Opinion 2013	External Scientific Report 2016
C-Cell and/or calcitonin system effects	22/287	10/129
Effect on follicular cells and/or thyroid hormone system	96/287	53/129
	149/416	

- **Would make a huge thyroid follicular cell CAG at the level 2B**
  - Not manageable for cumulative risk assessment

Refined assessments (Thyroid 2B): CAG number

- **Re-evaluation of AIs and proposals for appropriate grouping**
  - Disagreement with grouping for 32/53 (weight of evidence) and 12/53 (mechanistic information)
- **Use lead effect**
- **For other groups also:**
  - Propose more relevant and stringent criteria/guidance for grouping (e.g. liver, repro)



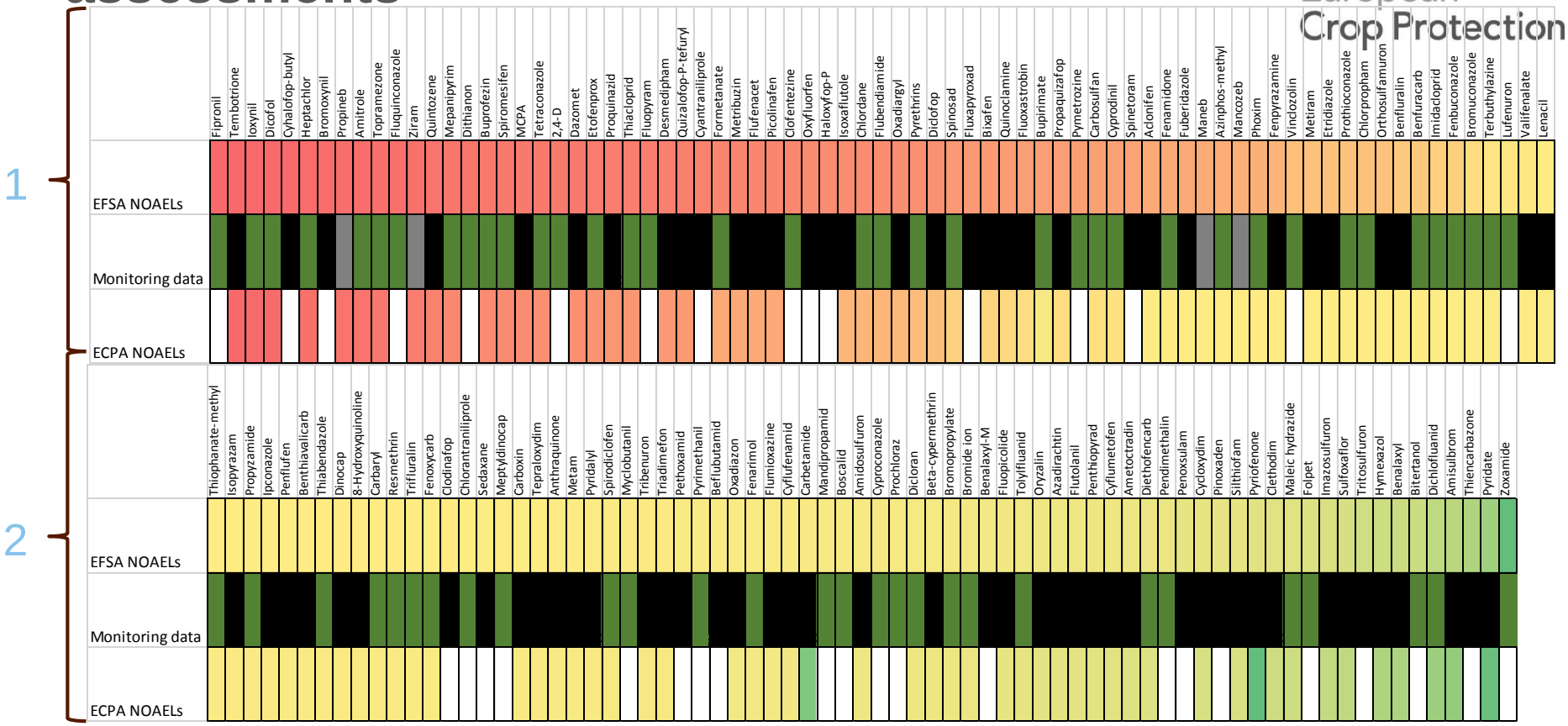
Refined assessments (Thyroid 2B): Exposure

- **Use monitoring data (2012-2013-2014 cycle) for chronic assessment and the combined MoE (MoE = NOAEL/estimated exposure) approach**

$$MOE_T = \frac{1}{(1/MOE_1) + (1/MOE_2) + (1/MOE_3) + \cdots}$$

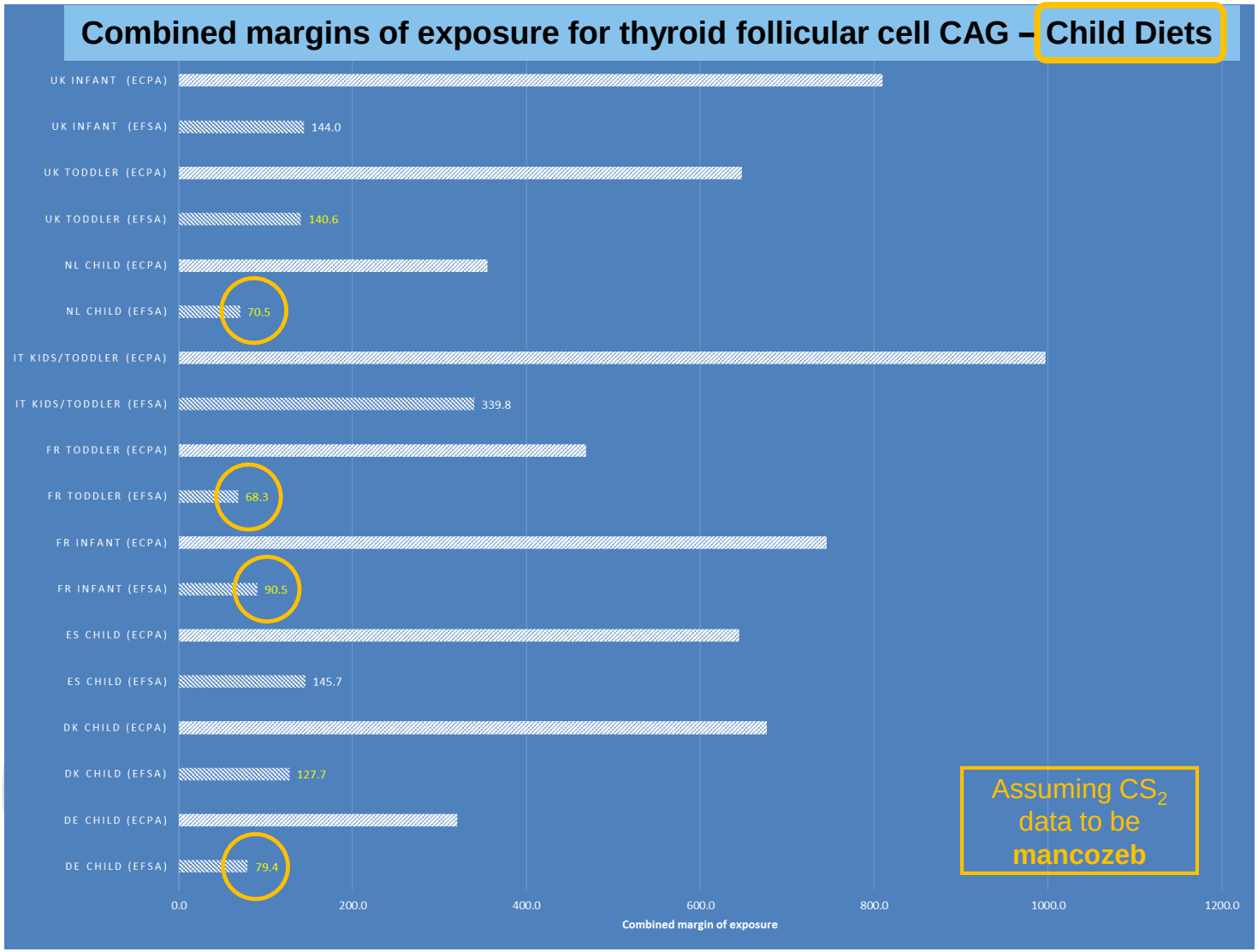
  - For the chronic thyroid assessment: monitoring data were available for 42 (out of 149) AIs, in 33 different commodities
  - Very few compounds were driving the cumulative risk assessment

Thyroid 2B – first preliminary comparative assessments

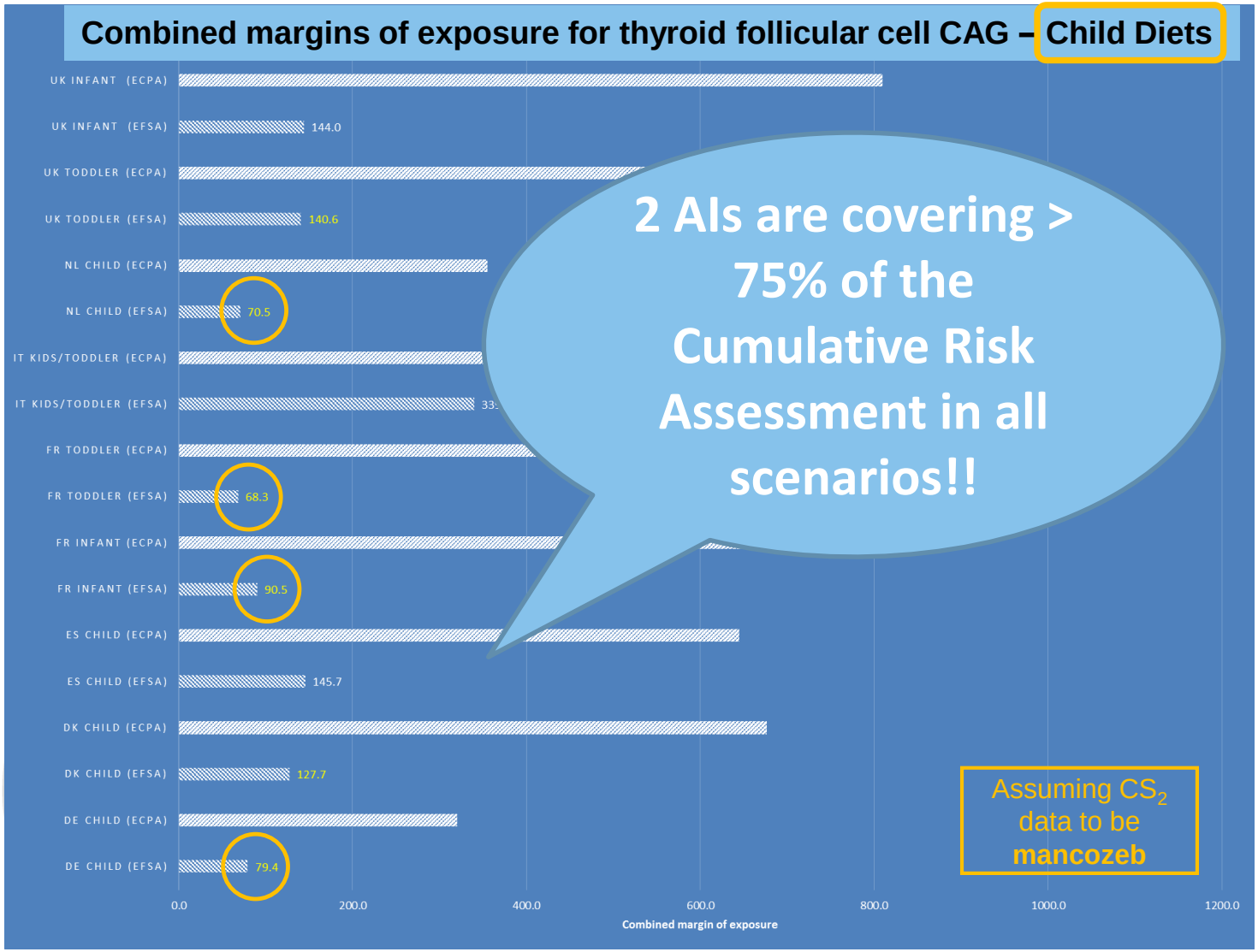


- **The top row (in both panes 1 and 2) comprises the names of the AS in the CAG, according to EFSA; the names are ordered from most to least potent (the colour coding in the row labelled "EFSA NOAELs" represents this variation in potency from most (red) to least (green).**
- **The bottom row ("ECPA NOAELs") indicates the same potency colour coding based on the ECPA view of NOAELs. White cells correspond to ASs that are proposed not to belong to the CAG.**
- **The "Monitoring data" row indicates for which ASs monitoring data are available (green) and not available (black) from the 2012-2013-2014 EUCP. Any dithiocarbamate ASs are monitored as CS_2 (grey cells) – hence the residue levels is a non-chemical specific integrated value**

Thyroid 2B – first preliminary comparative assessments



Thyroid 2B – first preliminary comparative assessments



Propose a workable approach

- Only the relevant AIs with relevant endpoints should be used and summed up in CAGs (→ CAGs of ≈ 10 members)

