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No. 140

WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals

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FOREWORD

This document is a report of the WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals which was held on 15-16 February 2011 in Paris, France. The workshop was held following the proposal from the 45th OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in February 2010.

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology of the OECD.

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REPORT OF THE WHO OECD ILSI/HESI INTERNATIONAL WORKSHOP ON RISK ASSESSMENT OF COMBINED EXPOSURES TO MULTIPLE CHEMICALS, 15-16 FEBRUARY 2011, PARIS, FRANCE

BACKGROUND

1. One of the aims of the OECD Existing Chemicals Program is to work with member countries develop common approaches to environmental assessments and so that they can share their experiences and points of view.

2. In February 2010, the 45th Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology welcomed the offer from the World Health Organization (WHO) to co-host the *International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals*[1] with the purpose of discussing a number of case studies on combined exposure that demonstrate the draft *WHO/IPCS Framework for Risk Assessment of Combined Exposures to Multiple Chemicals* and to identify needs for further work in this area. It was also decided that the OECD Secretariat would submit a proposal to the 47th Joint Meeting for further work in this area based on the outcome of the workshop.

WORKSHOP

3. The workshop was held on 15-16 February 2011 in Paris, France, at the OECD Headquarters. The workshop programme is outlined in Annex 1.

4. The workshop was organized by WHO and OECD, with input from the International Life Sciences Institute (ILSI), a non-governmental organisation in official relations with WHO. The workshop was attended by experts nominated by Canada, Czech Republic, Denmark, France, Germany, Italy, Japan, Mexico, the Netherlands, Poland, Turkey, the United Kingdom, Switzerland, the United States, the European Commission, the Business and Industry Advisory Committee to OECD (BIAC), International Council on Animal Protection in OECD Programmes (ICAPO), United Nations Environment Programme (UNEP), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), by members of the ILSI/Health and Environmental Sciences Institute (HESI) Mixtures Committee and of the WHO Combined Exposures Planning Group, and by WHO, International Life Sciences Institute/HESI and OECD. The list of participants along with their affiliations and contact details is attached to this document as Annex 9. The workshop was chaired by the following: Session A – Dr. Bette Meek; Session B – Dr. Theo Vermeire; Session C – Mr. Henrik Tyle and Dr. Gino Scarano.

[1] subsequently published with the following reference: M.E. (Bette) Meek, Alan R. Boobis, Kevin M. Crofton, Gerhard Heinemeyer, Marcel Van Raaij, Carolyn Vickers (2011) Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regulatory Toxicology and Pharmacology: doi:10.1016/j.yrtph.2011.03.010

Opening

5. Bob Diderich (OECD) and Carolyn Vickers (WHO) welcomed the participants on behalf of the Secretariat.

Purpose, Objectives and Specific Aims

6. The aims of the workshop were to:

- inform participants about the WHO framework and explore application of the framework through discussion of a number of illustrative case studies;
- share information about current issues in combined exposure assessment; and
- identify needs for further work on combined exposure assessments to be undertaken by the organisations present at the workshop or others.

Format of the Workshop

7. The workshop was divided into three sessions. In Session A, the WHO Framework was introduced and participants discussed several case studies. The opening presentations for this session are presented in Annex 2. Case studies and presentations of the cases discussed in the breakout sessions are included in Annex 3. Answers to questions posed to the breakout sessions during the case study discussions are included in Annexes 4-6 for each of the breakout sessions. In Session B, countries and other groups presented experiences and policy considerations regarding risk assessment of multiple chemical exposures (see Annex 7). Session C was designed for participants to consider priority actions to address barriers to implementing the use of risk assessment of combined exposures to multiple chemicals and also concluded on priorities for further work (see Annex 8 for answers from breakout groups on barriers/next steps).

Session A: WHO Combined Exposures Framework Introduction

8. Session A opened with a presentation on the main features of the WHO Framework by Marcel van Raaij (see Annex 2). This presentation included discussion of the terminology (designed to eliminate ambiguity), the problem formulation step to be conducted prior to commencing an assessment, and Tiers 0 through 3, with examples to demonstrate use of the tiers.

9. Bette Meek then presented an illustrative case study using the framework, based on a screening assessment of polybrominated diphenyl ethers highlighting differences in conservatism (caution) as well as assumptions and data used for Tiers 0 and 1 (see Annex 2).

Session A: Carbamates Case Study

10. Elizabeth Shipp introduced a case study of dietary exposure to N-methyl carbamates, and then three breakout groups discussed the carbamates case study (see Annex 3). The breakout sessions were facilitated by Alan Boobis, Marcel Van Raaij, and Elizabeth Shipp. Rapporteurs were Karluss Thomas, Rosemary Zaleski and Nancy Beck. This case addressed several tiers and several questions were posed to participants for this case study. Selected questions and a summary of answers are presented here (see details in Annex 4).

Question 1a: For this case study, was it advantageous to go through Tier 0 despite having a large amount of data?

11. Overall, participants considered Tier 0 to be useful even though the complexity of the Tier 0 carbamates' exposure data was more consistent with that of a higher tier. The

threshold of toxicological concern (TTC) approach used for the hazard assessment in this case study was considered to be adequately protective and appropriate for Tier 0. Participants also noted that Tier 0 could start with a broad assessment (e.g., using all exposure routes; all products in which the chemicals appear) to determine where to further focus efforts. Tier 0 was considered useful for streamlining the decision making process.

Question 1b: If you have data, do you have to use all of it?

12. Differing opinions were given about whether all available data for the assessment group needs to be used; one breakout group thought that all data should probably be used if available, but another group considered that some of the hazard data could be ignored (e.g., use maximum residue levels [MRLs] for the carbamates, or in other cases, use data only for the most potent chemical) at Tier 0 to determine the need for higher tier assessments. One group raised the possibility that different tiers could be used for different components or for hazard versus exposure. Considerations such as adversity of effects, available resources, or expected economic impacts of risk management could determine whether or not all data are used. Time-critical emergency situations might also dictate the use of TTC (for example) even if additional hazard data are available.

Question 2: How might the problem formulation determine which Tier is needed?

13. One group noted that although problem formulation should drive the assessment, it should not influence which tier is needed. On the other hand, problem formulation might need to be revisited as the assessment is refined; furthermore, sensitivity analysis was considered to be a key driver for refining tiers. At Tier 0, the most sensitive endpoint could be used whereas multiple modes of action (MOAs) could be considered at higher tiers. Participants reiterated that Tier 0 could start with a broader assessment (e.g., more chemicals in an assessment group) and be narrowed depending on results (see Question 1a discussion). One group noted that for ecological assessments, problem formulation can certainly have an impact on the tier chosen: data from only certain species/endpoints might be used in Tier 0, whereas multiple species might be considered at higher tiers. Regardless of exact tier suggested by the problem formulation stage, a major theme was the need for communication and transparency during the problem formulation stage to explicitly state the scope of the assessment (e.g., chemical groupings can influence the tier used), assumptions and uncertainties used.

