



Integration group charge questions

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Introduction

Aims

The **integration group** aims to develop a framework/decision-tree that simplifies the complexities of mixture assessments into methods that can be easily adopted by decision-makers in regulatory-, industry- and academics sectors. The aim is for a framework that:

1. is cross-cutting i.e. it can be applied to any scenario
2. considers tools that can be used for forecasting mixture risks based on potential exposure scenarios as well as retrospective mixture diagnostic approaches, based on field observations
3. is practical to apply
4. represents state-of-the art wrt the science of mixture interactions
5. is aimed at science-based policy development

The product of the workgroup is an executive summary and a graphical representation of a proposed framework, accompanied by a manuscript. The manuscript presents and explains the reasoning behind the framework, and provides guidance for users (e.g. in Supporting Information). Although it may link to some existing frameworks/guidance, the product may be at variance with some generally applied approaches mandated in current regulations. Any inconsistencies between our proposed framework and current mandates are signaled, but not solved.

How we will work

The integration group raises societal questions that must be addressed when carrying out mixture assessments. It also identifies current regulatory and practical frameworks and approaches to address these mixture problems e.g.: What different kinds of mixture problems are addressed by current regulatory regimes? How do they do that? How are they considering preventive policies for chemicals and mixtures? Do regimes that deal with prospective risks take a different approach to those that address retrospective risks? Can we learn anything from approaches used in other media, like sediment and soil? How do they address human health/ecosystem integrity as protection endpoints?

The group will adopt the principles of risk assessment (looking at a problem definition, (mixture) exposure assessment, (mixture) effects assessment and (mixture) risk characterization) with a solution-focused mindset. The group will also bring together well-established scientific theories and validated approaches for quantifying or recognizing mixture exposures, risks and impacts. This will cover both prospective and retrospective methods.

With an eye on both science and practicality, the integration group will review options to solve mixture problems and place these within an over-arching framework, probably using a tiered approach, with simple and conservative methods where possible, and more complex and specific methods when needed. Based on the 2014 JRC review ("Assessment of Mixtures – Review of Regulatory Requirements and Guidance), the workgroup will consider both *intentional* or *generated* mixtures (where we know or can anticipate the identity of the constituents) and *unintentional* or *coincidental* mixtures (where we can't).

The group's activities will be informed by scenarios and approaches developed in the breakout groups as well as by existing descriptions for (1) prospective scenario evaluations and (2) the retrospective prioritization of sites, stressors, mixtures and individual chemicals.

Workgroup approach

Pre-read and presentation

The integration group will prepare pre-read material for themselves and the scenario groups. The pre-read contains an overview of the range of societal questions that will need to be addressed, snapshots of current frameworks, our initial



ideas on tiering, and on prospective and retrospective approaches that are already in practice. This is just a starting point and we expect it to become heavily modified as the workshop proceeds.

The pre-read initially provides the other groups with a view of the 'point on the horizon' of the workshop and specifically of the integration group (a versatile, tiered, validated framework / decision tree for mixture risk and impact assessments). It also suggests where there are specific 'milestones' or requirements that should be taken into account in the breakout groups during the workshop, to ascertain usefulness of the scenario groups towards integration.

An initial presentation (on day 1) will highlight the input required from the scenario groups, the approaches and the output of the integration group, as well as suggested 'meeting points' between the scenario groups and the integration group.

Week agenda

The integration group explains what is required from the scenario workgroup outcomes (day 1).

The other groups acknowledge these, proceed with their charge questions, and then report progress to the integration group (all days).

The integration group will operate by (a) participating in the scenario groups on the first day and (b) through its own sessions, which may also include (c) some workshop participants joining (ir)regularly the integration group from the second day on. The exchange of information between the groups takes place in the daily exchange meetings. In this way, we hope to co-ordinate progress made by the scenario groups, providing mutually beneficial 'meeting points' where progress of any of the groups is matched with that of any other group (especially the integration group), and we will suggest 'points of attention' for workgroup chairs for their 'next steps'.

The charge questions below highlight the key tasks to address in the integration groups' own sessions.

Charge questions

As each exposure scenario has charge questions, the integration group will have overarching questions to address, which can be summarized in a few Key Questions:

1. What are the societal questions concerning mixture assessment that need to be answered?
2. What variety of approaches (mandates, frameworks, decision trees, etc.) are there for mixture risk assessment and management (prospective and retrospective)
3. What overarching framework / decision tree can be designed, such that all valid (science) and advantageous (practice) are adopted, and weaknesses acknowledged
4. What data are there to support the use of that overarching product? Where are gaps?