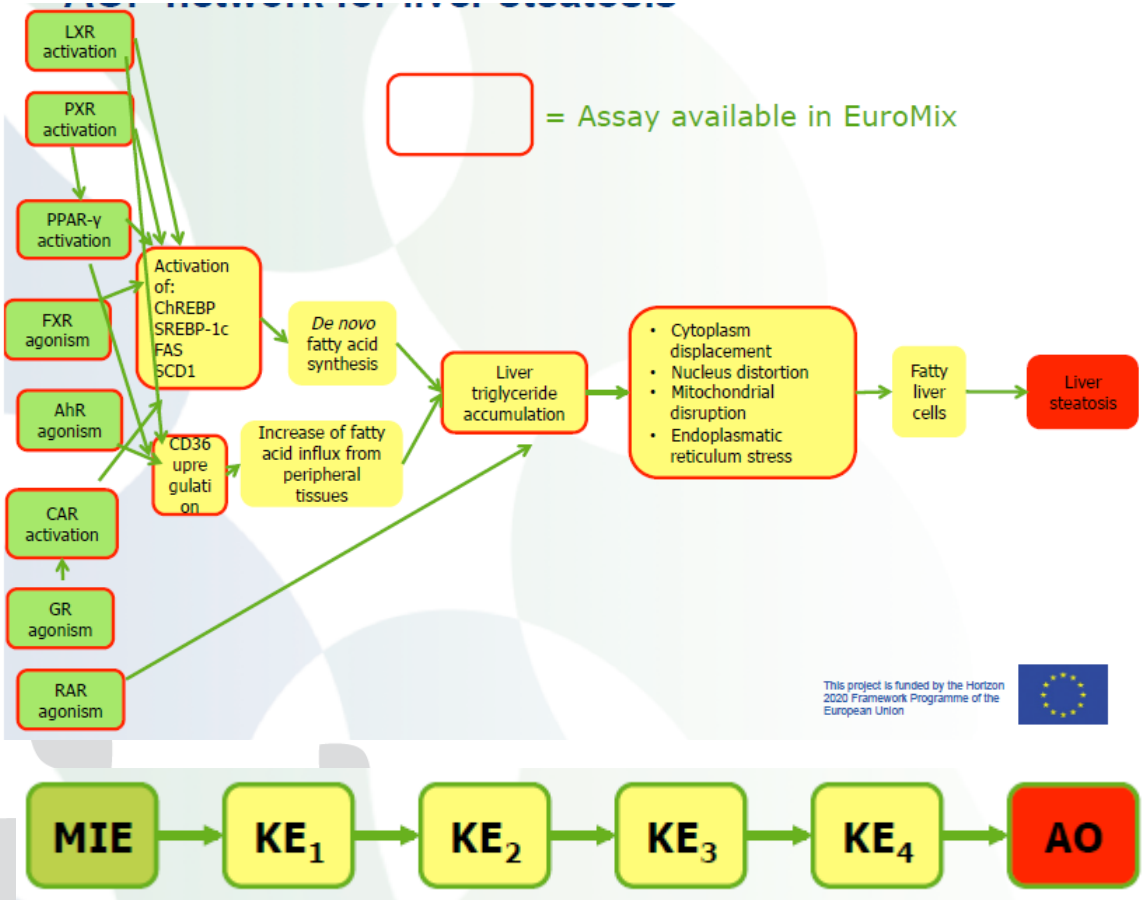
- Collect and bridge available monitoring data
- Consider the realistic human exposure situation (e.g. availability on the European market)
- *Non-dietary situations: Collect information on tank mixes or spray combinations on crops during season (co-exposures)*

- Proof-of-concept
- Workable approach

ECPA CIP Project – started in January 2017

- **Module 1**
  - Correct and relevant grouping
  - Relevant criteria for grouping
- **Module 2**
  - Selection of appropriate monitoring data for ECPA cumulative risk assessment (CRA) (quality criteria, access)
  - Access to probabilistic modelling
- **Module 3**
  - Develop a decision tree
  - Run impact assessment based on developed criteria/refined CAGs
  - Proof-of-concept approach for exposure-based CRA

EuroMix: Hazard-based refinement (example liver steatosis)



- **Determines the assay for triglyceride accumulation all MoAs?**
- **When to use:**
  - Proof-of-concept mixture tests
  - Test risk driver combinations?
- **Will the outcome reduce overall numbers in CAGs or refine PODs**
- **Other AOPs in preparation for liver? Other CAGs?**

EuroMix: Use of *in-silico* approaches for prioritization - liver

European Crop Protection

- Need to prove the reliability of the predictions
- Comprehensive data set is available for pesticides
- Assessments are used for prioritization of
  - mixture testing?
  - what else?
- *Could be used for subgrouping and TTC assessments?*

List of relevamt models for Liver Tox in Euromix:

- **DEREK Hepatotoxicity Alert Score - level 1/2**
- MULTICASE Consensus Highest - level 1
- Pizzo Alert Score
- COSMOS Nuclear Receptor model - level 3/4
- COSMOS LXR-binding Tanagra - level 3/4
- PADEL Predict Hepatotoxic - level 1
- **Toolbox rep.dose HESS alerts; Hepatox - level 2**
- Fera C4.5 model CDK descriptors
- **OCHEM AhR activity - level 3/4**
- **OCHEM PPARg activity - level 3/4**

Future cooperation with EuroMix and European bodies

- **Interaction is highly appreciated - continuous collaboration within the user group**
- **Company risk assessors need better access to exposure and consumption data and probabilistic modelling tools**
- **Company experts have the best knowledge of the toxicological data**
  - Hazard-based refinements / mechanistic data
  - Systemic vs external exposures
- **Technical exchange on scenarios and options can help to develop a better methodology**

Acknowledgements

ECPA J-TRAG

- Dave Johnson (Syngenta)
- Giovanna Semino-Beninel (Bayer)
- Frank Laporte (Bayer)
- Monika Bross (BASF)
- Neil Lister (Syngenta)
- Tina Mehta (Dow)
- Stephanie Melching-Kollmuss (BASF)

European
Crop Protection

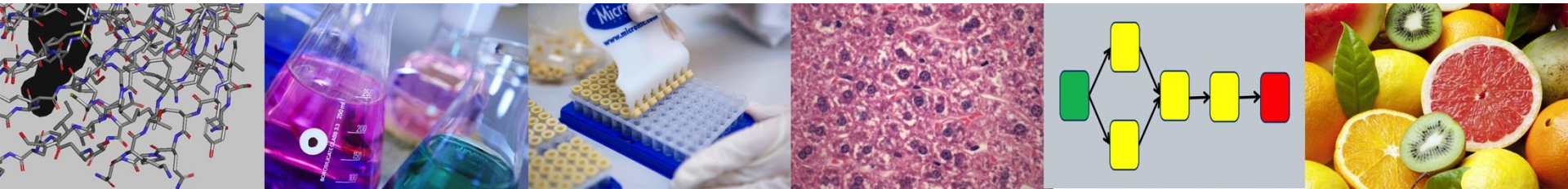
Thanks for your attention

Questions?

Euromix stakeholders' survey towards testing and risk assessment of chemical mixtures

Prof. Liesbeth Jacxsens
Prof. Wim Verbeke, Dr. Ellen Van Loo
Prof. Pieter Spanoghe
Faculty of Bio Science Engineering
Ghent University

Liesbeth.Jacxsens@ugent.be



Importance of stakeholders' consultation

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Stakeholder attitudes towards cumulative and aggregate exposure assessment of pesticides

Wim Verbeke [a,*], Ellen J. Van Loo [a], Filiep Vanhonacker [a], Ilse Delcour [b], Pieter Spanoghe [b], Jacob D. van Klaveren [c]

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[b] Department of Crop Protection, Ghent University, Coupure links 653, Gent B-9000, Belgium
[c] National Institute for Public Health and the Environment, RIVM, Bilthoven NL-3720 BA, The Netherlands

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

1. Objective

- Important new concepts in EUROMIX e.g. shift from single exposure to cumulative exposure

- Important tools in EUROMIX e.g. in silico, in vitro toxicological tests instead of in vivo testing

➔ Generate a shift in exposure assessment and toxicological evaluations in future

➔ Attitudes and perspectives of different stakeholder groups towards tools and concepts generated by EUROMIX are important

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

2. Methodology

- Identified stakeholders :
  - Chemical industry and associations
  - Agro-food chain actor (e.g. retail, food processor, farmer associations)
  - Government (regulator, authority)
  - University/ research institute
  - Consumer/Consumer association
  - NGOs

- By means of a quantitative stakeholder survey
- Validation of survey has been conducted during EFSA EUROMIX training
- First data collection has been done via EUROMIX trainings in March 2017

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

3. Stakeholder survey

SINGLE·RISK·ASSESSMENT → ↵

The·current·and·classical·approach·of·risk·assessment·tests·one·chemical·and·one·contamination·route·at·a·time.·¶

¶

¶

Q2.·Please·indicate·to·what·extent·you·agree·or·disagree·with·each·of·the·following·statements.¶

The·use·of·single·risk·assessment·is...¶

▪¤	Strongly· Disagree¤	Disagree·¤	Neither·agree· nor·disagree¤	Agree·¤	Strongly· Agree·¤	¤
▪ important··¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤	¤
▪ understandable¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤	¤
▪ acceptable¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤	¤
feasible¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤	¤
good¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤	¤
adequate¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤	¤

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3. Stakeholder survey

Question	Topic
2	The use of single risk assessment is…
3	The use of cumulative risk assessment is …
4	Please indicate your opinion on the level of combined risk for human health caused by chemical compounds belonging to the following chemical classes.
5	Please indicate to what extent you agree or disagree with the statements on how the risk of combined exposure to different chemicals should be assessed when it is implemented in European regulation.
6	The use of animal testing (in-vivo assays) to estimate toxicity is …..
7	The use of in-silico assays to estimate toxicity is……
8	
9	The use of in-vitro assays to estimate toxicity is…..
10	

3. Stakeholder survey

Question	Topic
11	The use of single risk assessment is…
12	
13	Please indicate to what extent you agree or disagree with each of the following statements about how combined should be managed.
14	Gender
15	Age
16	Country
17	Open remarks to EUROMIX

➔ 17 questions

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3. Stakeholder survey

Q4.· Please· indicate· your· opinion· on· the· level· of· combined· risk· for· human· health· caused· by· chemical·compounds· belonging·to·the·following·chemical·classes.¶

Which chemicals ?	No·Risk	Low·Risk	Moderate· Risk	High·risk
Food·contaminants·¶ (e.g.·mycotoxins,·acrylamide)	❍	❍	❍	❍
Environmental·pollutants·¶ (e.g.·dioxins,·heavy·metals)	❍	❍	❍	❍
Pesticide·residues·(biocides·and·plant· protection·products)	❍	❍	❍	❍
Bioactive·alkaloids·(e.g.·inherent·plant·toxins¶ as·erucic·acid,·tropane·alkaloids)	❍	❍	❍	❍
Chemical·migrants·from·food·contact·materials· (·e.g.·ink·compounds,·phthalates,·bisphenol·A)	❍	❍	❍	❍

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3. Stakeholder survey

Q5.·Please·indicate·to·what·extent·you·agree·or·disagree·with·the·statements·on·how·the·risk·of·combined·exposure·to·different·chemicals·should·be·assessed·when·it·is·implemented·in·European·regulation.·¶

▪ ¤ **Combined exposure modelling**	Strongly· Disagree¤	Disagree·¤	Neither· agree· nor· disagree¤	Agree·¤	Strongly· Agree·¤
▪ All·potential·routes·of·exposure·(food,·soil,· water,·air·exposure)·should·be·addressed,·before· we·implement·combined·risk·assessment¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤
▪ Grouping·of·chemicals·based·on·the·adverse· outcome,·without·considering·refinement·based· on·the·mode·of·action·is·too·conservative¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤
▪ Exposure·models·should·address·co-exposure,· including·the·consideration·of·kinetics¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤
Prioritisation·of·chemicals·to·be·tested,·should· be·based·on·their·contribution·to·the·exposure·¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤
All·chemicals·should·be·retained·in·an· assessment·group,·even·if·they·contribute·little· to·the·combined·risk¤	❍→¤	❍→¤	❍→¤	❍→¤	❍→¤

Q8. Please indicate to what extent you agree or disagree with each of the following statements.

In-silico assays	Strongly Disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
In silico assays can only be used as a screening tool to identify chemicals that require additional detailed toxicological testing	❍	❍	❍	❍	❍
In silico assays can only replace in-vivo-assays after they have been validated against the current practice (animal testing (*in-vivo* assays))	❍	❍	❍	❍	❍

Q10. Please indicate to what extent you agree or disagree with each of the following statements.

In-vitro assays	Strongly Disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
In-vitro assays can only be used as a screening tool to identify chemicals that require additional detailed toxicological testing	❍	❍	❍	❍	❍
In-vitro assays can only replace in-vivo-assays after they have been validated against the current practice (animal testing (*in-vivo* assays))	❍	❍	❍	❍	❍

4. How to participate ?

- Fill in a paper version and submit today in dropbox at the reception of the workshop or give to Liesbeth Jacxsens

- Fill in via on-line link :

- https://ghentagriecon.qualtrics.com/jfe/form/SV_2rzS921DHOHJSux

- We will consult you via e-mail after this workshop !

- Via the link available on the EUROMIX webpage :
- https://www.euromixproject.eu/2017/05/10/stakeholder-survey-opinion-on-tools-and-concepts/

- Many thanks for your collaboration !!

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

Stakeholder survey – opinion on tools and concepts

10th May 2017 News Sophie Jensen

On a daily basis we are exposed to a mixture of multiple chemicals via food intake, inhalation and dermal contact. The risk to human health that may result from this, depends on how the effects of different chemicals in the mixture combine, and whether there is any synergism or antagonism between them. The number of different combinations of chemicals in mixtures is infinite and an efficient test strategy for mixtures is lacking. Furthermore, there is a societal need to reduce animal testing, which is the current practice in safety testing of chemicals.

The EuroMix project will deliver a mixture test strategy and test instruments using novel techniques. The tests will result in data needed for refining future risk assessment of mixtures relevant to different stakeholders. Ultimately, this will provide information for future risk management decisions on the safety of chemicals in mixtures to be taken by the European Commission and the Codex Alimentarius.

More information on the EuroMix concepts and tools can be found in this presentation.

Therefore, we would like to hear your opinion on the tools and concepts under investigation within EuroMixa and are inviting you to participate in our stakeholder survey.

Seventeen questions have been selected to evaluate our concepts and tools acceptance and understandability.

If you have attended one of the EuroMix training workshops or information sessions, please click here.

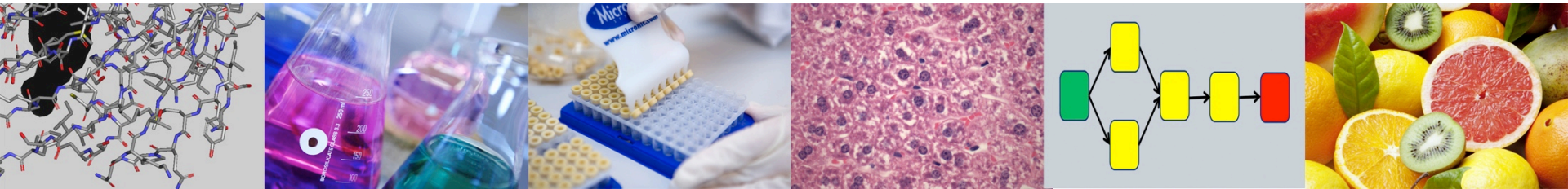
If you have NOT received any EuroMix training or taken part in information sessions, please click here.