Question 3: Are there key aspects of combined exposure that have been overlooked, omitted, or not realized within the framework as illustrated by this example?

14. More than one group suggested that guidance and work on grouping chemicals was needed (e.g., refinement at higher tiers based on exposure; development of consistent/harmonized assessment groups according to MOAs or common effects). Also, additional work (such as development of a case study) could be done to apply the WHO Framework to ecological assessments because considerations would likely be different than for human health assessments. Attention should also be given to whether/when it is appropriate to combine acute and chronic risks. Also, further work could address co-occurrence (e.g., whether high-end exposures to a large group of chemicals are likely to occur together).

Questions 4a and 4b: What are the current barriers / blockers that we face in utilizing this tiered approach? Are there difficult decision points?

15. Some barriers to using the tiered approach included the need to communicate details associated with use of probabilistic assessment; without this information, risk managers may be unwilling to use the results. Also, descriptions of how each tier improves the assessment and reduces uncertainty are needed (e.g., for carbamates, the reason to skip "Tier 2" was not transparent in the original evaluation from which the case study was drawn). In the regulatory

arena, there are multiple programs that might not allow assessments to easily fit into the framework because the chemicals (and different media such as air, water) are handled by different legislation or organisations. Other barriers include the lack of harmonization regarding "acceptable" margins of exposure for risk characterisation. Data availability might be a disincentive to using the tiered approach. In the scientific arena, examples of barriers included uncertainties about how to group chemicals, determining relevant co-exposures in relevant timeframes, as well as how to assess persistence and bioaccumulation. A group of barriers were related to communication, including public fears and media scrutiny and the difficulty in documenting/communicating uncertainty.

Chair's Summary

16. The chair of Session A, Bette Meek, summarized the main topics of discussion. She noted, generally, the usefulness of Tier 0. Also, a number of comments addressed problem formulation, and suggested additional considerations during this stage of the process would include availability and amount of data and relevant regulatory constraints. There is also a need to be careful about expressing uncertainty. Further, it is important to distinguish scientific certainty from public health protection; by building in a high degree of conservatism (caution) that results in no risk, public health would be protected even if the science regarding the particular assessment is uncertain. How the results are communicated was also considered to be important – the public should understand the uncertainties and degree of caution in the assessment. Finally, potential use of the framework for ecotoxicity endpoints needs to be additionally considered.

Session A: Tier 0 Case Studies

17. Susan Felter introduced case studies that demonstrated the use of Tier 0 of the WHO Framework, and three breakout groups discussed the Tier 0 case studies (see Annex 3). The assessments considered by one or more of the groups included: 1) chemicals in surface water chosen based on their detection in Minnesota lakes; 2) 37 branched- and straight-chain unsaturated carboxylic acids and esters of these with aliphatic saturated alcohols used as food additives; 3) industrial air emissions of commercial hexane that contains several structurally-related constituents; and 4) 94 pharmaceuticals in surface water. The breakout sessions 1 and 2 were facilitated by Linda Teuschler and Keith Solomon, with Moiz Mumtaz and Marcel Van Raaij as co-facilitators for group 3. Rapporteurs were Gino Scarano, Lonneke Van Leeuwen and Jean-Lou Dorne. Selected questions and a summary of answers are presented here. Detailed answers from each of the three breakout groups are presented in Annex 5.

Question 1a: Are the conservative assumptions in the Tier 0 useful for screening-level approaches?

- Are they so conservative that they are unlikely to be discriminating?
- Are they sufficiently conservative to ensure adequate health-protection?
- If not, how could / should this be addressed?

18. The numbers of chemicals included in an assessment could dictate conservatism (e.g., unknown chemicals in the media or product that are not assessed could lead to an underestimation of risks whereas including too many in an assessment group regardless of adverse outcome could overestimate risks). Thus, there may be practical limits to the number of chemicals that could be included in an assessment group. Information on whether chemicals are already determined to be Generally Recognized as Safe (GRAS), a designation of the U.S. Food and Drug Administration, could help shape the assessment.

19. There was a suggestion that using highest intake values divided by lowest body weights is sufficiently conservative. For food additives, the assessment was considered very conservative in many respects and the breakout group considered this to be appropriate for Tier 0 but would require revision at higher tiers. On the other hand, the drinking water intake values chosen for the surface water example would not be sufficiently conservative for cases in which other assumptions were also not conservative.

20. The TTC approach was considered reasonable and very health protective for the surface water example, especially because all detected compounds, regardless of adverse outcomes, were assessed using dose additivity. TTC may not be good for pharmaceuticals, however, given that they have specific biological effects (combined with the fact that they were not generally included in the groups of chemicals used to develop the TTC approach). Also, other approaches are needed for hormonally-active compounds. For commercial hexane, it was assumed that the hazard values were conservative enough despite some problems with using TTC for n-hexane and the choice of Cramer class.

Question 1b: Are the Tier 0 exposure assumptions sufficiently conservative to allow for:

- Changes in ratios?
- Multiple route / route to route extrapolation?
- Spatial & temporal variation?

21. Variability in concentrations of constituents (e.g., in a commercial product) that have different toxicities could lead to insufficient or overly conservative assessments and participants suggested uncertainty analyses be conducted to address this concern. Also, data on natural compounds in food (or other media) similar to those in the assessment group should be evaluated; differences in the relative contributions from anthropogenic and natural sources could influence the assessment.

22. Route to route extrapolation should be carefully considered, and could result in certain (e.g., portal of entry from inhalation) effects being missed when using the TTC method, which is based on oral studies.

23. With respect to spatial and temporal variation, one group noted that bioaccumulative chemicals should receive special attention to ensure sufficient health protection. Again, predictive tools for estimating bioaccumulation could be used to help inform temporal changes. Participants also noted that spatial/temporal variations should be considered at higher tiers. Others noted that samples need to be representative of the situation. For example, for surface water case study, samples were taken from Minnesota lakes in the United States and thus, extrapolation to other areas is not necessarily appropriate.

Question 2: For each of these examples, was the grouping appropriate?

24. In the case of commercial hexane, n-hexane differs from the other components and thus, the grouping using universal application of Cramer class 1 to all components was not considered appropriate. In addition, the TTC method isn't designed to be used with neurotoxic compounds, the target toxicity for n-hexane. For pharmaceuticals, it was considered appropriate to group different MOAs at lower tiers, but other methods of grouping should be used for higher tiers (e.g., not combining different MOAs into a single group). In general, the Cramer class was considered inappropriate for compounds such as pharmaceuticals and pesticides that have specific bioactive properties. Generally, weight of evidence of the data should be considered.

Question 3: What other data and methods not represented in these examples could be used for a tier 0 assessment?

25. Several predictive methods (QSAR) and use of physicochemical properties could help estimate exposures. Also, there are many models for assessing pharmaceuticals (which can also be used to address degradation products), although they are not harmonized or transparent. One method is to use the lowest therapeutic dose divided by uncertainty factors; however, even using therapeutic doses, many pharmaceuticals don't have pediatric uses and therefore, therapeutic doses are specific to adults. Also, some therapeutic doses are specific to short term use whereas others are used for a longer time period; this should be considered when comparing with exposure scenarios (e.g., drinking water is generally a long-term exposure).

