TECHNICAL REPORT

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Public consultation on the terms of reference of the Scientific Committee Working Group on

"Harmonisation of risk assessment methodologies for human health and ecological risk assessment of combined exposure to multiple chemicals"

European Food Safety Authority (EFSA)

Question number: EFSA-Q-2016-00456

Correspondence: scer@efsa.europa.eu

Background

Human and ecological risk assessment of combined exposure to multiple chemicals ("chemical mixtures") poses a number of challenges to scientists, risk assessors and risk managers, particularly because of the complexity of the problem formulation, the huge number of chemicals involved, and the toxicological profiles and exposure patterns of these chemicals in humans and species present in the environment. The development of harmonised methodologies for combined exposure to multiple chemicals has been identified by EFSA Scientific Committee as a key priority area for EFSA and a number of EFSA panels and units have initiated activities to support harmonisation of risk assessment methods for both the human health and the ecological area.

In the human risk assessment field, recent examples include the opinion of the PPR panel dealing with an approach to group pesticides into "cumulative assessment groups" based on their toxicity (EFSA PPR panel, 2013). In addition the CONTAM panel published a number of opinions exploring case-by-case studies for the human risk assessment of multiple contaminants using both whole mixture and component-based approaches. The whole mixture approach has included examples such as mineral oil saturated hydrocarbons, hexabromocyclododecanes and component-based approaches have included TEF approaches for non-*ortho* polybrominated biphenyls, several groups of marine biotoxins, ergot alkaloids, polyaromatic hydrocarbons and pyrrolizidine alkaloids (EFSA CONTAM Panel, 2005; 2008, 2009,a,b; 2011, 2012a,b).

In ecological risk assessment of multiple chemicals, the PPR panel in their "Scientific Opinion on the science behind the development of a risk assessment of Plant Protection Products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees)" discussed approaches for the risk assessment of multiple residues of pesticides in bees and the SCER unit recently published a scientific report "towards an integrated environmental risk assessment of multiple stressors on bees: review of research projects in Europe, knowledge gaps and recommendations" (EFSA PPR panel, 2012; EFSA, 2014).

From a horizontal perspective, the Scientific Committee of EFSA has identified this topic as priority for guidance development and the SCER unit has published in 2013, a scientific report reviewing the available international frameworks dealing with human risk assessment of combined exposure to multiple chemicals. The report has also identified key needs for future work in the area of combined toxicity of chemicals from a consultation of EFSA panels, units and the Scientific Committee. A key recommendation was the need to collect data in the area of human, animal and environmental toxicology of mixtures for substances of relevance to EFSA (EFSA, 2013). As a consequence, the SCER unit has:

a) Launched two procurements to collect data to fulfil these recommendations:

The first procurement "metabolic interactions and synergistic effects of chemical mixtures for human risk assessment using systematic review" was initiated in December 2012 and was finalised and published in May 2015 (Quignot et al., 2015a).

The second procurement dealt with "combined toxicity of multiple chemicals: evidence-based approach for animal health and ecological risk assessment using systematic review" was published in July 2015 (Quignot et al., 2015b).

b) Organised a scientific colloquium in September 2014 on "Harmonisation of human and ecological of risk assessment of combined exposure to multiple chemicals" (EFSA, 2015).
c) Launched three procurements were launched on "Outsourcing preparatory work for integrating new approaches in chemical risk assessment" in human health, animal health and ecological risk assessment" aiming to develop toxicokinetic tools and dynamic energy budget

models for single chemicals and multiple chemicals in the free software R (EFSA-M-2014-0235).

- 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 (EFSA-Q-2014-00918; EFSA-Q-2015-00640).
- Procurement call 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 (EFSA-Q-2015-00554).
- Article 36 Agreement "Modelling human variability in toxicokinetic and toxicodynamic processes using Bayesian meta-analysis, physiologically-based modelling and in vitro systems" aiming to develop a global web-based platform (http://www.efsa.europa.eu/en/art36grants/article36/gpefsascer20101).

All these background activities will support the development of a guidance document (GD) on the harmonisation of for human health and ecological risk assessment of combined exposure to multiple chemicals at the SC level. In practice, the results of the data collection exercises will provide case studies to illustrate applications of these methods in the regulatory area (pesticides, contaminants etc.).