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

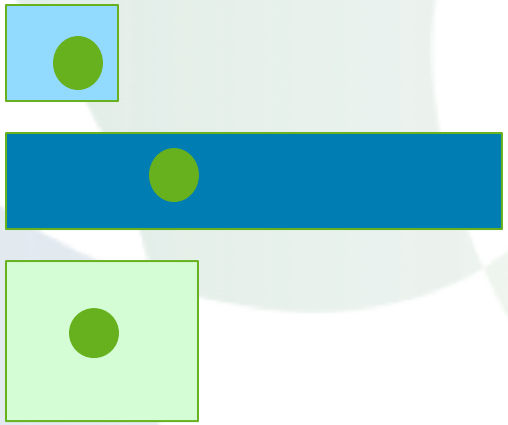
Aggregate exposure within EuroMix

Cecile Karrer[1], Marc Kennedy[2], Natalie von Goetz[1], Amelie Crépet[3]

[1]ETH Zurich (CH), [2]Fera (UK), [3]ANSES (F)



Aggregate exposure modelling

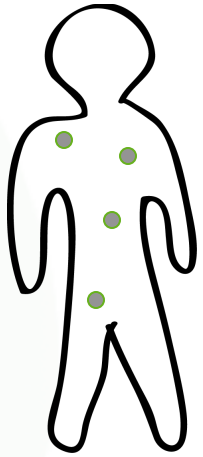


Oral uptake

Inhalation

Dermal uptake

D_{agg} =



Source x containing substance

Intake route y

Consumer

$$D_{xy} = \frac{C_x * q_{xy}}{bodyweight} * r_{uptake}$$

$$D_{agg} = \sum_{x=1}^{n} \sum_{y=1}^{m} D_{xy}$$

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

Aggregate exposure models (tools)

Model (Tool)	Owner	Scope
MCRA	RIVM (NL)	Food
PACEM	RIVM, ETH Zurich (CH)	Cosmetics and household cleaners
CREME	Crème Global (IRL)	food
CRÈME Cosmetics	Crème Global (IRL)	Cosmetics
BROWSE, BREAM	FERA (UK) and Partners	pesticides
AOEM	BfR (D)	pesticides
SHEDS	US-EPA (US)	All sources

ETH Zurich: Several research models, e.g. for PBDEs, UV filters

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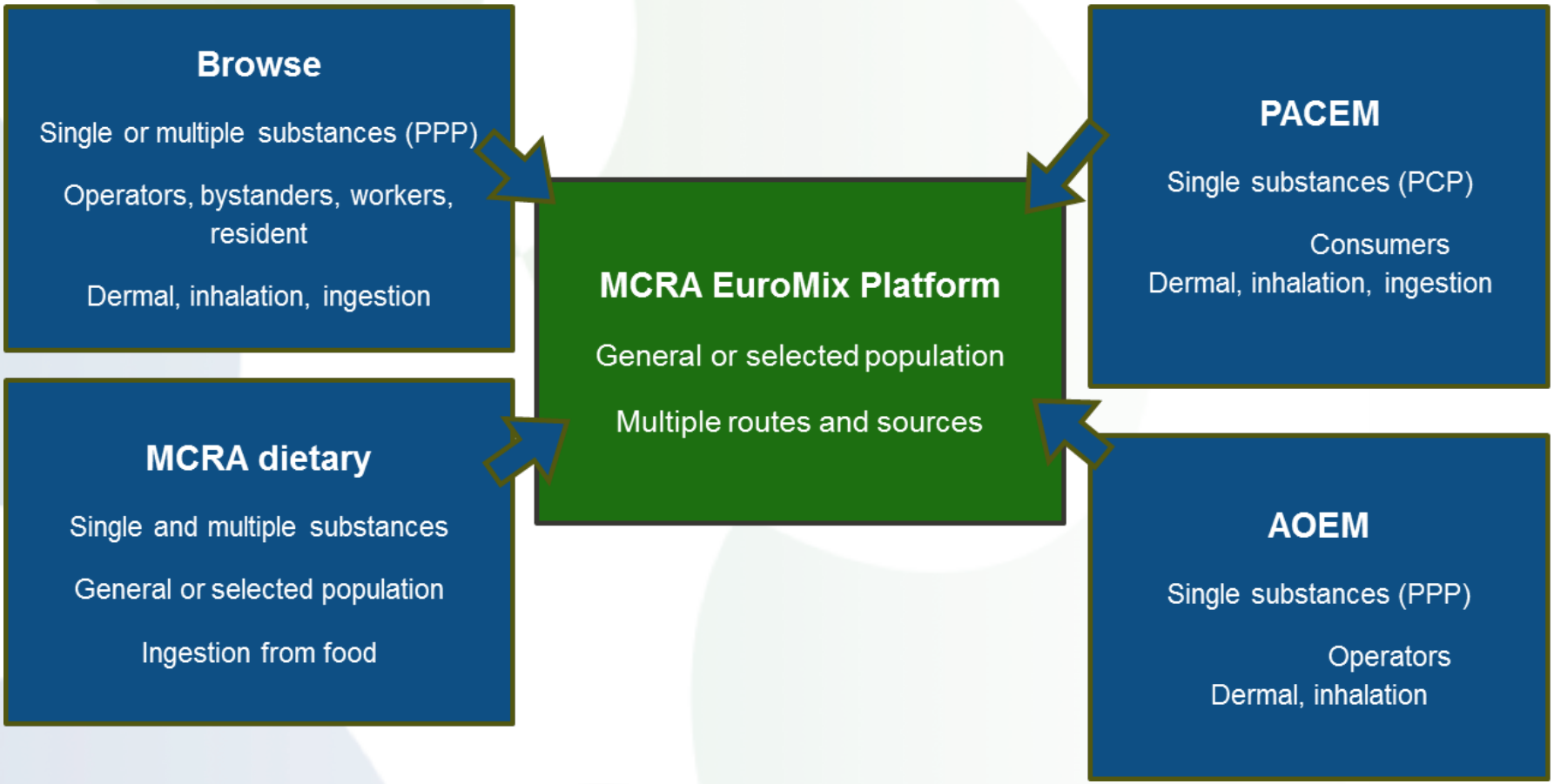
EuroMix model platform



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Case studies for aggregate (and cumulative) exposure

Food	Non-Food	Substances	Responsible
MCRA	PACEM	BPA, BPS, BPF (CAG Endocrines)	ETH Zurich
MCRA	BROWSE	Triazoles (CAG Steatosis)	FERA
MCRA	Prob dust, air	Pyrethroids (CAG Neuro)	ANSES, INERIS

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

Data background

EFSA has **dietary** intake and concentration data available:

- EFSA comprehensive database (full consumption data of many European countries covering all age groups)
- Monitoring data of Member States in standard formats (not always freely available)

Non-dietary exposure (**pesticides**)

- Less data freely available (inventory at EFSA)

Non-dietary exposure (**cosmetics**)

- Use data from research projects in CH and NL in PACEM
- Few monitoring data available at national level, much more data owned by producers (not freely available)

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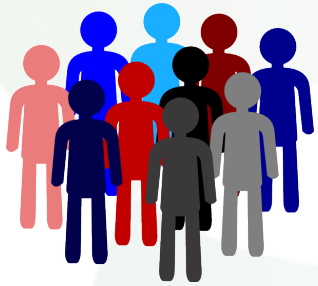
Case study Bisphenols (BPA, BPS, BPF)

MCRA EuroMix Platform

R models

(Probabilistic)

MCRA

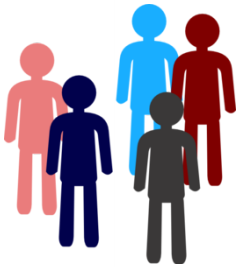


3362 French individuals
3 - 79 years
Biometric details and
food consumption survey

INCA 2 survey, Lioret et al. 2010, Dubuisson et al. 2010

Exposure for adults

PACEM

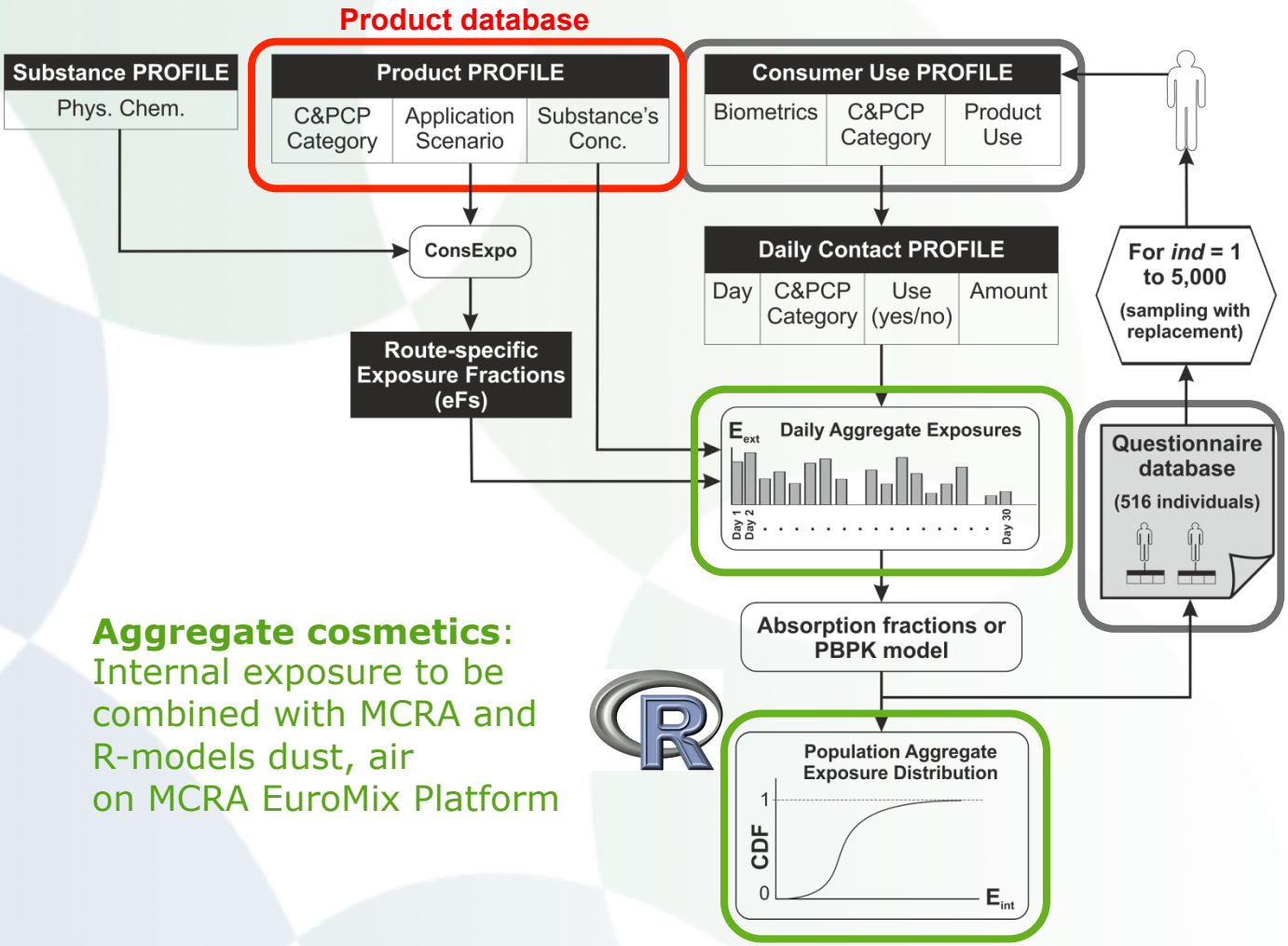


516 Dutch individuals
20 - 73 years
Biometric details and
survey on PCP use

Dudzina et al. 2015

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

PACEM: Workflow for exposure calculation



Questionnaire database

Aggregate cosmetics: Internal exposure to be combined with MCRA and R-models dust, air on MCRA EuroMix Platform

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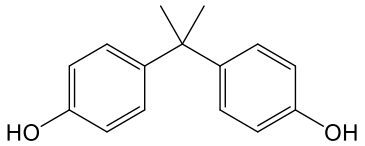
Exposure distributions for total BPA

(internal exposure, dermal absorption fraction 0.2)

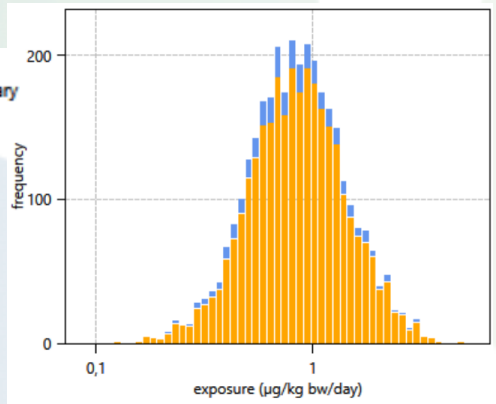
only for illustration, not final

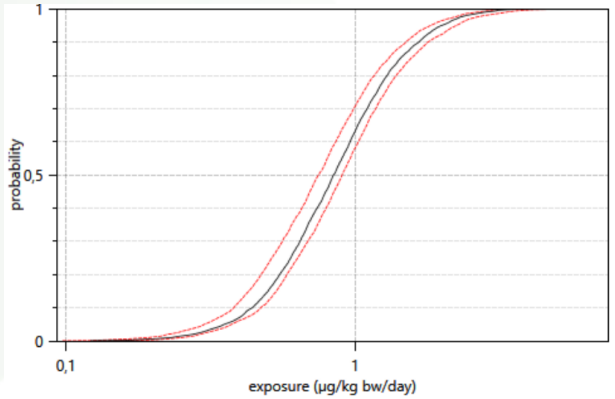


Stacked transformed exposure distribution (100.0 % positives)

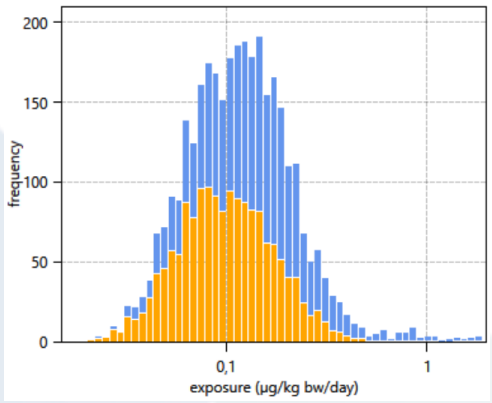
OIM cumulative exposure distribution

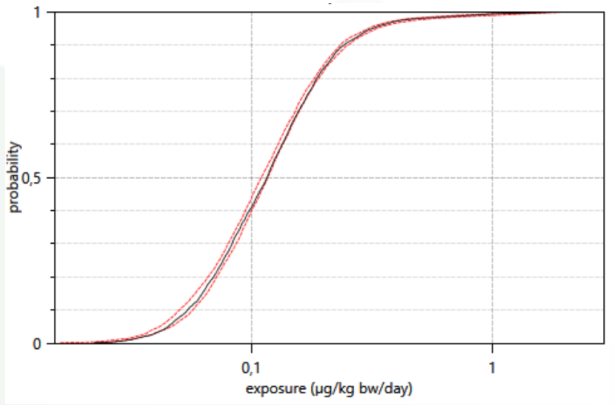
pessimistic





optimistic





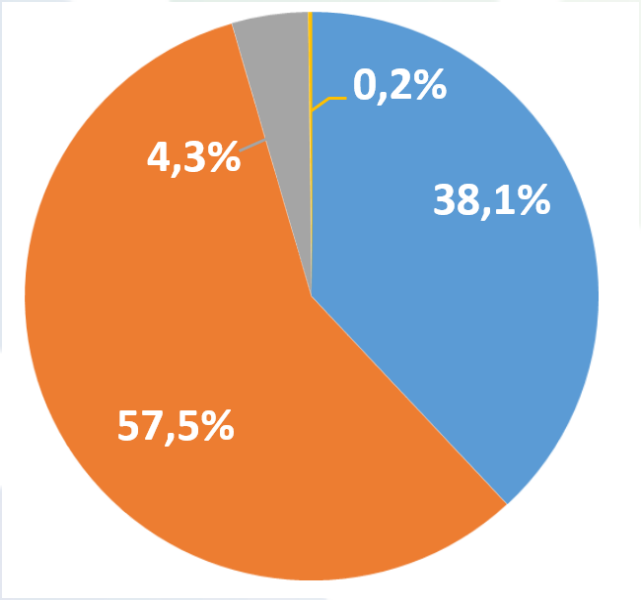
This project is funded by the Horizon 2020 Framework Programme of the European Union