Question 4: What issues need to be considered in communicating the results of a Tier 0 assessment?

26. The TTC approach should be communicated to the public so that they can understand the level of conservatism (caution). Also, communication of the level of conservatism (caution) is needed so that if the results of a Tier 0 assessment suggest that higher tiers should be evaluated, the public can understand that this might not necessarily equate to a public health risk. More generally, one group noted that assessments should be communicated using lay language and should include explanations about what cannot be done. Also, the need to describe uncertainties was recognized; one group suggested that they should not be quantified but qualitative descriptors could be used for the public. Comparisons should also be made to put the assessment into context (e.g., if natural background exposures are large, this can be mentioned). More work is needed to communicate that addressing/decreasing uncertainties can increase assessment costs. Clarity is especially needed in the problem formulation stage – the reader should understand what the assessor is trying to achieve. Risk communication experts should be engaged early in the process. Although communication to the public is important, the message should always be tailored to the audience because it is also important to communicate with risk managers in a continuing dialogue.

Chair's Summary

27. The Session A Chair summarized the key points from the Tier 0 case study discussion. Firstly, she noted that there are ways to test the boundaries of the TTC approach, by alternative predictive methods (e.g, for genotoxicity and carcinogenicity). Also, it may be necessary to assess persistent and bioaccumulative chemicals separately. Communication is important and should differ depending on the audience (public vs. risk manager). Also, words should be chosen wisely when communicating with the public. Other themes that emerged included the fact that there are risk management possibilities at all tiers and that management is necessary and possible even if information is lacking for some components.

Session A: Additional Questions to Address All Tiers

28. In addition to the above questions, the following general questions were answered depending on whether enough time was available to answer the above questions. Questions that elicited responses are here, with a more complete list in Annex 6.

Question 1: Within the problem formulation:

- How would the criteria for grouping differ depending on the question that you are asking?

- How would the grouping differ when you have data-poor examples?

29. One group noted that for the carbamates case study, rationales for excluding certain exposures (e.g., occupational and residential use exposures) were not made and the scientific rationale for the grouping was also not sufficient. It was also noted that the criteria may differ depending on the goal of the assessment and that at higher tiers, mode of action might be a more prominent consideration. Also, the surface water example indicates that the relevant area is a certain region in the US and that the same chemicals might not be grouped together in another geographic region. When considering ecological assessments, there could be very different groupings compared with those for human health, which would be influenced by the problem formulation step. For data poor chemicals, participants considered that groups would likely be broader to ensure adequate health protection.

Question 2: Have a discussion on particular methodologies / scenarios that people use for assessment groupings – what are the appropriate criteria for consideration of combined exposures?

30. When considering methods and scenarios that might be important for grouping chemicals, one breakout session noted that although such assessment groups could be built based on common effects and common MOAs at Tier 0, they could also add more MOAs (even if a common MOA is used as well) at higher tiers in particular.

Session B: Current Issues in Combined Exposure Assessment

31. Session B included presentations on work that has been done in the United Kingdom with intersex fish and estrogenic mixtures and in Denmark with risks to two-year old children of endocrine disrupting chemicals. Policy development and consideration at the U.S. Environmental Protection Agency, the European Commission and CEFIC were also presented. See Annex 7 for all Session B presentations.

32. The Chair of Session B, Theo Vermeire, summarized some key themes emerging from the presentations, including general recognition of the need for combined exposure assessments, the existence of some regulatory requirements, as well as current impediments and issues to be addressed in developing further requirements. In particular, legislative compartments created by sector-specific approaches create data "silos" as well as impediments to conducting an assessment based on all sources of exposure. He noted that while a number of impediments had been identified, the presentations illustrated efforts being made to identify and implement solutions.

Session C: Further Work on Combined Exposures Assessment

33. In Session C, breakout groups discussed barriers to implementation of combined exposure assessments as well as priority actions to address the barriers, using two open-ended questions:

- What are the barriers/challenges to implementing risk assessments of combined exposures to multiple chemicals?

- What are some priority follow up actions?

34. Each of the three breakout groups in Session C debated the above questions, and the detailed answers are presented in Annex 8. Bette Meek, Martin Wilks and Thomas Hutchinson facilitated these sessions while Petra Kunz, Virginie Bergeron and Neil Carmichael were rapporteurs. The breakout group presentations were discussed in a plenary session led by co-chair Henrik Tyle.

35. Based on these responses and the initial plenary discussion, draft conclusions and possibilities for further work related to risk assessments of combined exposures to multiple

chemicals were presented to the full group of participants during a final plenary session. This final session, in which participants discussed and revised the draft conclusions, was led by co-chair Gino Scarano. Michelle Embry was rapporteur.

Final Conclusions for Priority Actions

36. Several key themes reappeared throughout Session C and in previous sessions. For each of these themes, participants agreed on several final conclusions as possible priority actions for further work on combined exposure assessment.

Coordination/Harmonization

37. In this key area, the workshop determined that a *multi-sector, multi-stakeholder, global coordinating/working group* could be formed that would encourage cross-sector, multi-disciplinary coordination (e.g., research & regulatory programs; human health and environmental). Such a group could engage in early coordination with communications experts.

38. The workshop was also of the view that this type of umbrella group could draw both from the organizational structures of, and work being done at, some or all of the following existing initiatives and institutions:

- WHO / IPCS
- OECD Categorization, QSAR
- Mode of action / AOP
- Tox Cast
- National agencies / International agencies
- Local governments
- International societies (e.g., SOT, SETAC, ISES)
- ECETOC, HESI, CEFIC, JTOC
- Research programs (e.g., EU Framework programmes [NoMiracle, Contamed, and more])

39. Another activity that could encourage harmonization and coordination would be to establish a repository/e-resource for case studies, references, guidance, etc. (perhaps via OECD).

Case Studies

40. Participants also suggested a list of additional case studies of specific substances or with certain attributes to demonstrate important aspects of assessment of combined multiple chemical exposures:

- Natural substances
- Non-chemical stressors
- Genotoxic carcinogens
- Ecotoxicity examples
- Data rich substances
- Data poor substances

- Mix of data rich and data poor examples
- Mixed MOAs
- Use of existing examples to test the WHO Framework
- Effects-based cases
- Prospective studies (example from start to finish, rather than retrospective Framework application to an existing assessment)

41. It wasn't decided who would prepare these case studies. Instead, any government or organization interested in continued work in this subject area could initiate such cases, with the proposed global coordinating group playing a role in sharing information.

