Environment International 120 (2018) 544–562

Contents lists available at ScienceDirect

Environment International

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

Review article

Current EU research activities on combined exposure to multiple chemicals☆

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ARTICLE INFO

Handling Editor: Robert Letcher

ABSTRACT

Humans and wildlife are exposed to an intractably large number of different combinations of chemicals *via* food, water, air, consumer products, and other media and sources. This raises concerns about their impact on public and environmental health. The risk assessment of chemicals for regulatory purposes mainly relies on the assessment of individual chemicals. If exposure to multiple chemicals is considered in a legislative framework, it is

Abbreviations: AO, adverse outcome; AOP, adverse outcome pathway; BMD, benchmark dose modelling; BQE, biological quality element; CA, concentration addition; CAG, cumulative assessment group; CMEP, chemical monitoring and emerging pollutants; CRA, cumulative risk assessment; DART, developmental and reproductive toxicity; DEB, dynamic energy budget; EBT, effect-based tools; EDC, endocrine disrupting chemical; EQS, environmental quality standard; HBM, human biomonitoring; IA, independent action; IATA, integrated approach to testing and assessment; IPRA, integrated probabilistic risk assessment; iPSC, induced pluripotent stem cells; LOE, lines of evidence; MCR, maximum cumulative ratio; MCRA, Monte Carlo risk assessment tool; MEC, measured exposure concentration; MoA, mode of action; MRA, mixture risk assessment; MSFD, Marine Strategy Framework Directive; NAM, new approach methodology; PBTK, physiologically based toxicokinetic (model); PEC, predicted exposure concentration; PNEC, predicted no effect concentration; QSAR, quantitative structure activity relationship; RDT, repeated dose systemic toxicity; TK, toxicokinetic; SMRI, similar mixture risk indicator; SYRINA, systematic review and integrated assessment; TTC, Threshold of Toxicological Concern; WFD, Water Framework Directive

☆ The views expressed are those of the authors and do not necessarily represent the official position of their organisations.

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https://doi.org/10.1016/j.envint.2018.07.037
Received 4 May 2018; Received in revised form 25 July 2018; Accepted 26 July 2018
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usually limited to chemicals falling within this framework and co-exposure to chemicals that are covered by a different regulatory framework is often neglected. Methodologies and guidance for assessing risks from combined exposure to multiple chemicals have been developed for different regulatory sectors, however, a harmonised, consistent approach for performing mixture risk assessments and management across different regulatory sectors is lacking. At the time of this publication, several EU research projects are running, funded by the current European Research and Innovation Programme Horizon 2020 or the Seventh Framework Programme. They aim at addressing knowledge gaps and developing methodologies to better assess chemical mixtures, by generating and making available internal and external exposure data, developing models for exposure assessment, developing tools for *in silico* and *in vitro* effect assessment to be applied in a tiered framework and for grouping of chemicals, as well as developing joint epidemiological-toxicological approaches for mixture risk assessment and for prioritising mixtures of concern. The projects EDC-MixRisk, EuroMix, EUToxRisk, HBM4EU and SOLUTIONS have started an exchange between the consortia, European Commission Services and EU Agencies, in order to identify where new methodologies have become available and where remaining gaps need to be further addressed. This paper maps how the different projects contribute to the data needs and assessment methodologies and identifies remaining challenges to be further addressed for the assessment of chemical mixtures.

1. Introduction

Humans and wildlife are exposed to an intractably large number of different combinations of chemicals *via* food, water, air, consumer products, materials and goods. The possible combinations of mixtures are increased by use of *inter alia* pharmaceuticals, drugs, tobacco and occupational exposures. Taken together, this raises significant concerns about the impacts on public and environmental health. The risk assessment of chemicals for regulatory purposes does only in rare cases take into account the “real life” exposure to multiple chemicals, but mainly relies on the assessment of individual chemicals. If exposure to multiple chemicals is considered in a legislative framework, this is usually limited to chemicals falling within this framework and neglects co-exposure to chemicals that are covered by a different piece of legislation (Evans et al., 2016). A detailed overview of the different legislative requirements for assessing mixtures in EU legislation can be found in Kienzler et al. (2014, 2016).

Guidance documents are available within specific regulatory sectors and international frameworks have been proposed (Kienzler et al., 2014, 2016). However, a harmonised, consistent approach for performing mixture risk assessments and management across different regulatory sectors is lacking. As outlined in the Commission Communication on the combination effects of chemicals - Chemical mixtures (EC, 2012), there are several open issues to address, such as a lack of understanding of real co-exposures, lack of information on combined toxicity, interactions, chemicals' modes of action and criteria for grouping chemicals.

Several EU research projects are presently underway, funded by the current European Research and Innovation Programme Horizon 2020 (EC, 2013; Karjalainen et al., 2017) or the Seventh Framework Programme (FP7; EC, 2006). They aim at addressing research gaps, by *e.g.* generating and making available internal and external exposure data, developing models for exposure assessment, developing tools for *in silico* and *in vitro* effect assessment to be used in a tiered framework and for grouping of chemicals, as well as developing joint epidemiological-toxicological approaches for mixture risk assessment and for prioritising mixtures of concern.

The research projects and several European Commission services and EU agencies have joined forces to link these projects, map the achievements and identify remaining gaps. These aspects were also discussed in a workshop entitled ‘Advancing the Assessment of Chemical Mixtures and their Risks for Human Health and the Environment’, on 29–30 May 2018, at the Joint Research Centre in Ispra, Italy. The main features of these projects are presented in this publication, as well as how the projects link to specific aspects of mixture risk assessment. However, the list of projects presented below is not exhaustive, as it focuses on ongoing projects funded by EU research and innovation programmes and related activities within EU institutions. Nevertheless, considering the listed projects we expect to cover the current main areas of mixture research and development, in order to draw the conclusions presented at the end of this document.

2. Main concepts and terminology in the assessment of mixtures

2.1. Terminology

Many different terms are used in the context of chemical mixtures. This publication follows the terminology proposed by WHO/IPCS and published in Meek et al. (2011). It is important to distinguish exposure to the same chemical from multiple sources and/or by multiple pathways, which is termed “aggregate exposure”, while exposure to multiple chemicals *via* single or multiple sources and/or pathways is termed “combined exposure to multiple chemicals”. Chemicals grouped together for evaluation of combined exposure are referred to as an “assessment group”. The term “chemical mixture” refers to a combined exposure to multiple chemicals, and is defined as any set of multiple chemicals, regardless of their source, that may or may not be identifiable and that may contribute to joint toxicity in a target population (ATSDR, 2004). Manufactured products, such as pesticide formulations or cosmetic products are considered “intentional mixtures”, whereas coincidentally formed and variable mixtures originating from one or several sources, such as surface water contaminations or pesticide residues in food, are considered unintentional mixtures. In order to facilitate the readability of the document, we generally refer to Mixture Risk Assessment (MRA) as representing the assessment of risks from combined exposures to multiple chemicals. Only in the field of plant protection products, the EU legislative framework uses the terms “cumulative risk assessment” (CRA) and “cumulative assessment groups” (CAGs), which we therefore use in that context.

In the context of this paper, risk assessment is referred to as defined by WHO/IPCS (2004): “A process intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system. The risk assessment process includes four steps: hazard identification, hazard characterization (related term: *Dose–response assessment*), exposure assessment, and risk characterization.” MRA therefore applies this definition in the context of combined exposure to multiple chemicals.

2.2. Concepts for mixture risk assessment

2.2.1. Mixtures in regulatory toxicology

The risk from exposure to chemical mixtures can be assessed as a whole (whole-mixture approach), or based on the individual

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