This raises some further questions, as follows:

Rationale

1. What features should we take into account when designing an over-arching framework?
 - a. What are the societal questions regarding mixtures? Ideas from participants are welcome
Starting point Policy: refer to existing descriptions of regulatory principles and practice (e.g., JRC, WHO-ICPS). What are current regulatory frameworks that already address (if only partially) mixture assessment? In what way do they mention mixtures and deal with them? Do any of them refer to the use of the ecosystem service concept in defining protection goals and levels of acceptable / unacceptable effects in aquatic ecosystems? What is the regulation answering?
 - b. What are the protection goals for current frameworks that deal with prospective mixture risk assessment? Do they differ from those used in retrospective mixture risk assessment?
 - i. For species?
 - ii. For biodiversity?
 - iii. For ecological functions?
 - c. Starting point Science: What current scientific principles are used for prospective mixture assessment? **The scenario groups are invited to think about the following**, perhaps keeping the



source-pathway-receptor chain in their minds. They should also consider mixtures of known compositions as well as those with unknown compositions:

Hazard

- i. What approaches have been described in the literature?
- ii. How are bioavailability aspects of mixtures dealt with?
- iii. Dose-effect relationships regarding mixtures (species, biodiversity, functions)
- iv. Which mixture assessment models are used: Simple Similar Action, Independent Joint Action, mixed-model approaches?
- v. How can we recognize interactions that might require an approach other than simple concentration addition? How important is mode / mechanism of action? How would this influence the decision-making process?
- vi. How to address mixtures, when we lack data on the toxicity of specific compounds, but toxicity data for groups of substances are available? Can we adapt a human-toxicology TTC-based approach?
- vii. Does a consideration of species traits offer particular insights for mixture assessment?

Exposure

- viii. What criteria could be used for characterizing exposure scenarios and co-exposures?
 - ix. Prioritization: How to identify the most important groups of compounds for mixture modeling for each scenario?
 - x. How to evaluate mixtures where we know with high confidence the constituents (e.g. pesticide formulation) vs those where we don't (e.g. dredge spoil, road runoff)? Do different approaches result from this?
 - xi. Risk and Emergent species assemblage traits? Food web vulnerability?
 - xii. **Ideas from participants are welcome**
 - d. *Ibidem* for retrospective risk assessment
 - i. *Refine?*
 - ii. **Ideas from participants are welcome**
2. Discussion on frameworks / approaches
- a. Can the various scientific approaches for assessing risks from mixtures be sorted so that they fit into a tiered system (simple and conservative when possible, more complex and precise when needed)
 - b. Can prospective and retrospective approaches fit into one over-arching decision tree or framework, or must they be kept separate?
 - c. What data are available to underpin the use of scientific principles to deal with mixtures? What data are likely to be missing? How could these data gaps be filled?
 - d. What is the conceptual (appropriateness of method) and numerical (appropriateness of outcomes) validity of different approaches to mixture assessment?
 - e. **Ideas from participants are welcome**
3. Development of an overarching approach based on the Starting point Policy, Starting point Science, Discussion of frameworks / approaches
- a. Can we design a **first-draft overarching thinking scheme** (liaising pro- and retrospective, known defined and undefined mixtures, etc) which can be a prototype for an overarching framework / decision-tree (which can then be tested in the other groups)?
 - b. Can we debate with the scenario groups the scientific appropriateness and the practical application of this draft thinking scheme, given their charge questions? What can be improved?
 - c. Which universal principles (and/or 'easy wins') for such a scheme are to be adopted without further debate to format a **second-draft overarching framework / decision tree**, early in the workshop by all scenario groups? Which issues can be provisionally left "pending"?
 - d. Can we extract the key "not-negotiable" outlines of our draft framework/decision tree mid-week?
Identify:
 - i. non-negotiable principles – don't debate these any more
 - ii. key issues that we don't have the answers to and require most debate and



- iii. nice-to-have elements that would be good if there is time but are not critical
 - e. **Ideas from participants are welcome**
4. Can we address practical questions, given the first and second drafts? For example:
- a. Do the agricultural, domestic waste water and urban scenarios co-occur? How likely is this? Do they co-occur in time and space?
(These are only examples. There will be others e.g dredge spoil, contaminated land leachate, landfill leachate, contaminated sediments. We could perhaps map out what all the possible scenarios could be and whether they are likely to occur. How will they be integrated into an assessment framework?)
 - b. When dealing with multiple sources of mixtures, is it adequate to simply add components from each scenario and remove duplication?
 - c. How important is knowledge of mode of action in chemical grouping to ensure the most appropriate toxicity mixture model is used?
 - d. How can temporal and spatial differences between the individual scenarios be addressed?
 - e. Can a river basin or even a catchment level approach be developed using basic information on the basin/catchment (land use, river order, types of settlements, etc), generic exposure scenarios (developed by the other WGs) and basic fate modelling (rough estimates of dissipation for chemicals travelling down the river)?
 - f. **Ideas from participants are welcome**

If you have any suggestions for supplementing please contact the integration group via Leo.Posthuma@rivm.nl