Contribution to total exposure to total BPA

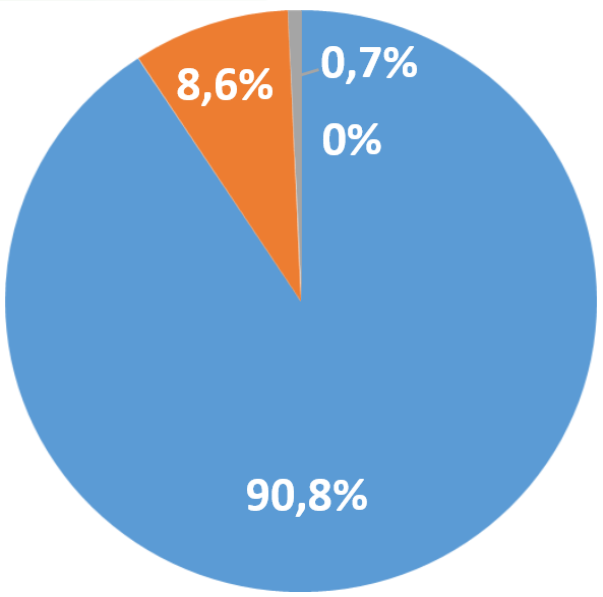
only for illustration, not final

Exposure model for assessing dietary exposure

EFSA Optimistic
<LOD=0



EFSA Pessimistic
<LOD=LOD



dietary dermal oral non-dietary inhalation

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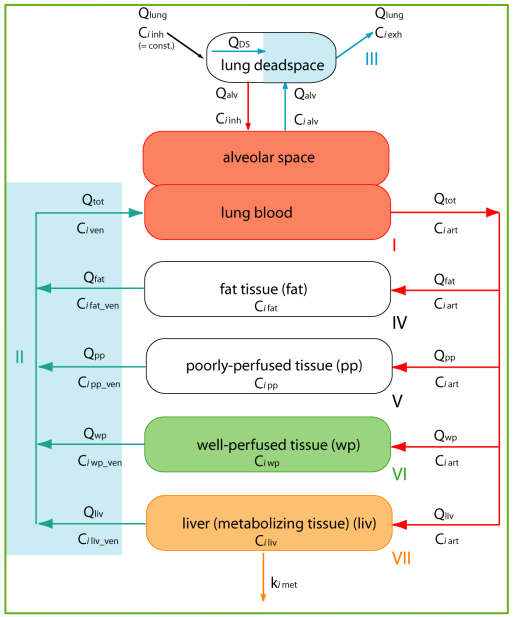
Ongoing work: PBPK model for BPA, BPS, BPF

PBPK modelling for aggregating different exposure routes internally, taking into account metabolism

Cumulation of exposure from BPA, BPS, and BPF



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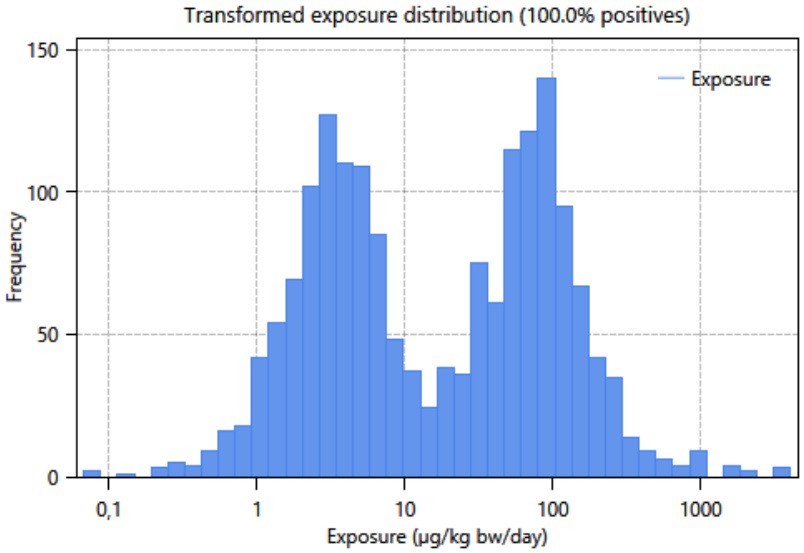
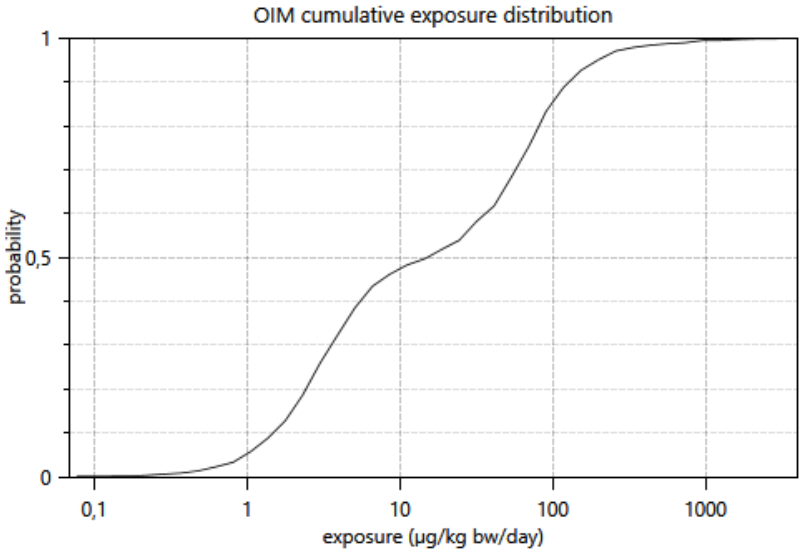
Aggregate exposure to Triazoles

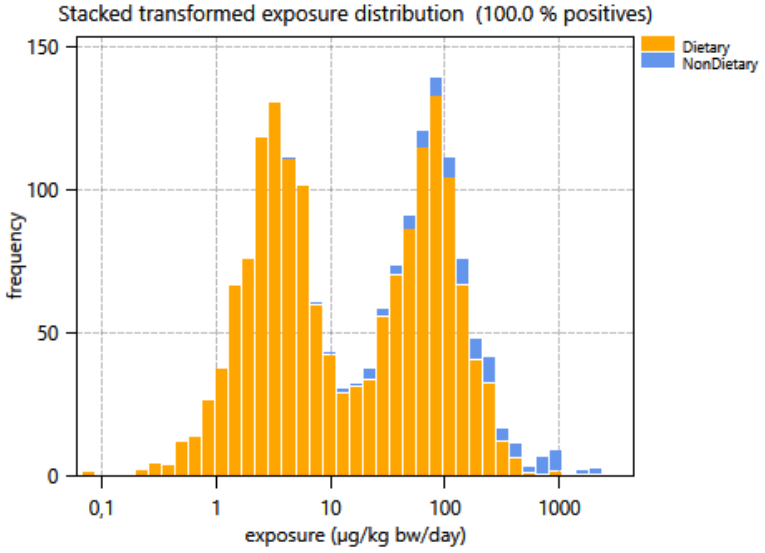
(non-food data from BROWSE; only for illustration, not final)

EuroMix

- Aggregate
- Total

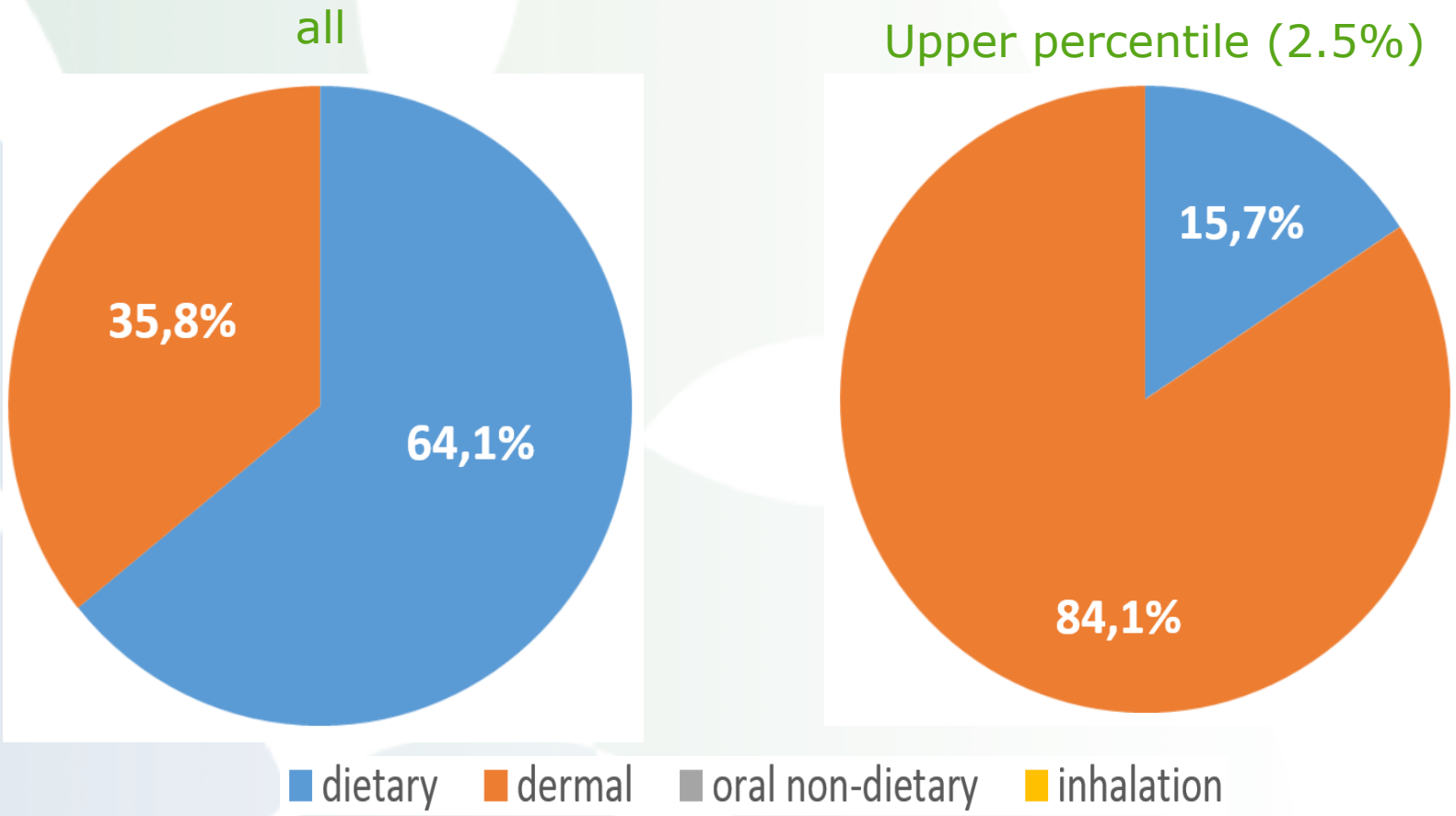






Contribution to total exposure for Triazoles

(only for illustration, not final)