Development/Refinement of Tools and Approaches

42. There was general support for the WHO framework which is a high level organizing framework within which specific assessment tools and methods are employed. Several ideas for research into new assessment tools or for refinement and clarification of existing methods were suggested:

- Tools to facilitate clarity in problem formulation
- Guidance on prioritization/triggers (problem formulation)
    - One example would be to use monitoring data (e.g., either effects on individuals or organisms or analytical chemistry data) to determine the need for doing an assessment
- Additional work on assessment scoping and availability of data (e.g., use of the Maximum Cumulative Ratio)
- Grouping (hazard and exposure)
    - Draw from WHO/IPCS Mode of Action activities and OECD Adverse Outcome Pathways work
- Potential for interaction (e.g., deviation from additivity)
- Examination and refinement of Tier 0 methods (e.g., TTC) and development of additional methods and different approaches (e.g., use of information from U.S. Food and Drug Administration on chemicals generally recognized as safe (GRAS), etc.)
- Additional work on specific assessment tools to be employed in the assessment tiers (e.g, QSAR models)
- Exposure tools for lower tiers (physicohemical properties, use profiling, ECETOC Targeted Risk Assessment tools, etc.)
- Guidance on defining relevant exposure scenarios
- Guidance on the use of probabilistic models for exposure refinement
- Development of models for co-occurrence
- Mining datasets to inform development of models for co-occurrence
- Examine WHO/IPCS framework for environmental risk assessment application
- Methodology to quantify/qualify uncertainty and conservatism (caution)
    - Draw on international efforts underway on single substances (hazard and exposure) to characterize uncertainty

Communication

43. There was general agreement that attention to communication is needed for these types of assessments, which can be quite complex and because assumptions need to be transparent. In addition, the way in which the concepts are communicated should take into consideration the appropriate audience. Participants supported the following key points:

- Guidance on use and interpretation of these types of assessments for risk management
- Education and outreach (similar to work being done in the area of MOA communication involving, for example, training for risk assessors) to a broader community
- Generic, high level guidance on making assessments transparent to both the public AND risk managers. For example, what components should be routinely discussed?
- Clarification of uncertainty at various tiers (especially the lower tiers)

44. Finally, it was noted that a UNEP global chemical outlook on chemicals, to be released in 2012, will include information on cocktail effects.

ANNEX 1

WORKSHOP PROGRAMME

WHO OECD ILSI/HESI International Workshop on
Risk Assessment of Combined Exposures to Multiple Chemicals

Workshop Programme

Workshop Date: 15-16 February 2011, commencing at 09.00
Workshop Venue: OECD Conference Centre, 2 rue Andre Pascal, Paris 16th Arrondissement, France

Background and Workshop Goals

The World Health Organization has developed a Framework for Risk Assessment of Combined Exposures to Multiple Chemicals through an international workshop held in 2007, expert input and public consultation in 2009. The framework was finalized in 2010, and is in press. The framework is a high-level document designed to aid risk assessors in identifying priorities for risk management for a wide range of applications where co-exposures to multiple chemicals are expected. It is based on a hierarchical (phased) approach that involves integrated and iterative consideration of exposure and hazard at all phases, with each tier being more refined (i.e. less conservative and uncertain) than the previous one, but more labour, modelling and data intensive. It includes reference to predictive and probabilistic methodology in various tiers. Case studies have been developed to test and illustrate the framework. A number of organizations have used, or are considering use of, the framework in risk assessments or the development of case studies to explore its use in specific scenarios. A number of regulatory authorities are presently considering whether or not to establish further requirements for risk assessments of combined exposures.

The goals of this Workshop are to:

- Inform participants about the WHO framework and explore application of the framework through discussion of a number of illustrative case studies.
- Share information about current issues in combined exposure assessment.
- Identify needs for further work on combined exposures, which may be undertaken by the organizations present at the workshop, or others.

The conclusions of the workshop will be prepared in its final session. A report of the workshop will be published on the internet, and conveyed to the OECD Joint Meeting, participants in the WHO Harmonization Project and other interested stakeholders. This workshop was planned by the Worskshop Secretariat (WHO, OECD and ILSI/HESI) and the WHO Combined Exposures Planning Group members. Additional participants include individuals from multiple countries, the European Union, industry groups and NGOs.

Workshop Schedule

DAY 1

09.00 Workshop Opening

The workshop will be opened by *Bob Diderich, OECD*.

- Participants will be invited to introduce themselves (name and organization).
- Practical announcements by host

09.30 Overview *Carolyn Vickers, WHO*

- Introduction to the issue, workshop goals and expected outputs

SESSION A: WHO COMBINED EXPOSURES FRAMEWORK

Chair: Bette Meek, WHO Combined Exposures Planning Group Chair

09.40 Main features of the WHO Framework *Marcel van Raaij*
Questions

10.30 *Coffee*

11.00 Illustrative case study on PBDEs *Bette Meek*

11.30 Introduction to 1st case study discussion (10 mins) *Elizabeth Shipp*

1st Case study discussion in groups: Carbamates

13.00 *Lunch*

14.00 Plenary: Presentations by groups and discussion

15.00 Tier 0 assessments *Susan Felter*

15.30 Coffee

16.00 2nd Case study discussion: Tier 0 examples

17.30 *End of Day 1*

DAY 2

SESSION A (Continued)

09.00 Plenary: Presentations by groups and discussion

SESSION B: CURRENT ISSUES IN COMBINED EXPOSURE ASSESSMENT

Chair: Theo Vermeire

09.50 Country experiences (15 minute presentations)

- Real World Chemical Mixtures: Opportunities and Challenges for Environmental Risk Assessments
  United Kingdom *Tom Hutchison*

- Exposure of 2-Year Olds to Endocrine Disrupters: An Example of the Use of Dose Addition
  Denmark *Shima Dobel*

10.30 *Coffee*

11.00 Policy aspects (15 minute presentations)

- Cumulative Risk Assessment: Status of Activities at the US EPA
  Gino Scarano

- Mixture Toxicity: EU Commission Status Report
  Patrick Murphy

- Control of Chemical Mixtures: Point of View of a Scientific Panel of the European Commission
  Marco Vighi

- Outcomes of the December 2010 CEFIC Workshop "Cumulative Risk Assessment: How and When? Approaches for Future Strategies on Mixtures"
  Carlos Rodriguez

12.15 *Lunch*

SESSION C: FURTHER WORK ON COMBINED EXPOSURES ASSESSMENT

Co-Chairs: Henrik Tyle; Gino Scarano

13.30 Introduction to the session

13.40 Group Discussions: Brainstorming on barriers to implementation of combined exposure assessments and possible priority actions to address the issues

14.30 Plenary: Presentations by groups followed by discussion (Group chairs and rapporteurs will provide a panel)

15.30 *Coffee*

16.00 Presentation of proposed conclusions and recommendations for further work Agreement on conclusions and recommendations

17.30 *End of Day 2*

WORKSHOP DOCUMENTS

Workshop Programme

List of Participants

WHO Framework for Risk Assessment of Combined Exposures to Multiple Chemicals

Case Study Discussion Materials

ANNEX 2

SESSION A PRESENTATIONS

(see separate file: ENV/JM/MONO(2011)10/ANN2)

ANNEX 3: CASE STUDIES

(see separate file: ENV/JM/MONO(2011)10/ANN3)

ANNEX 4

BREAKOUT GROUP QUESTIONS/ANSWERS FOR CARBAMATES CASE STUDY

Group 1

Group 1

Facilitator: Alan Boobis

Rapporteur: Karluss Thomas

Was Tier 0 Advantageous?