Objectives

As per EFSA's Founding Regulation (EC) No 178/2002 of the European Parliament and of the Council, "the EFSA Scientific Committee (SC) shall be responsible for the general coordination necessary to ensure the consistency of the scientific opinion procedure, in particular with regard to the adoption of working procedures and harmonisation of working methods". In this context, objective 4 of the EFSA Strategy 2020 implementation plan "Prepare for future risk assessment challenges" echoes this key responsibility of the SC in objective 4.2 " Support for the development and use of harmonised methodologies for risk assessment across the EU and internationally" (http://www.efsa.europa.eu/sites/default/files/151008.pdf).

In this context, this topic has been prioritised in September and December 2015 by the SC (2015-2018) for guidance development with the aim to developing a GD to harmonise methodologies for both the human and the ecological dimension.

Previous and current supporting EFSA activities of relevance are described in the above section (Background). Other key activities of relevance include:

1. other SC WGs and projects of horizontal nature for methodological development (e.g. environmental risk assessment, uncertainty, weight of evidence, biological relevance, MUST-B).

2. the work of other EFSA panels in this area (e.g. PPR panel and the CONTAM panel). All these activities will be taken into account in the GD. In addition, methodological developments by national and international organisations (WHO, FAO, OECD, US-EPA, FDA, etc.) will also be taken into account. In this context, particular attention will be given to the activities of the three non-food committees and the Joint Research Centre (JRC) of the European Commission, the work of sister agencies (ECHA, EMA, EEA), the WHO network on combined exposures and the OECD working group on combined exposure to multiple chemicals. This will enable the coherent linkage of all these activities in the respective documents, avoid duplication of work, and ensure consistency and harmonisation of terminology and methodologies.

Finally, in order to support the working group, during the development of the guidance, two technical/scientific reports on human health and ecological risk assessment respectively will be produced by the group. These reports aim to illustrate the application of tiered approaches for human

and ecological risk assessment of multiple chemicals with case studies taken from the results of the two published data collection exercises. This will allow the practical implementation of the guidance within the work of the relevant EFSA panels in a fit for purpose manner.

Terms of Reference

EFSA requests the Scientific Committee to develop a guidance document (GD) on the harmonisation of risk assessment methodologies for human health and ecological risk assessment of combined exposure to multiple chemicals. The GD should be an overarching document relevant to the work of scientific advisory bodies and panels dealing with chemical risk assessment both within and across regulatory applications and sectors.

- The WG should review available tools for different risk assessment contexts and develop a harmonised framework for human and ecological risk assessment of combined exposure to multiple chemicals using tiered approaches.
- The tiered approaches should start from first scientific principles for all relevant steps i.e. problem formulation, hazard identification and characterisation, exposure assessment, risk characterisation and uncertainty analysis. For each step, tiered approaches for harmonisation of methodologies should be developed where feasible (purpose of the assessment, data availability, resources) and include explicit description of assumptions.
- Circumstances under which harmonisation between human and ecological risk assessment may not be possible or relevant (e.g. in view of the state of science, regulatory framework) should also be discussed.
- In developing the guidance, work should start from and build on European (e.g. European Commission, ECHA, EFSA) and international (e.g. US-EPA, WHO, OECD) methods and frameworks, to ensure inter-agency cooperation, consistency and avoid duplication of the work.
- Case studies should be annexed in the GD to explore the feasibility and spectrum of applications of the proposed methods and approaches for human health and ecological risk assessment.
- In line with EFSA's initiative on Transparency and Engagement in Risk Assessment (TERA), the draft GD will be subject to public consultation. The published GD will be presented and discussed at an international event.

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Abbreviations

ECHA: European Chemicals Agency
EFSA: European Food Safety Authority
EEA: European Environment Agency
EFSA CONTAM Panel: European Food Safety Authority Scientific Panel on Contaminants in the Food Chain
EFSA PPR: European Food Safety Authority Scientific Panel on Plant Protection Products and their Residues
EMA: European Medicines Agency
FDA: US Food And Drug Administration
FAO: Food and Agriculture Organization of the United Nations
JRC: Joint Research Centre of the European Commission
OECD: Organisation for Development and Economic Cooperation
SCER: EFSA's Scientific Committee and Emerging Risks Unit
US-EPA: United States Environmental Protection Agency
WHO: World Health Organization