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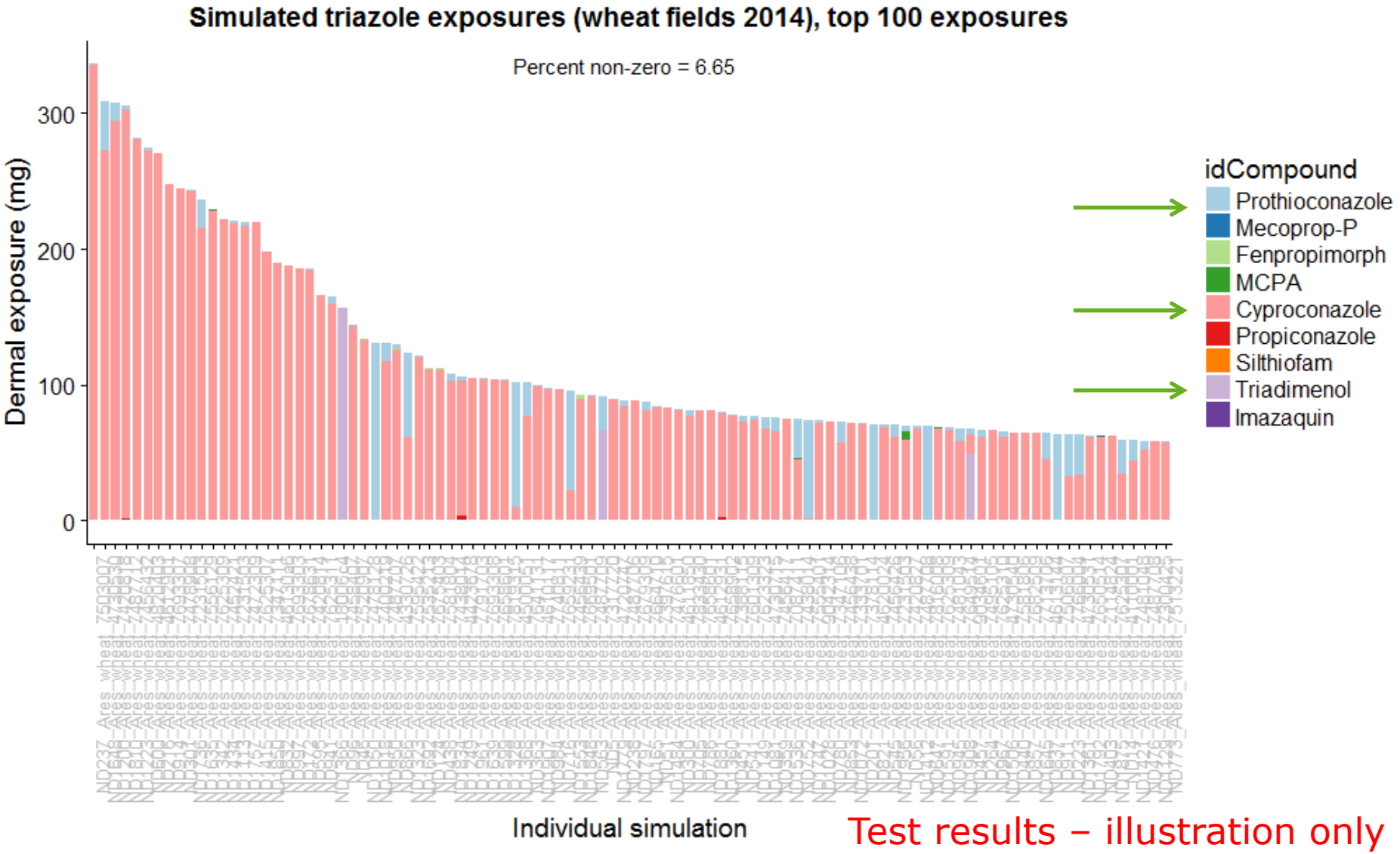
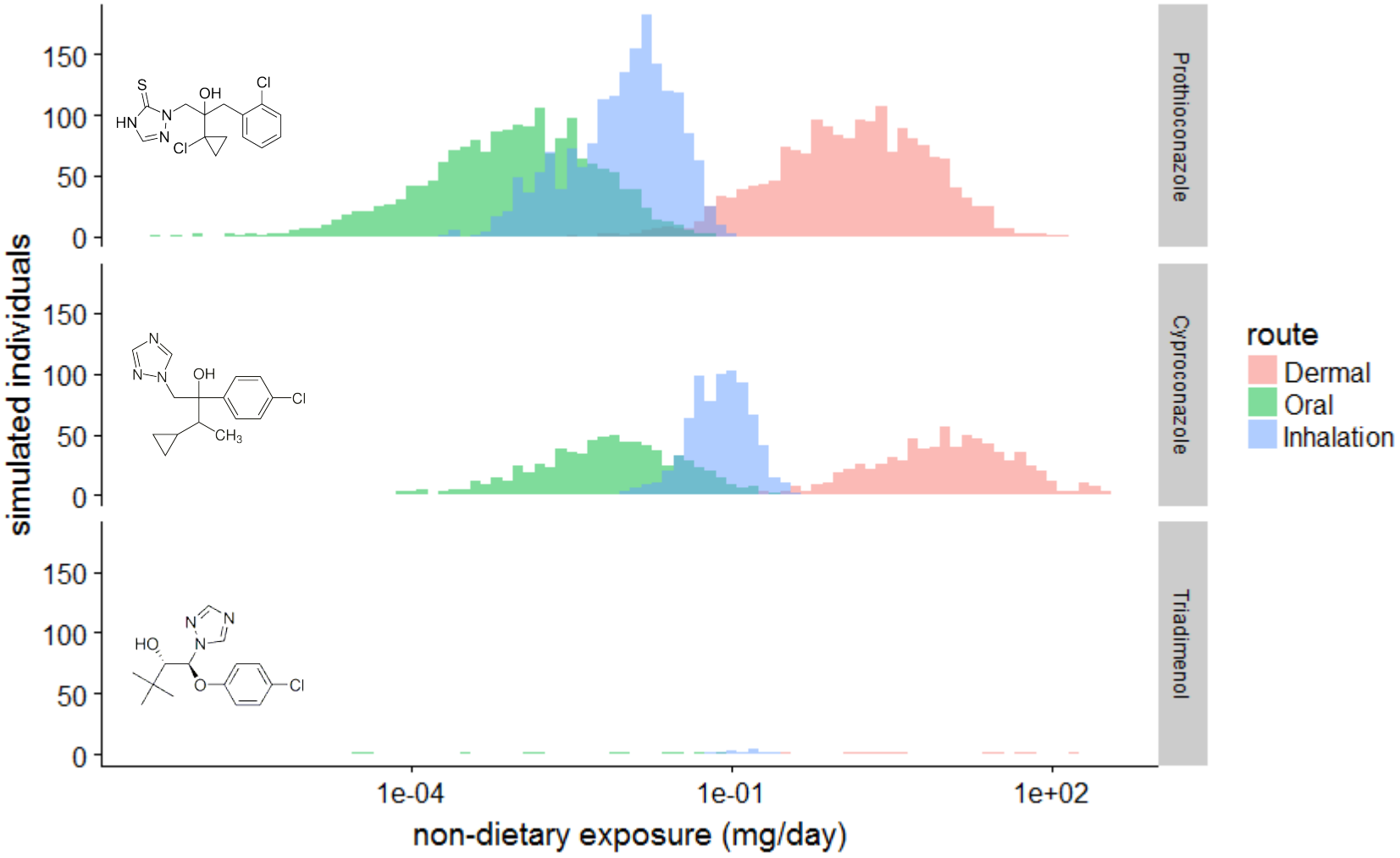
UK residents non-food exposure, wheat fields, RPF-weighted



Test results – illustration only

UK residents simulations Wheat fields, RPF-weighted

Test results – illustration only



Challenges

- Optimistic/pessimistic scenario: Treatment of non-detects needs to be harmonized; “medium” scenario needed
- Scarce data for non-food, right relation to food sources needs to be made clear
- Model Platform needs to be well documented, and simple enough to be usable by an average user

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EuroMix participants

22 beneficiaries from 16 countries linked to international organisations including WHO, FAO and EFSA. EuroMix is coordinated by RIVM.

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Ministry of Health, Welfare and Sport

WAGENINGEN UR
For quality of life

folkehelseinstituttet

BfR
Bundesinstitut für Risikobewertung

anses
French agency for food, environmental and occupational health & safety

INERIS
controlling risks for sustainable development

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Karolinska Institutet

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DTU Food National Food Institute DTU

ETH zürich

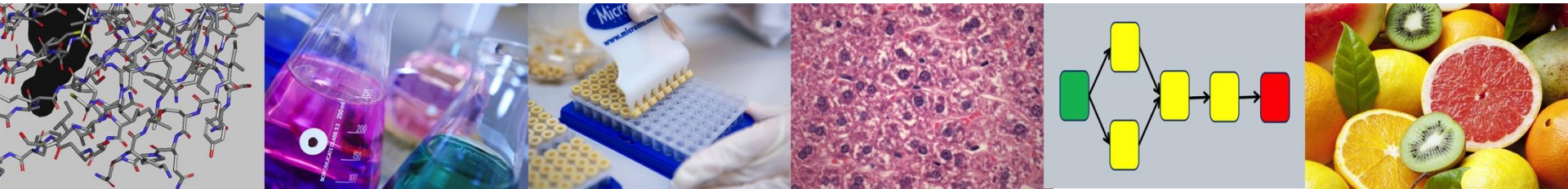
fera

matís

Open data and model platform

EuroMix Stakeholder Workshop, 18 May 2017, Brussels, Belgium

Hilko van der Voet, Wageningen University & Research



Objective EuroMix

Model integration and a web-based model and data toolbox

- To integrate hazard, exposure, toxicokinetic and toxicodynamic modelling approaches for mixtures;
- To integrate the various models and data into a web-based model and data toolbox openly accessible for stakeholders;
- Identify uncertainties and their influence on the results of cumulative and aggregated risk assessment.
- Building on Monte Carlo Risk Assessment (MCRA) platform developed in Acropolis project (2010-2013)

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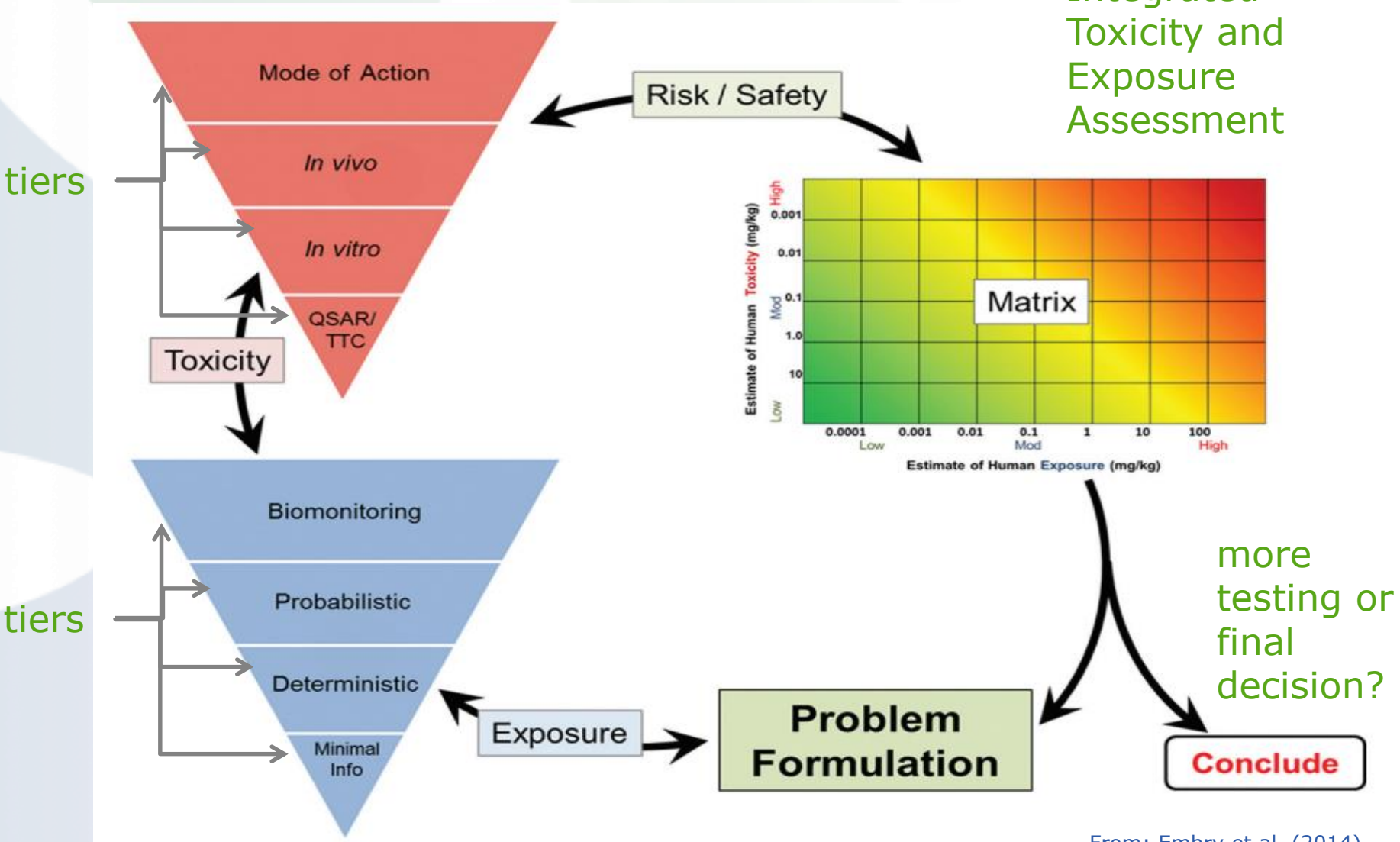
Setting the stage: Compare Exposure to Toxicity (Hazard)

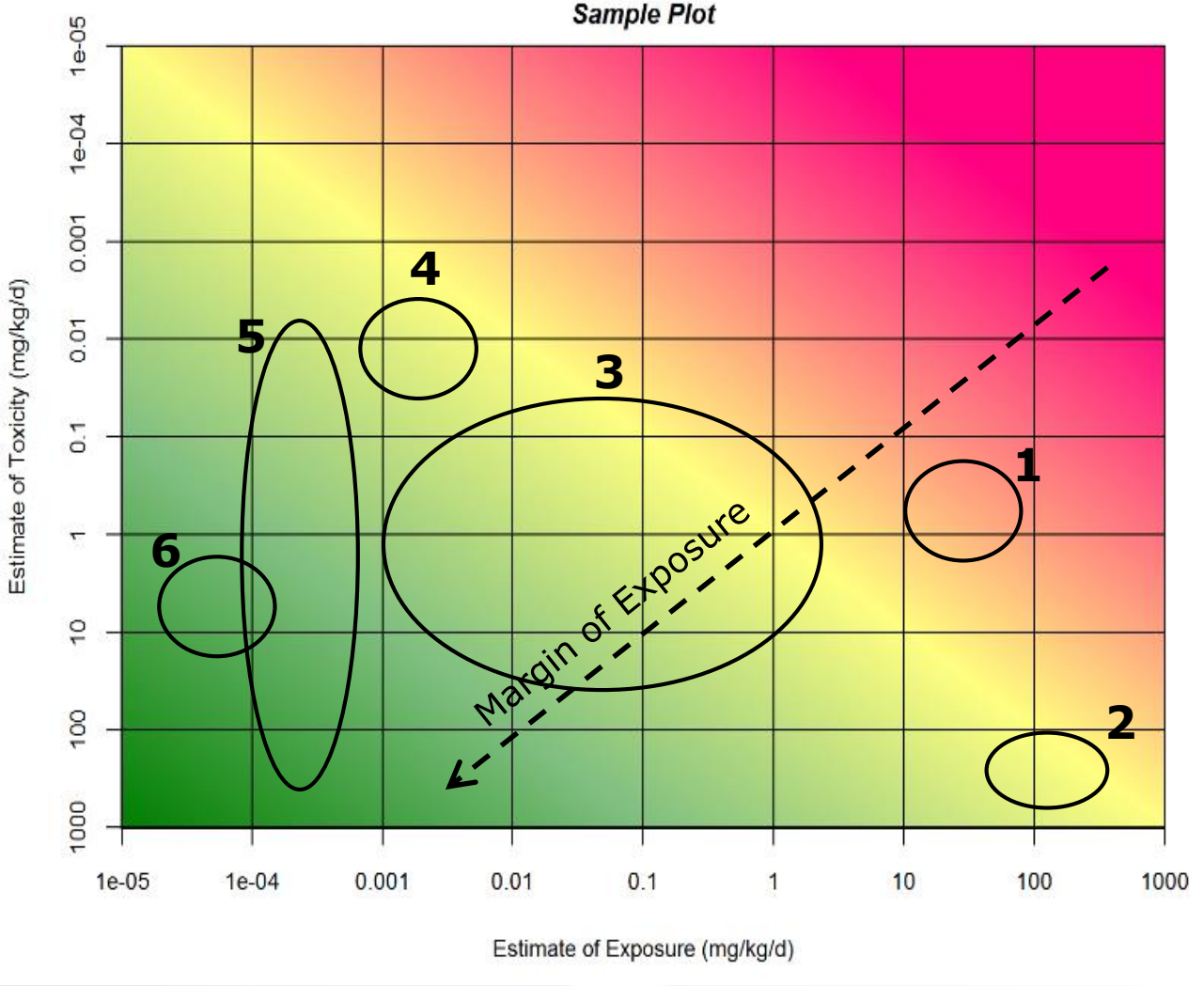
EuroMix

Integrated Toxicity and Exposure Assessment



From: Embry et al. (2014)