- Not in this case, but might be useful in others where similar data is available.
- Tier 0 helped to determine primary drivers for hazard or exposure
- Could there be differential tiering for individual components in mixture

Do you have to use all of the data

- No, don't need to use all of the hazard data, but you do need most of the exposure data
- Use the hazard data for most potent chemical to drive the exposure assessment
- Tier 0 should not have used measured data.
- Check to make sure exposure estimates are consistent with use data.
- Tier 0 data would have better focused on MRL

How might problem formulation determine which tier is needed

- Problem formulation is intended to define the scope of the assessment for the risk assessor and risk manager and ensure an appropriate level of dialogue between them.
- Problem formulation (e.g., co-occurrence of compounds in surface water, pesticide residues in diet) should drive the assessment, but should not influence which tier is needed
- During refinement of assessment, problem formulation may need to be revisited
- Assessment Goal should influence assessment; risk assessment vs. risk management
- Sensitivity analysis is important for refining tiers.

Are there key aspects of combined exposure that have been overlooked, omitted, or not realized within framework

- The framework should include more discussion of how to refine grouping based on exposure as you move through tiers.

What are current barriers/blockers that we face in utilizing this tiered approach?

- Decisions to move to next tier were not transparent (Tier 2 was omitted)
- Details associated with use of probabilistic assessment would be helpful.
- Include a narrative that describes how each tier improved the assessment and reduced uncertainty.
- Policy basis for considering a group of chemicals together e.g., specific health concern

Group 2

Discussion questions: Carbamates

- In this case, was it advantageous to go through Tier 0 despite having a high degree of data?
  - If you have the data, do you have to use all of the data?
- Overall: Start at tier where data & analyses are readily available
  - If analysis done use it (as in this case); generally use all data that are accessible and workable
- Place for deterministic
- **Purpose of exercise- public protection**
- Communication needs / adversity of effects
- Resource balance / Economic impact
- For this case, Tier 0 exposure seems higher tier

Discussion questions: Carbamates

- How might the problem formulation determine which Tier is needed?
  - Assists in determining tier
    - checklist of the type of data needed for each tier- how to get started
  - Additional questions to ask in problem formulation (data quality / availability)
  - Time pressure impacts tier
  - Principle of plausibility to focus efforts; concepts such as sentinel of exposure
  - Make assumptions explicit; acknowledge uncertainties
  - Tier 0 could be more certain than other tiers if sure it is conservative

Discussion questions: Carbamates

- Are there key aspects of combined exposure that have been overlooked, omitted, or not realized within the framework as illustrated by this example?
  - Development of common assessment group
    - Organophosphates and carbamates?
  - Timeframe – acute effect or chronic evaluation
  - Concentration co-occurrence considered?

Discussion questions: Carbamates

- What are the current barriers / blockers that we face in utilizing this tiered approach?
  - Are there difficult decision points?
  - Regulatory
    - (multiple programs) –broader issue – not framework specific
    - How large of an MOE is needed?
  - Resources
    - Data availability
  - Scientific
    - How to group chemicals
    - Is this conservative enough?
    - Develop improved RA methods (in addition to HI)
    - Relevant co-exposure in relevant timeframe
    - Persistence / bioaccumulation
  - Improved documentation of uncertainties / assumptions

Discussion questions: Carbamates

- What other additional guidance would you like to give?
- Any additional questions or discussion points?

  – What can be done with fundamental information?

Group 3

Discussion questions: Carbamates

- In this case, was it advantageous to go through Tier 0 despite having a high degree of data?
  - If you have the data, do you have to use all of the data?
    - one side might have more data than the other – offset is okay
    - starting at a tier 0 provides a global view of hazard and exposure.
      -broader view of different routes, products, etc.
    - Important to consider both from the outset
    - Useful to streamline and speed decision-making
    - Might not have a choice, may only have higher tiered data on some members of the group

- How might the problem formulation determine which Tier is needed?

How to select relevant endpoints

Species differences

May consider multiple species in higher tiers

Multiple Modes of Action- default to the most sensitive endpoint?

May consider multiple MOA in higher tiers

Do you use the most sensitive endpoint?

Group Formation

Make question/scope clear up front- what are you trying to solve

Need to be able to pick common endpoint

Be careful mixing acute and long term data

Start with wider group to make sure nothing is missed.

Number of substances should be addressed - how big or small can a group be?

- Are there key aspects of combined exposure that have been overlooked, omitted, or not realized within the framework as illustrated by this example?

Ecotoxicity

Additional questions may need to be added to FW for ecotox

- criteria and data availability might be different than for human health
- targets may change, depending on time of the year, etc
- need narrow the problem from the start
- broaden as more data is available

Species extrapolation in Ecotox particularly complex-

- broader array of species/sensitivites considered.

Good idea to do ecotox case study

Discussion questions: Carbamates

- What are the current barriers / blockers that we face in utilizing this tiered approach?
  - Are there difficult decision points?

    Communication, public fears and media scrutiny

    Communication of uncertainty and risk management

What other guidance would you like to give?

Any additional questions or discussion points?

Questions for all tiers

- Have a discussion on particular methodologies / scenarios that people use for assessment groupings – the appropriate criteria for consideration of combined exposures?

Groupings according to common end point, mode (s) of action, consider "'alternative" mode(s) of action.

ANNEX 5

BREAKOUT GROUP QUESTIONS/ANSWERS FOR TIER 0 CASE STUDIES

Group 1

Questions for consideration – Tier 0

- Are the conservative assumptions in the Tier 0 useful for screening-level approaches
  - Are they so conservative that they are unlikely to be discriminating?
    - **What is considered a reasonable assumption for conservatism?**
      - Exposure assumptions – highest consumption/lowest body weight?
      - Hazard assumptions – conservative; is there a GRAS-like (Generally Recognized as Safe) alternative to TTC that can play a role here?
    - **TTC approach needs to be explained well to all audiences (stakeholders) to highlight conservatism**
    - **The number of substances could play a role (is there a limit)?**
  - Are they sufficiently conservative to ensure adequate **health-protection?**
    - **If the exposures are low enough, yes**
  - If not, how could / should this be addressed?
    - **QSARs for exposure (use of p/chem data in use clusters)? –**
      - **ECETOC –Targeted Risk Assessment – a tool for use/exposure**

- **Are the Tier 0 exposure assumptions sufficiently conservative to allow for:**
  - **Changes in ratios** (of mixture composition)
    - For commercial hexane, all same Cramer Class I, so changes in ratios don't change the HI calculation
    - It may be an issue if there is more than one Cramer class among the components in the mixture
      - Uncertainty analyses could be important
  - **Multiple route / route to route extrapolation**
    - Portal of entry (inhalation) effects for commercial hexane (nasal) makes extrapolation to oral exposure uncertain (i.e., TTCs are oral exposures)
    - REPDOSE – Fraunhoffer looking at inhalation route in the context of TTC approach
  - **Spatial & temporal variation**
    - Yes, but:
      - Would be important for higher Tiers (eco and hh)
      - What about for bioaccumulative chemicals – for which TTC may not be appropriate, but there may be other Tier 0 approaches for these chemicals – like the EpiSuite BCF/BAF model
- **For each of these examples, was the grouping appropriate?**
  - No, because we knew that n-hexane was different….(commercial hexane without n-hexane would not be an issue)
    - Is n-hexane toxicity specific enough that it should not be considered in Cramer classification series (Class 1)? (Is there something about chemical structure that suggests Cramer rules should not apply?)
  - Yes, because components are structurally similar
  - Yes, because the mixture is a defined entity that exists commercially

- **What other data and methods not represented in these examples could be used for a tier 0 assessment?**
  - EpiSuite BCF/BAF model
  - QSARs for exposure (use of p/chem data in use clusters)?–
    - **ECETOC –Targeted Risk Assessment – a tool for use/exposure**
- **What issues need to be considered in communicating the results of a Tier 0 assessment?**
  - **If you fail Tier 0, there needs to be effective communication that failure @ this level does not necessarily translate to risk**

Group 2

Pharmaceuticals

2011 02 15

Questions for consideration – Tier 0

- Are the conservative assumptions in the Tier 0 useful for screening-level approaches
  - Are they so conservative that they are unlikely to be discriminating?
  - Are they sufficiently conservative to ensure adequate health-protection?
  - If not, how could / should this be addressed?
- Specific comments (blue)
  - Surrogate ADIs for pharmaceuticals, hormones based on minimum therapeutic dose with a UF. Therapeutic dose for adults readily available.
  - Removal of pharmaceuticals from surface water → risk management possibilities.
  - Public concerned about involuntary exposure of children to pharmaceuticals. Problem: information on paediatric doses is limited.
  - Therapeutic dose of one drug may be based on short-term usage, while the TD of another may be based on life-long use.

Questions for consideration – Tier 0

- Since the compounds are intended to have a biological effect, TTC is not most applicable. EFSA review shows that NOAEL for rodenticides is lower than TTC.
- TTC not protective for hormonally-active chemicals (oestrogen example).

- General Comments
  - When you have better (evaluated) data, skip Tier 0. Exception - when you have very little time.
  - If UFs are use, have they been validated? → Transparency: what part of this method has been validated?
  - Harmonisation. Importance of rationale.
  - Other simple tools may be available to replace the Cramer classes, i.e., models of genotoxicity and carcinogenicity(*in vivo, in vitro*). Advantage of Cramer is that it is harmonization, alternatives, may not be harmonized.
  - Time available influences decision on what amount of information you use.

Questions for consideration – Tier 0

- When assessing pharmaceuticals, lessons may be learned from other groups of substances, i.e., pesticides. Information on concentrations of degradation products is small at this time.

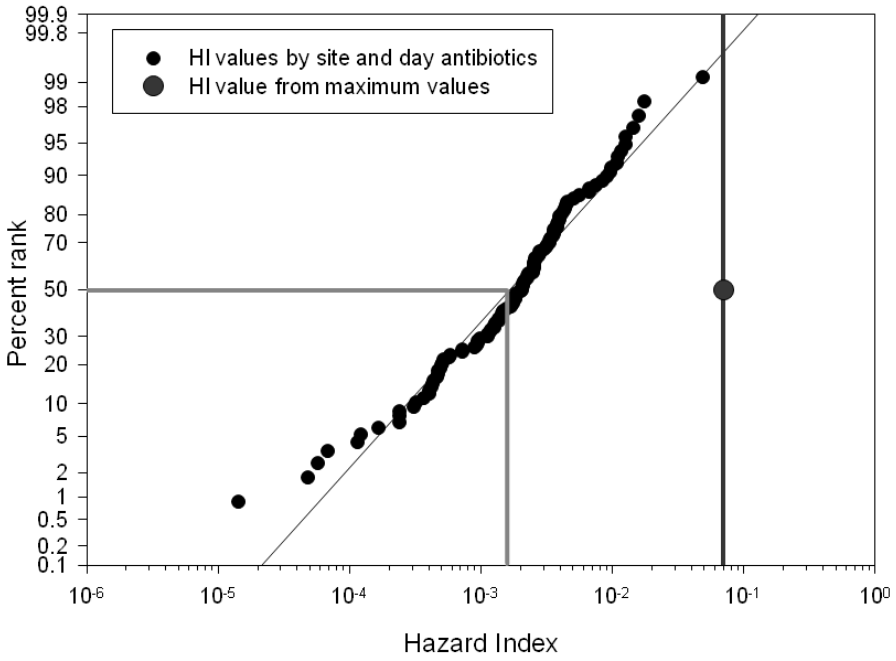
- **Are the Tier 0 exposure assumptions sufficiently conservative to allow for:**
  - Changes in ratios
  - Multiple route / route to route extrapolation
  - Spatial & temporal variation
- In assessing single pesticidal chemicals for WHO drinking water standards, water can only represent 20% of daily intake. Pharmaceuticals not applied on food crops → surface water by far largest source of exposure. However, natural compounds in food may be important (phytoestogens).
- Use of pharmaceuticals in pandemic, although rare may cause temporal and spatial spikes. Worst case numbers likely included those kind of situations. Seasonal peaks in use of parmaceuticals not more than a factor 1.5 or 2. HIs are relatively small and, if peak missed not a large problem.

- **For each of these examples, was the grouping appropriate?**
  - Is it appropriate to group pharmaceuticals based on the differences in MoA? Appropriate for lower tiers but higher tiers should address side effects.
  - General consensus, Cramer-based TTC for bioactive substances: not recommended.

Tier E3R2 (Case 6 not in report)

- Data on antibiotics (and carbamazepine) from Lissemore et al. (2006) on surface water (Grand River, Ontario).
- Samples 2-weeks apart.
- Chemicals analyzed:
  - Monensin, lincomycin, trimethoprim, sulfadimethoxine, sulfamethazine, total erythromycin, sulfathiozole, sulfamethoxazole, doxycycline, sulfachlorpyridazine, sulfamerazine, sulfamethizole, roxithromycin, oxytetracycline, tylosin, tetracycline, chlortetracycline

Case 6 results



- **What other data and methods not represented in these examples could be used for a tier 0 assessment?**
- Large number of models for designing pharmaceuticals are available and could be used to address degradates. Problem, not harmonized or transparent.
- QSARS may not be appropriate for bioactive molecules.