Comparing substances



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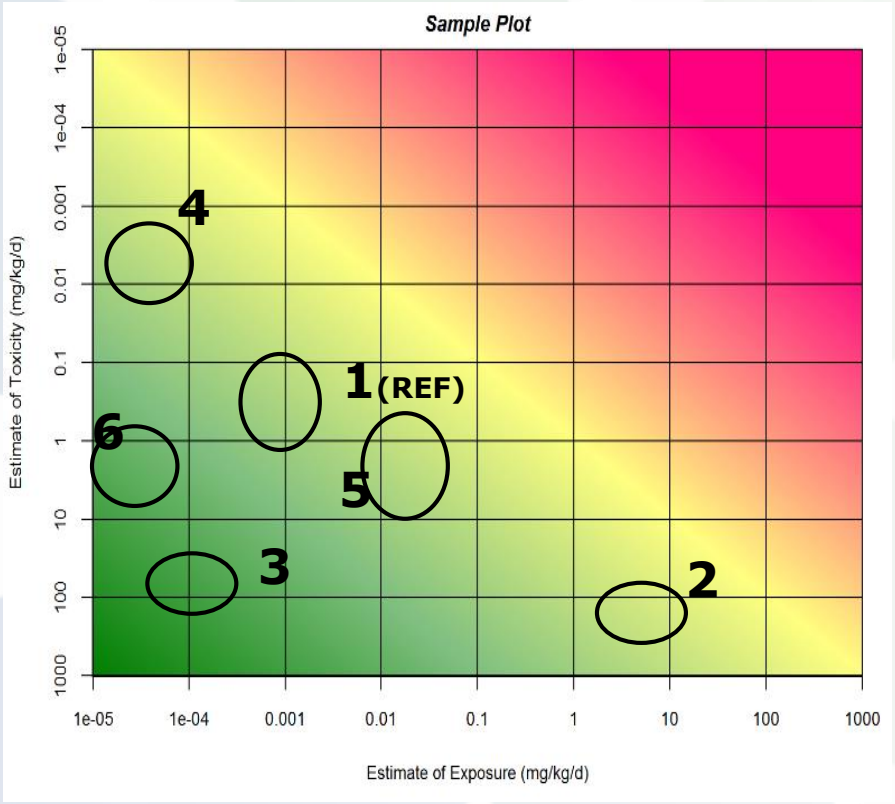
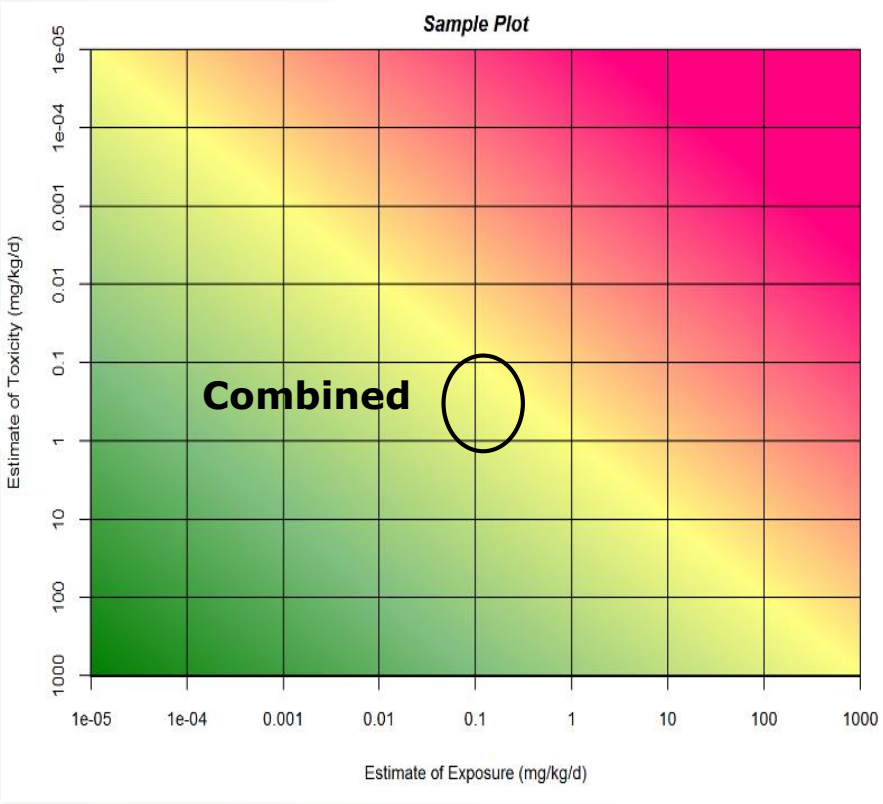
Cumulative risk assessment





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EuroMix data model - Primary entities - Definition questions

Populations
Data

National, European?
Age group, gender?

Health effects
Data

Definition?
Level (all, organ, effect, MoA)?

Sources of Exposure
Data

Test systems/Responses
Data

Dietary sources (foods)?
Food-as-eaten vs. food-as-measured
Also non-dietary?

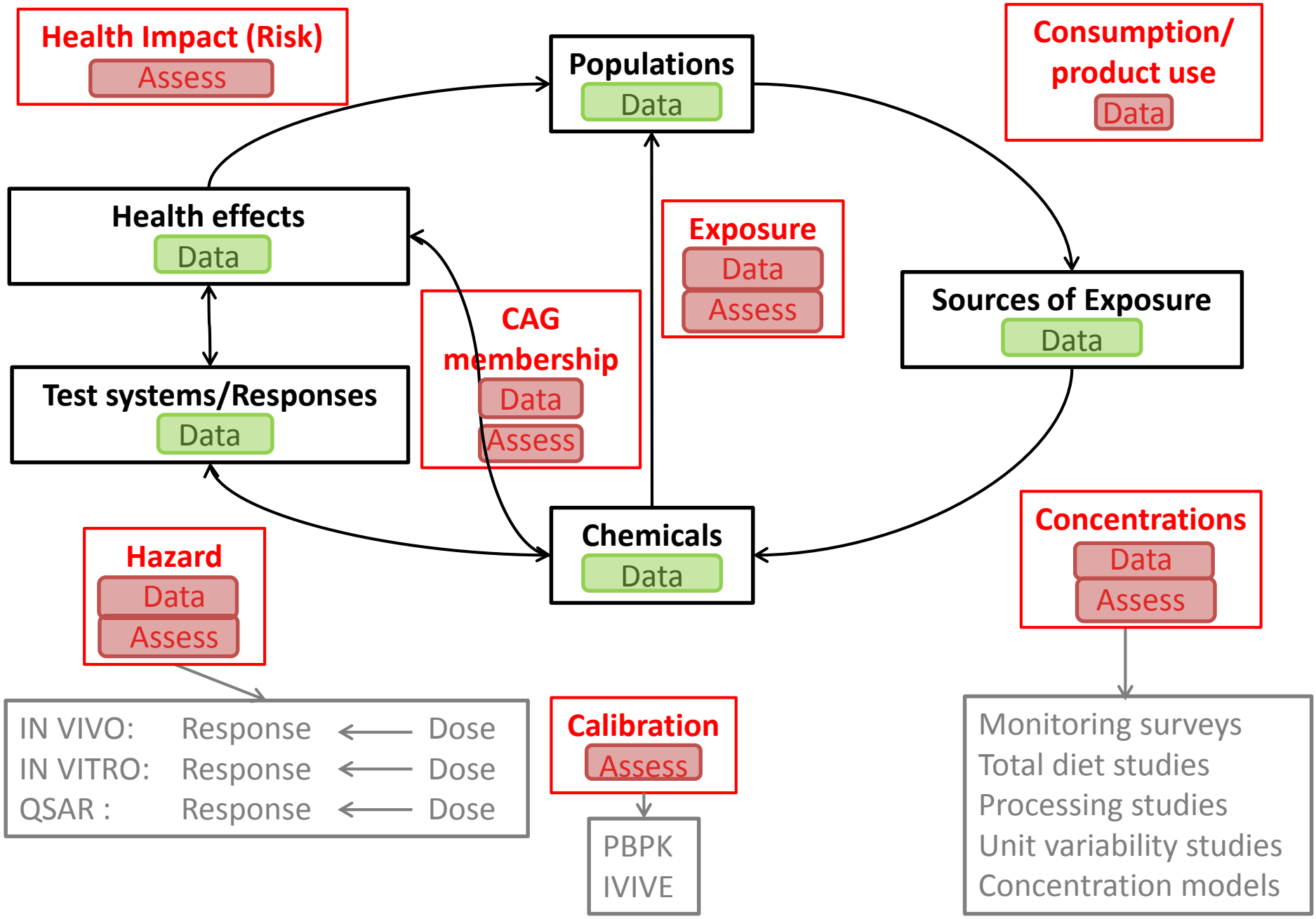
In vivo? In vitro? In silico?
What will be measured?

Chemicals
Data

Which are relevant?
Restrict to regulatory category? (e.g. pesticides, additives)

Proper coding systems needed: AOP wiki? FoodEx? EFSA Param?
Also allow alternative coding systems

EuroMix toolbox Overview



MCRA data organization principles

- Importance of flexible data model
- Input of calculations = data
- Output of calculations = data
- Keep data as much as possible under management of data managers
- Distributed system, not necessarily centralization of data
- e.g. omics data organised via European Bioinformatics Institute
- Options for data sharing, data managers decide (not the system manager)
- Create web services for interaction between systems

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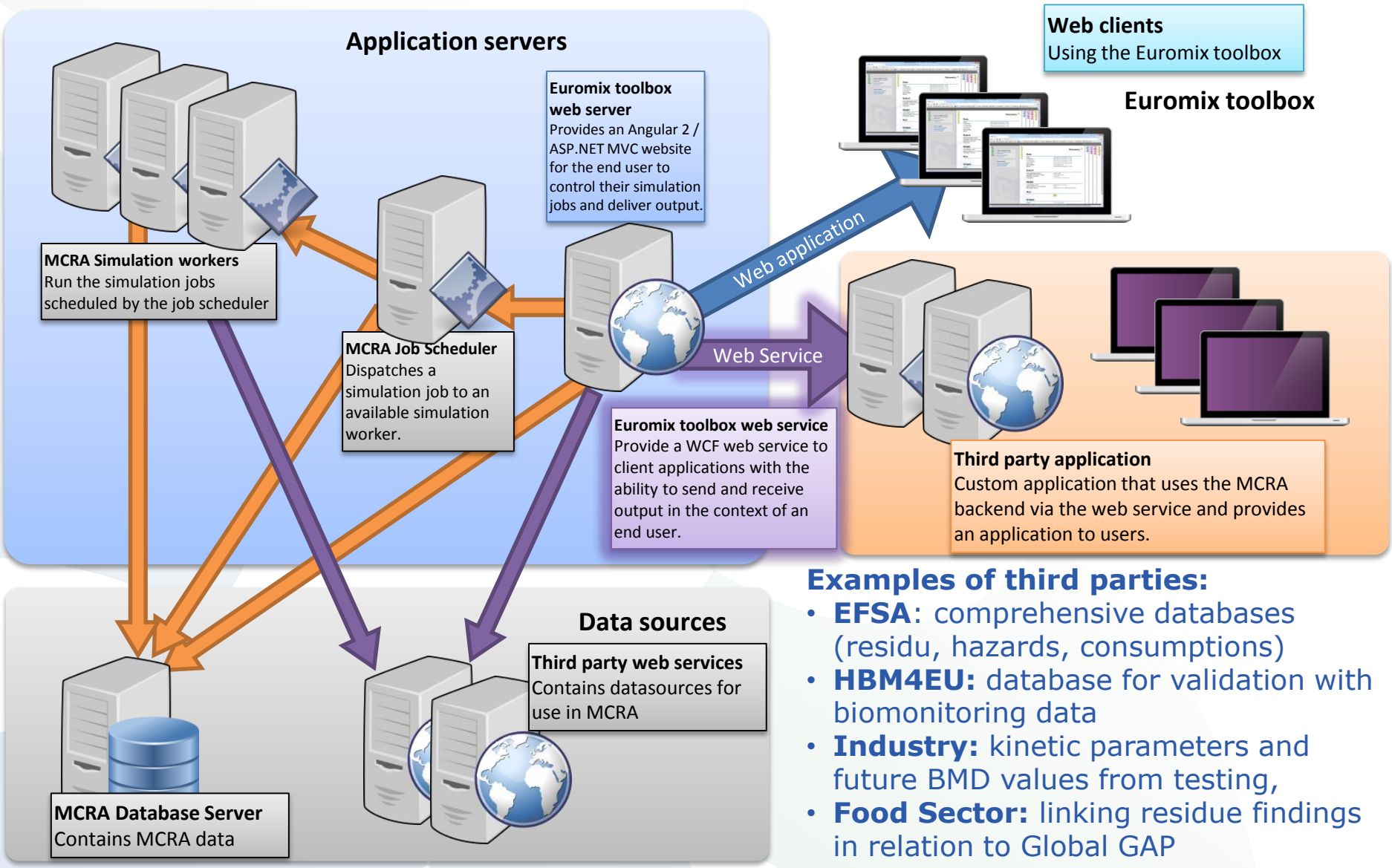
Global Infrastructure



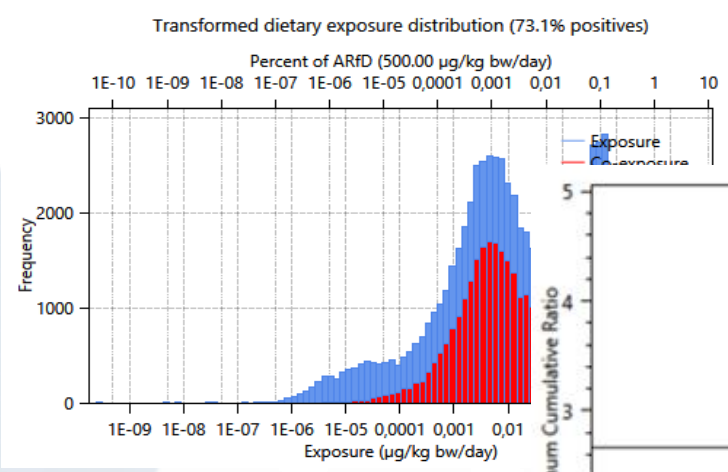
Examples of third parties:

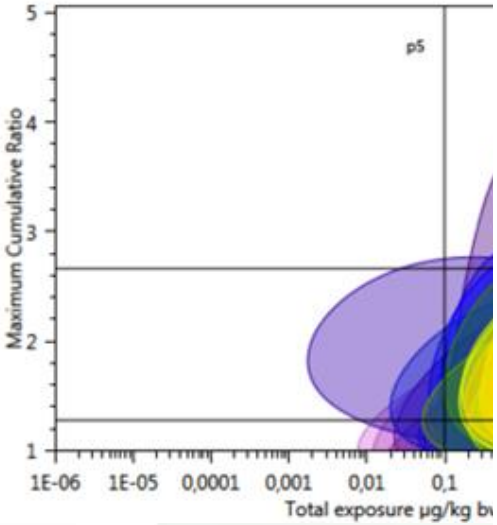
- **EFSA**: comprehensive databases (residu, hazards, consumptions)
- **HBM4EU:** database for validation with biomonitoring data
- **Industry:** kinetic parameters and future BMD values from testing,
- **Food Sector:** linking residue findings in relation to Global GAP

Modules for mixtures of substances

EuroMix

1. Visualise and tabulate co-exposure



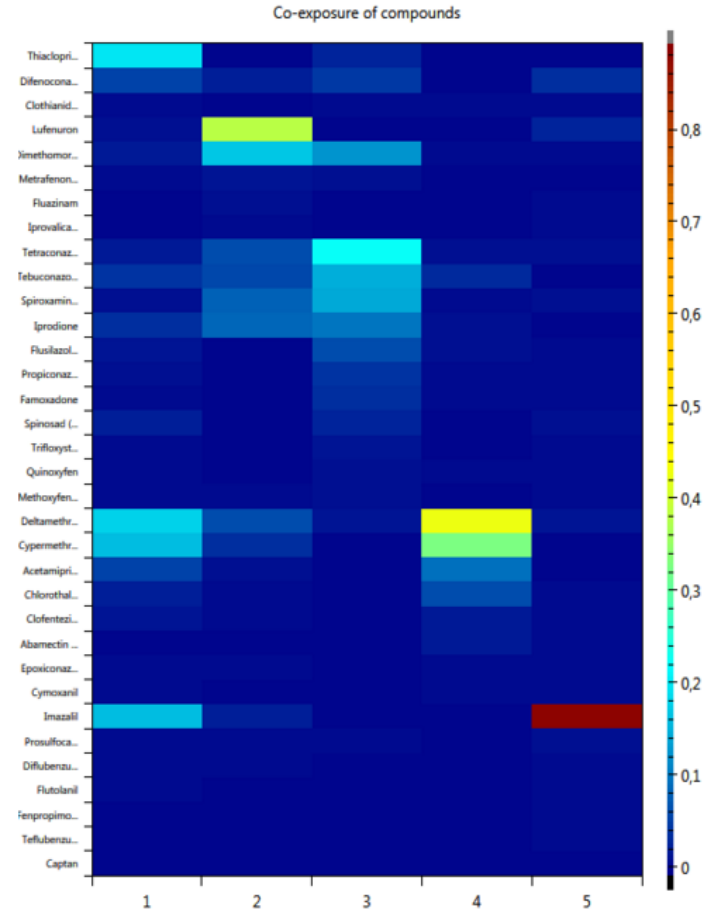


Number of compounds	%
0	0.0

Mixture selection

Number of compounds 39, number of exposure days 153 (out of 4079)
Ratio cutoff value = 5, total exposure cutoff value = 0 % (0 µg/kg bw/day)

Exposures are risk based (RPF's); 5 mixtures are estimated, sparseness constraint = 0.001

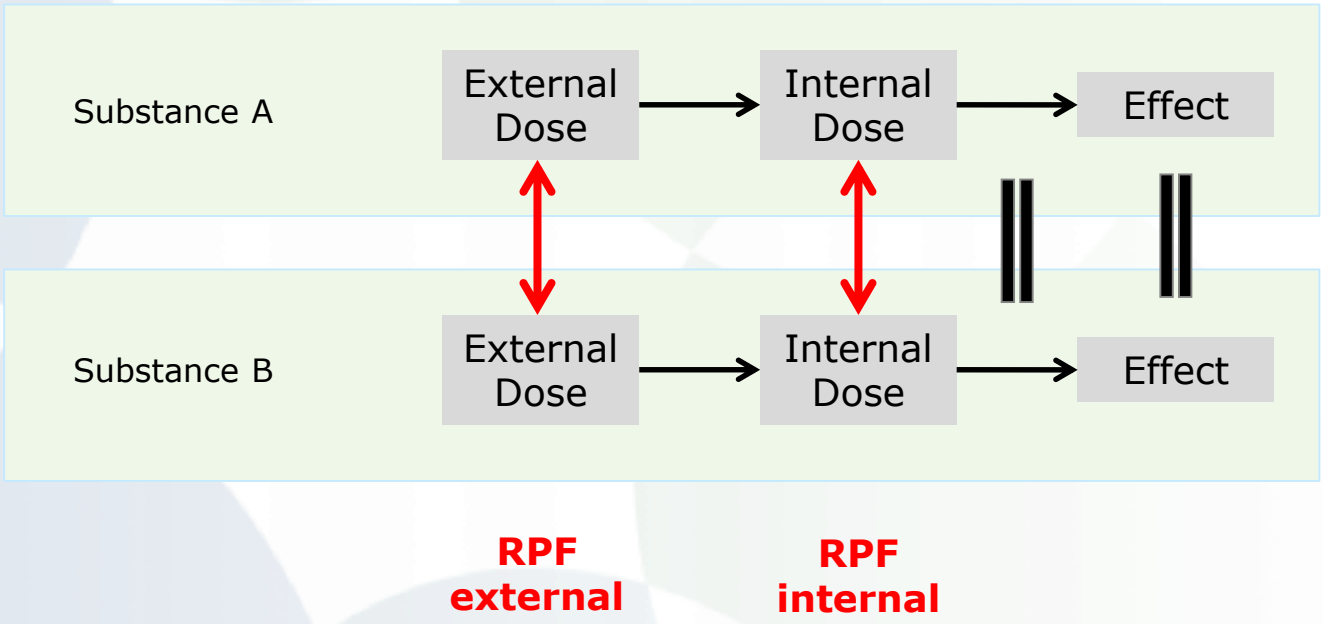


2. Maximum Cumulative Ratio (cumulative / highest single)

3. Models for mixture selection

Dose additivity model with kinetics

- Relative Potency Factors (RPFs) often based on external doses (no kinetic modelling)
- Kinetic models are needed in combination with in-vitro data
- If kinetic models are used, RPFs should be based on internal doses
- Also model uncertainty of RPFs from dose-response data!



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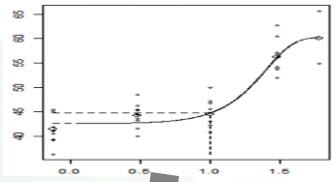
In-vitro in-vivo extrapolation

- How to link three types of data:

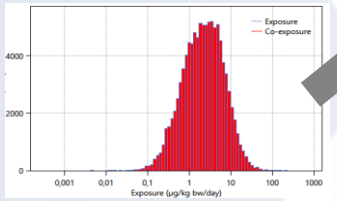


In-vitro dose-response data

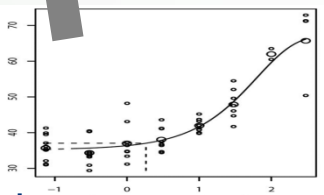
1. In vitro test system

2. In vivo test system

3. Target, human



Human exposure data



Animal dose-response data

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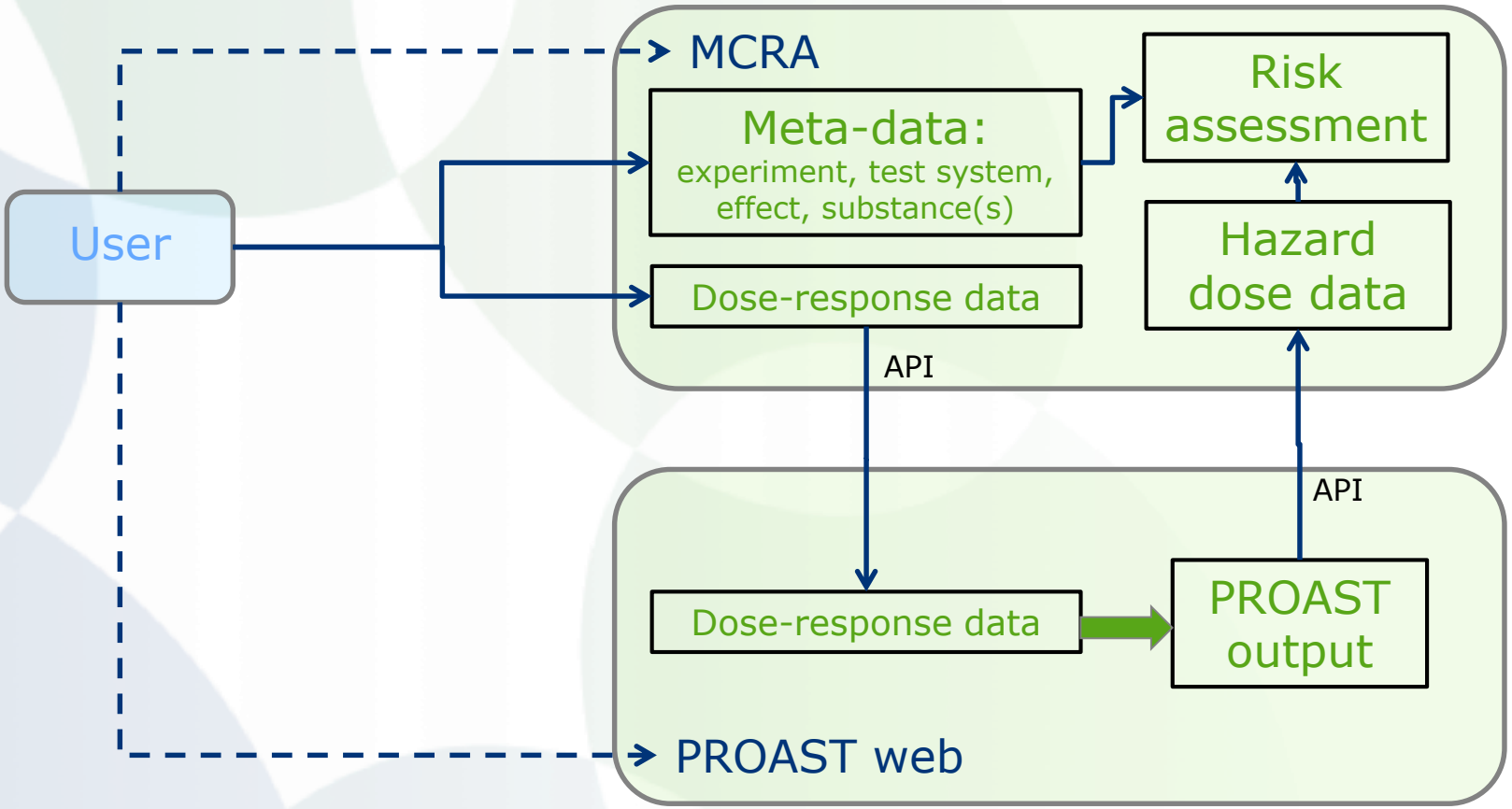
Linking to other programs (example dose-response modellling)

Design of EuroMix Toolbox:



API = Application Programming Interface

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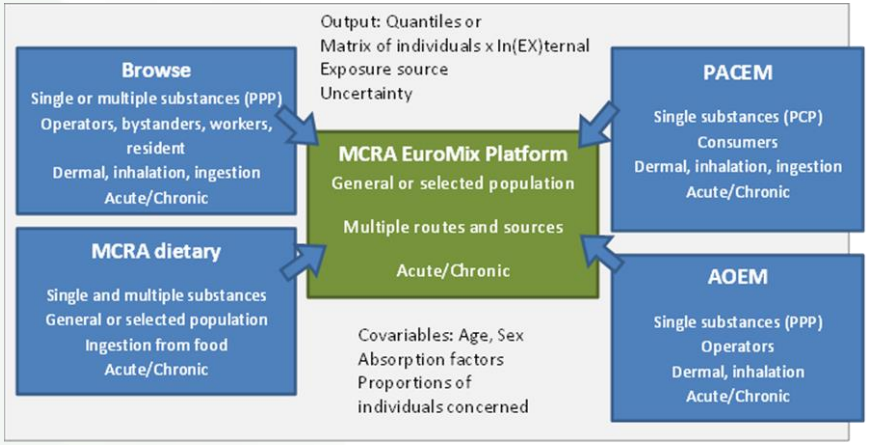
Links to external data sources



- Data from EuroMix partner models
  - Nondietary exposure
  - Dose-effect modelling (PROAST)
- EMBL-EBI ArrayExpress and BioStudies databases
  - Platform for multivariate data from omics methods
- EFSA Data Warehouse
  - Data on consumption, occurrence, tox, ...
- JRC Information Platform for Chemical Monitoring Data (IPCHEM)
  - Not yet much useful data for EuroMix
  - EuroMix could provide its data to IPCHEM

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Exploitation of results

- A web-based infrastructure will help to harmonize the approach on disputable issues (interest of regulators)
- For other chemicals than pesticides, there is an interest of risk managers to meet future regulatory requirements and or concerns of European citizens
- Platform can be useful for stakeholders. Current cumulative risk assessment for cumulative pesticide might be refined with new test information
- Combining multiple exposure routes (dietary and non-dietary) and biomonitoring of interest to DG ENVIRONMENT and JRC

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

Conclusions

- EuroMix will deliver a web-based platform
- Modular system of exposure, hazard and risk models for mixtures
- Data repository for EuroMix data
- Open platform, linking to external models and data
- Multi-tier, based on retain-and-refine principle
- Deterministic and probabilistic approaches

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Thanks to all EuroMix participants!