- **What issues need to be considered in communicating the results of a Tier 0 assessment?**
- Try to communicate in layman's words.
- Important to explain what we cannot do (in addition to what we can do)
- Explain uncertainties.
- Make comparisons (i.e., phytoestrogens in food)
- For tier 0, how should uncertainty be characterized or expressed quantitatively?
- You don't quantify it, you qualify.
- Qualitative evaluation of uncertainty based on categories. Descriptive. Each assumption is categorised (+++, ++, +, +-, --, ---).
- It is important to communicate that as uncertainty is reduced down, costs increase.

Using the drug-laced water supply of San Jose and evaporating out all the water, artists Jon Cohrs and Morgan Levy create All-Salt, an all-purpose medicine for just about anything that ails you, all without having to go see a doctor for a prescription! Why didn't we think of that -- all the drugs in our water supply being wasted on mutating frogs and fish, and we could be recycling it and trimming the cost from our health care bills!

Group 3

Questions for consideration – Tier 0

- Are the conservative assumptions in the Tier 0 useful for screening-level approaches
  - Are they so conservative that they are unlikely to be discriminating?

Food additives (FA): Logical, plausible, maximum not taken here, intended not to be average but to be conservative since additive added to certain foods . However, room for interpretation assumption of production volume and 10% population exposed to additives. Assuming full biovailability, absorption….

Natural sources of additives in food could be higher /lower since some of them are part of some food commodities/products. Relative ratio between the two would help to see whether added FA of concern or not.

TTC chemical mixture in surface water: the assessment took maximum levels. 1L for children's water consumption may not be the worst case according to some databases.

TTC approach useful ? No tox data for of the 14 chemicals what alternative would we have ?

Questions for consideration – Tier 0

- Are they sufficiently conservative to ensure adequate health-protection?

Mixture with known tox data versus TTC approach : more conservative compared to chemical specific data as shown in table.

Conservatism in exposure ensures adequate health-protection. All factors together cumulate conservatism.

- If not, how could / should this be addressed?

Samples should be representative of the situation/environment we are dealing with.

This does not include an exhaustive RA of all chemicals from the lake and regions but explores the methodology.

Questions for consideration – Tier 0

- Are the Tier 0 exposure assumptions sufficiently conservative to allow for:
  - Changes in ratios
  - Multiple route / route to route extrapolation

  Uncertainty in Route to route extrapolation since only PO

  TTC values derived from oral database. Extrapolation of TTC to other routes (inhalation …) carefully addressed.

  - Spatial & temporal variation

  Not dealt with in this example.

Questions for consideration – Tier 0

- For each of these examples, was the grouping appropriate?

  No grouping in surface water. FA grouped according to structure and ADME.

- What other data and methods not represented in these examples could be used for a tier 0 assessment?

  QSAR modelling or go to higher tier

- What issues need to be considered in communicating the results of a Tier 0 assessment?

  Clarify formulation of the problem, assumptions you make to be on the "safe side".

  Message synthesised and tailored to audience.

Questions for all tiers

- Within the problem formulation
  - How would the criteria for grouping differ depending on the question that you are asking?

    Goal driven-tailored for specific assessment.

    Modes of action in higher tiers.

    TTC surface water example does not apply to other situations (lakes, regions,…)

    Ecotox –criteria for grouping structural similarities

  - How would the grouping differ when you have data-poor examples

    Broader groups

ANNEX 6

ADDITIONAL BREAKOUT GROUP QUESTIONS/ANSWERS

How would the criteria for grouping differ depending on the question

- The scientific rationale for the grouping was not sufficiently made.
- Rationale for excluding certain exposures was not made.

Questions for all tiers

- Within the problem formulation
  - How would the criteria for grouping differ depending on the question that you are asking?

    Goal driven-tailored for specific assessment.

    Modes of action in higher tiers.

    TTC surface water example does not apply to other situations (lakes, regions,…)

    Ecotox–criteria for grouping structural similarities

  - How would the grouping differ when you have data-poor examples

    Broader groups

Questions for all tiers

- Have a discussion on particular methodologies / scenarios that people use for assessment groupings – the appropriate criteria for consideration of combined exposures?

Groupings according to common end point, mode (s) of action, consider "'alternative" mode(s) of action.

ANNEX 7

SESSION B PRESENTATIONS

(see separate file: ENV/JM/MONO(2011)10/ANN7)

ANNEX 8

SESSION C BREAKOUT GROUP ANSWERS ON BARRIERS TO IMPLEMENTATION AND NEXT STEPS

Group 1

Questions for Consideration – Session C

- What are the barriers/challenges to implementing risk assessments of combined exposures to multiple chemicals?

For phthalates data available, but combine these with other chemicals, with same & different MOA it is unclear how to proceed. For Regulation: How to group chemicals? What are common effects? Which chemicals to address? And which of those first?

Regulatory as well as scientific impediments are of importance. I.e. current limitations in epidemiology.

A lot of scientific methods are available, but translation into regulatory application seems difficult. For short term-paralell exposure studies are availabe, but missing for chronic-longterm exposure. Also communication on longterm exposure issues is missing.

1

- What are the barriers/challenges to implementing risk assessments of combined exposures to multiple chemicals? (cont'd).

In Europe, it is a barrier that everything is sectorial (i.e. agencies, chemical groups ..), the coordination is difficult. But experience shows that when methologies has evolved there is a legislative driver. Often communication within/between agencies/research and so on.

A barrier is the enormity of the task, we can not do anything. Cutting down to /prioretisation of important areas is curcial. Tier o should help with this.

The scope of the framework is very wide, however individual agencies do have a clearer scope. The case studies are very helpful.

Having all exposures in mind.

2

- Priority follow up actions? Next steps?

Methodologies are available and it is critical how to plan the next steps.

More prospective case studies (i.e. Danish studie).

For hazard assessment the methodology is there, but could be more applied (i.e. Asia).

Data on the exposure site is sometimes difficult to judge. Give some ideas on how to use such data. Again communication and explanation of the used methologies. i.e. by the use of examples (i.e. ways to do a tier 1 approach, phthalates as an example group).

For ecotoxicological risk assessment examples are needed.

Important to include other activities (i.e. SETAC Symposium on mixtures). Form umbrella groups, like it was formed for MOA (HESI...). The space to do this exists, we should think about how to do it.

3

- Priority follow up actions? Next steps? (cont')...

Working other sorts of levels. Getting more people involved (i.e. scientists, risk assessors). COORDINATION! Started already at a high level for this meeting, but a reach-out is needed. The larger regulatory component may complicate this. Bringing together OECD QSAR, Toxcast and others. Keyplayers are interested and engaged.

Data sets for a ecotoxicological case study exists (i.e. Switzerland).

There are case studies out there, that can be used to "test" the framework, for example with QSARS. Additional model developments should be included, see if usable.

Use of OECD guidelines. Could trade platforms be used to apply

Tier priority excercises, walking thourgh the tiers (i.e. case studies). OECD tools should brought into this. Other approaches to TTC.

Start from the effect side to determine if there is a risk, and if so, go on with more detailed effect as well as analztics data.

4

Group 2

Questions for Consideration – Session C

- What are the barriers/challenges to implementing risk assessments of combined exposures to multiple chemicals?
- Clear problem formulation;
- Need a systematic approach to grouping of chemicals (e.g., mode of action) from both hazard and exposure perspective;
- Need more work on terminology to have a common understanding of basic concepts (e.g., mode of action);
- Need harmonization on how we treat toxicity values;
- Need guidance on data poor vs data rich scenarios;

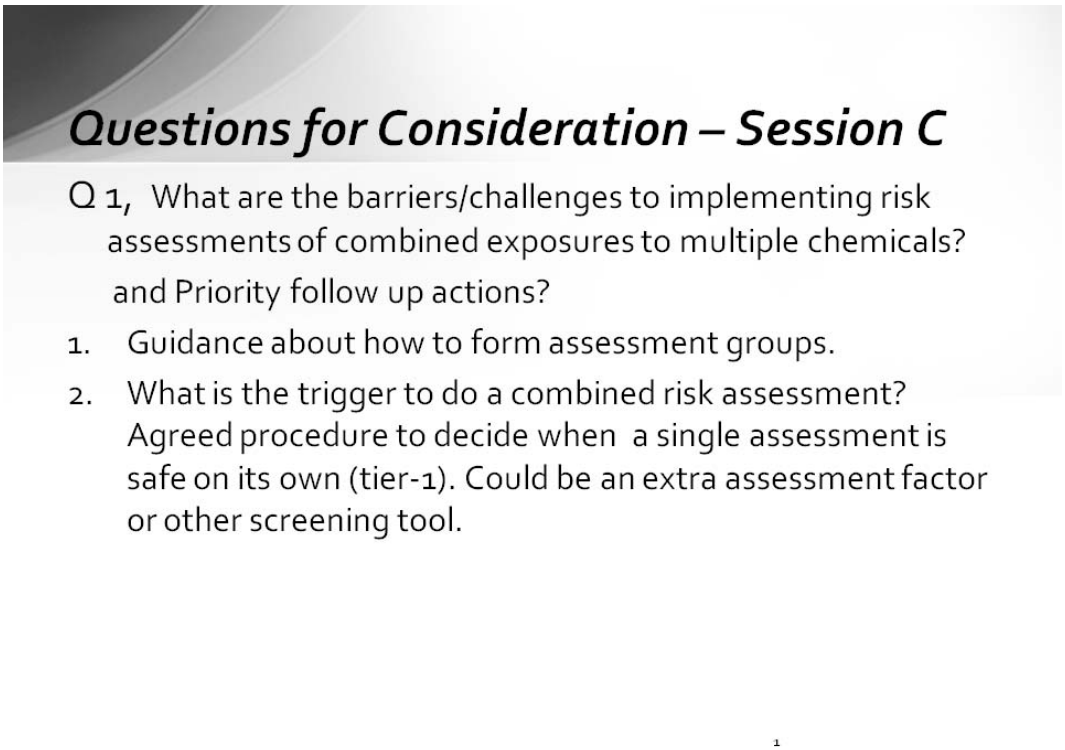
1

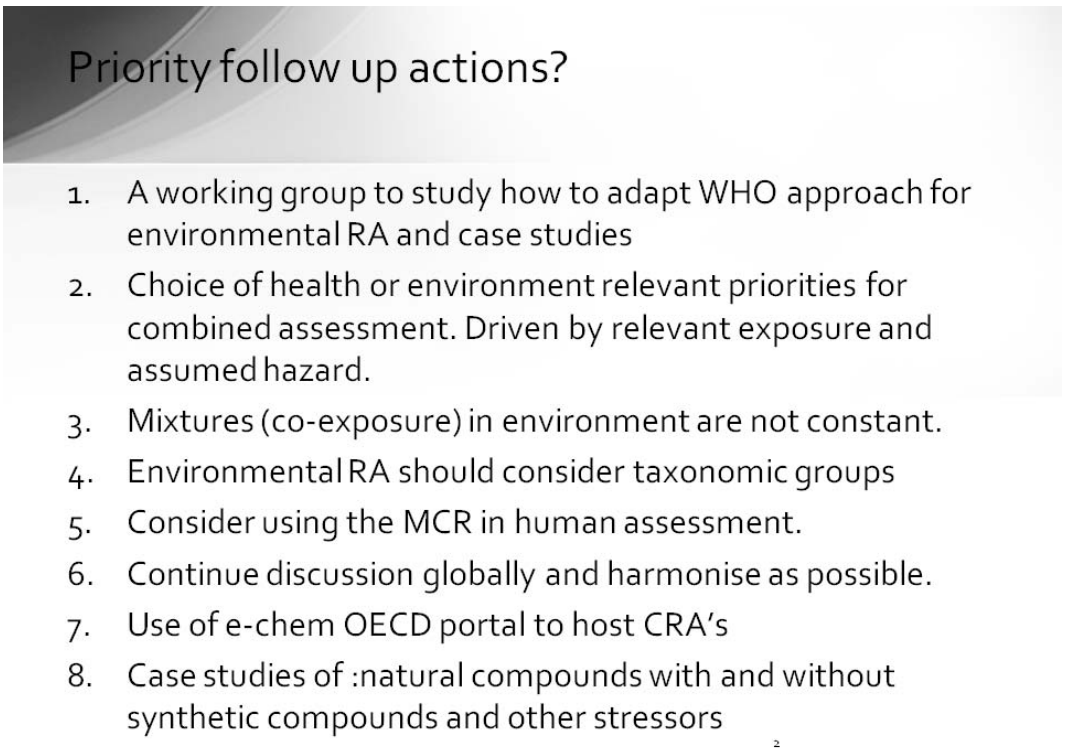
Priority follow up actions?

- Development of tools for grouping chemicals;
- How do you use results of risk assessment to inform risk management (e.g., include risk management when deciding how to group);
- More work on MCR (where a few substances of a mixture drive the risk); it might provide short-cuts;
- More linkages between eco and human health assessors to learn from each other;
- Keep investing in exposure assessment/modelling;

2

Group 3


Questions for Consideration – Session C
Q 1, What are the barriers/challenges to implementing risk assessments of combined exposures to multiple chemicals?
and Priority follow up actions?
1. Guidance about how to form assessment groups.
2. What is the trigger to do a combined risk assessment? Agreed procedure to decide when a single assessment is safe on its own (tier-1). Could be an extra assessment factor or other screening tool.
1


Priority follow up actions?
1. A working group to study how to adapt WHO approach for environmental RA and case studies
2. Choice of health or environment relevant priorities for combined assessment. Driven by relevant exposure and assumed hazard.
3. Mixtures (co-exposure) in environment are not constant.
4. Environmental RA should consider taxonomic groups
5. Consider using the MCR in human assessment.
6. Continue discussion globally and harmonise as possible.
7. Use of e-chem OECD portal to host CRA's
8. Case studies of :natural compounds with and without synthetic compounds and other stressors
2

ANNEX 9

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15-16 February 2011

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