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Perspectives of European Commission Services on tools for risk assessment of chemical mixtures

Helen Clayton
DG Environment Unit C1 Clean Water
European Commission

EuroMix Stakeholder Workshop: Towards Harmonisation of Implementation of Test Strategies for Chemical Mixtures in Europe

Brussels 18 May 2017

Contents

- What do we need for mixture risk assessment?
- IPCheM (Information Platform for Chemical Monitoring) – how can it help and how can we help it?
- Some other relevant Commission initiatives
- Improving the assessment of risk from mixtures of chemical pollutants in surface waters

What do we need for mixture risk assessment? - I

Exposure data

- *Adequate limits of detection/quantification?*
- *Effective concentrations (bioavailability, equivalence)?*
- *Exposure routes?*
- *Spatial and temporal aspects?*

What do we need for mixture risk assessment? - II

Hazard data

- *Toxicity and other properties?*
- *Additive/synergistic/antagonistic interactions?*
- *Specific sensitivities (humans)?*
- *Population relevance of potential effects (ecosystems)?*

IPCheM – how can it help and how can we help it? - I

IPCheM portal

https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html

Tutorials/videos

https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html#tutorials

IPCheM – how can it help and how can we help it? - II

Features

- Access from a single platform
- Scope to host orphan databases
- Several matrices
- Various search functions (including by location)

Aims

- Link with more exposure databases (yours?)
- Link with tox data for risk assessment
- Link with data on observed effects (illness etc)

Some other relevant Commission initiatives

- Inter-service group (ISG) on mixture effects (ENV, EMPL, GROW, JRC, RTD, SANTE, EFSA, ECHA, EEA…)
- Fitness check of the chemicals legislation
- Non-toxic environment strategy (consistent with aim in 7th Environmental Action Programme to address combination effects of chemicals)
- Other research support – HBM4EU, SOLUTIONS
- Activity on effect-based methods under the WFD

SOLUTIONS FP7 project 2012-18

2nd SOLUTIONS Workshop on Prioritisation Methodologies jointly held with the FRAM Center for Future Chemical Risk Assessment and Management Strategies at Gothenburg University

"Integrating Mixture Risk Assessment into Prioritization Procedures under the EU Water Framework Directive"

9 – 10 February 2017

University of Gothenburg, Sweden

SOLUTIONS mixture workshop discussion groups

DG 1 How to identify priority mixtures?

DG 2 How to identify drivers of mixture risks?

DG 3 How to set Environmental Quality Standards (EQS) for priority mixtures?

Risk assessment of chemical mixtures in surface waters - I

Current situation

- Water Framework Directive (WFD) lists priority substances (pollutants in surface waters posing a risk at EU level to the environment and to human health); Environmental Quality Standards Directive specifies EQS (most sensitive endpoint)
- Risk assessment mostly on substance-by-substance basis.

  Some exceptions (groups):
  - **PAHs (EQS for marker compound)**
  - **Dioxins and dioxin-like compounds (EQS for sum of three types using TEQs)**
  - **Group of PBDEs (EQS for sum of 6 congeners)**

Risk assessment of chemical mixtures in surface waters - II

Current situation *continued*

- Watch list contains substances to be monitored temporarily to determine the risk posed by them (should they be PS?)
- First watch list (2015) contains 10 substances/groups of substances including (as groups, but without an EQS)
  - **beta-estradiol and estrone**
  - **three macrolide antibiotics**
  - **five neonicotinoid pesticides**
- How to deal with ever-growing list of individual priority substances? (33 PS in 2001 -> 45 PS in 2013 -> ??) More holistic approach to assessing chemical status under the WFD?

Risk assessment of chemical mixtures in surface waters - III

Activity on Effect-Based Tools/Methods (EBT/EBM)

- *Under the Common Implementation Strategy (CIS) for the WFD*
- *Overseen by CIS Working Group Chemicals*
- *Led by volunteer Member States (IT, SE), CH and the JRC*
- *Following up work on an earlier technical document (2014) on aquatic effect-based tools*
- *Aiming to deliver outputs by the end of 2018*

Risk assessment of chemical mixtures in surface waters – IV

Main objective of the EBT/EBM activity

To examine and further document the possible implementation of EBT/EBM for monitoring and assessment of chemical status in the WFD context, bearing in mind their possible application under the Marine Strategy Framework Directive.

- Relevant to more holistic approach to assessing chemical status and to overcoming detection/quantification difficulties.
- Relevant to considering links between chemical and ecological status, but NB human health!

Risk assessment of chemical mixtures in surface waters – V

- Particular tasks for EBT/EBM activity:
  - Identifying relevant MoAs (effects; e.g. Cumulative Assessment Groups) and available EBTs for them
  - Deriving trigger values
  - Assessing the robustness and comparability of different tools, and their maturity for routine implementation (also their cost)
  - Identifying the most significant contributors to the pollution effect → measures
- Other considerations:
  - Usability alongside traditional chemical analysis
  - Equivalent level of protection (trigger value cf EQS)
  - Coordination with approaches under other legislation
  - Coverage of secondary poisoning (not just direct ecotoxicology)

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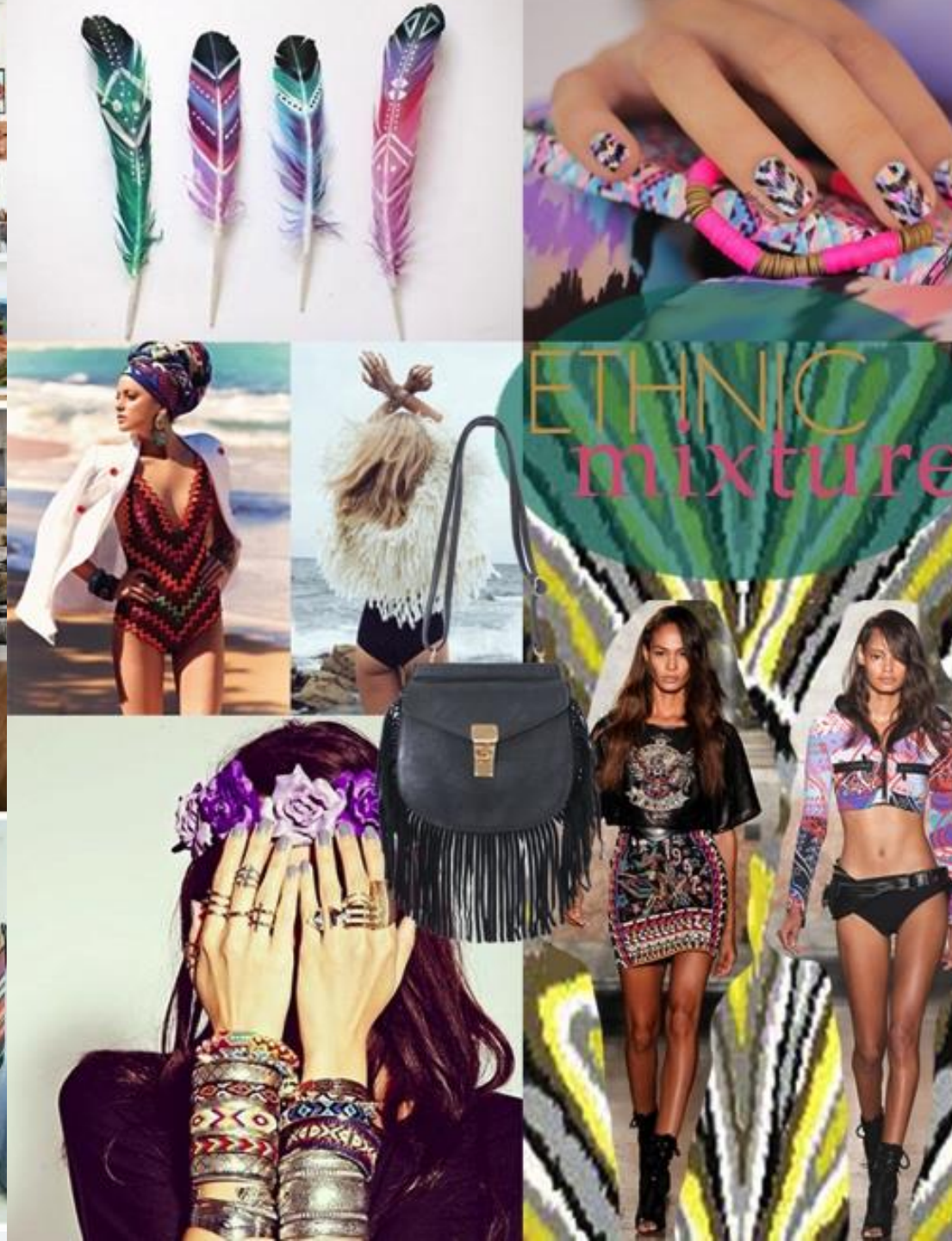
ETHNIC
mixture

EuroMix

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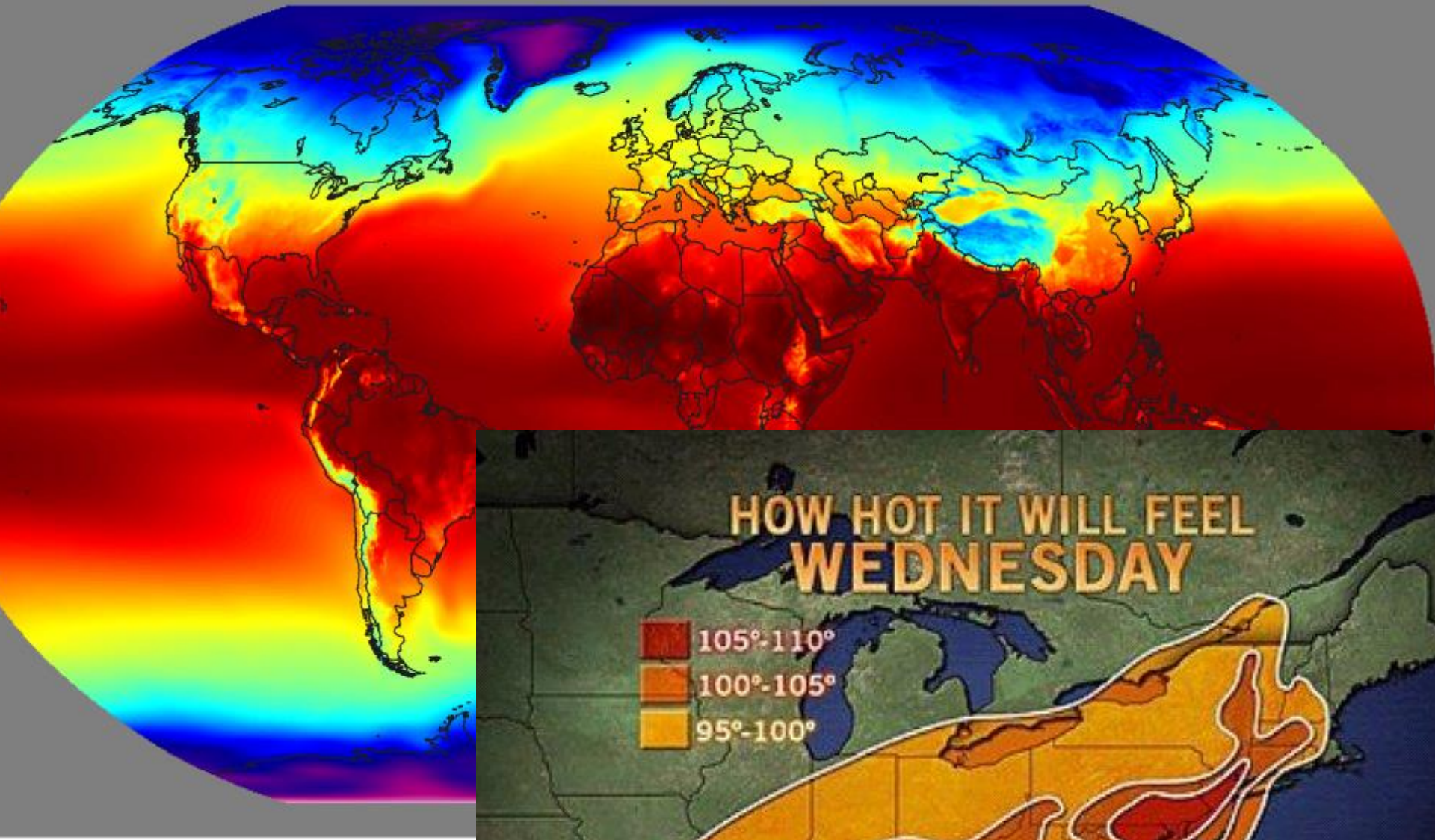
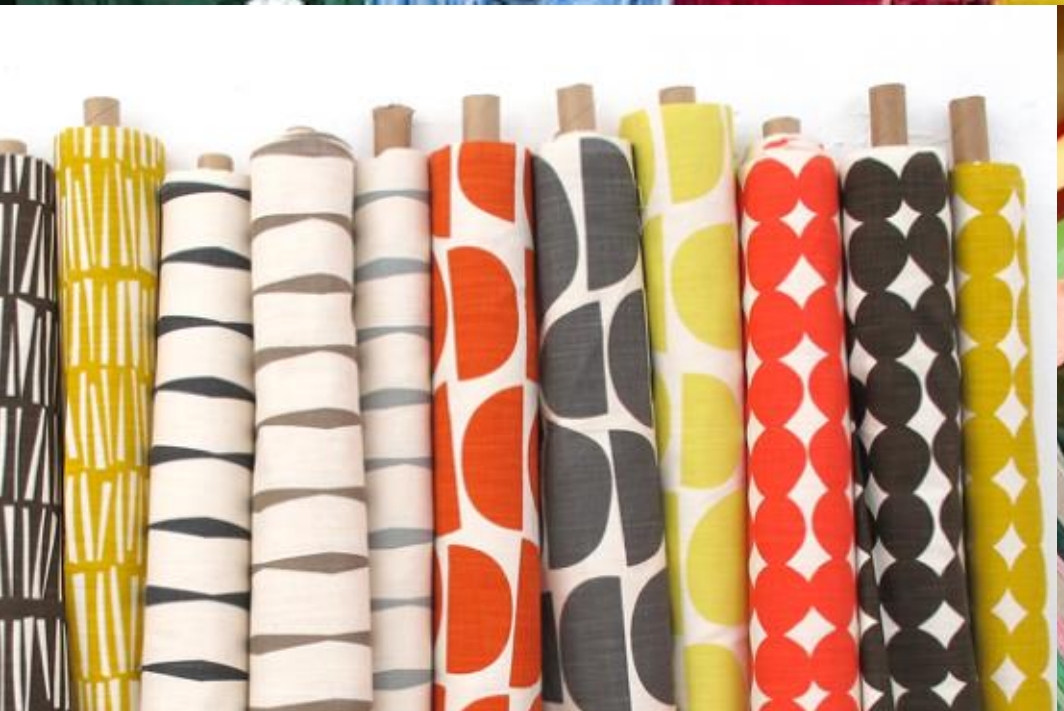


HOW HOT IT WILL FEEL
WEDNESDAY
105°-110°
100°-105°
95°-100°



EuroMix

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