



**EDC-MixRisk**  
safe chemicals for future generations



## ***The Chemical Cocktail Challenge***

**“A workshop on results and conclusions from the two H2020-funded projects, EDC-MixRisk and EuroMix, and their implications for future needs for chemical mixture risk assessment”**

***26 March 2019, Brussels, Belgium***

### **MIXTURES AND FOOD SAFETY**

Sabine JULICHER, European Commission, DG Sante

Abstract:

Progress through collaboration is essential to address not only the regulatory requirements, but also the growing concerns of consumers and stakeholders regarding exposure to chemical mixtures. The Commission is committed to move ahead in this important area with the final goal of an integrated approach for assessing exposure to chemical mixtures in all relevant areas. Both the EDC-MixRisk and the EuroMix projects mark significant breakthroughs in our understanding of human daily exposure to chemical mixtures, their role is prominent in providing information for future risk management decisions on the safety of chemicals in mixtures.

The methodology for assessing human exposure to mixtures of chemicals remains a challenge. In the field of pesticides residues, efforts for developing an appropriate methodology for the assessment of the risks from multiple residues have been going for more than a decade. The ongoing evaluation to check whether the EU pesticides legislation is still ‘fit for purpose’ highlighted the need for increased efforts in addressing the cumulative and synergistic effects of pesticide residues. Towards this end, DG SANTE is closely cooperating with the European Food Safety Authority (EFSA) and Member States on the development of an EU-harmonised approach for assessing the risk of the dietary cumulative exposure to multiple pesticide residues.



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#### **HOW RESEARCH CONTRIBUTES TO SOLVING THE MIXTURE CHALLENGE**

Maria Pilar Aguar Fernandez, European Commission’s DG Research & Innovation, Health Directorate

Abstract:

My opening statement, on behalf of the European Commission’s DG Research & Innovation, which is funding through Horizon 2020 the two projects, EDC-MIXRISK and EuroMix, will highlight some of the achievements of the two projects. Furthermore, I will present some of the past and present policy initiatives such as those related to endocrine disruptors or mixture toxicity that have been the guiding forces behind to drive research forward. Finally, I will briefly describe relevant features from the proposed new Framework Programme for Research and Innovation, Horizon Europe.



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### **EUROMIX HIGHLIGHTS AND KEY RECOMMENDATIONS**

Jacob van Klaveren<sup>1</sup>, Alfonso Lampen<sup>2</sup>, Hilko van der Voet<sup>3</sup>

(1) RIVM, National Institute for Public Health and the Environment, The Netherlands, (2) German Federal Institute for Risk Assessment, Dept. Food Safety, Berlin, Germany, (3) Wageningen University & Research, Biometris, The Netherlands

Abstract:

**We still don't know much about the consequences of exposure to chemical mixtures. Research under the EuroMix project will help stakeholders closing the gap.**

EuroMix aimed to establish novel testing and assessment strategies for chemical mixtures, to develop appropriate mixture risk assessment methodology and to implement this in a well-accessible inter-operational data and model platform.

Human biomonitoring studies show that people have a considerable number of man-made chemicals in their bodies, and European regulations stipulate the need to consider the potential mixture effect. However, animal testing should be reduced, and new testing methods are required. For the EuroMix team, the question was simple: How do we translate these good intentions to effective actions?

The team delivered a test strategy to generate missing toxicity data needed for future risk assessments. They tested many chemicals and ran several case studies with a large number of chemicals affecting three adverse outcomes; liver steatosis, skeletal malformation and endocrine disruption. They also developed a novel risk modelling approach aligned with needs in Europe and elsewhere.

The approach starts with in silico modelling grouping chemicals into cumulative assessment groups. Then in vitro assays are used to investigate the appropriateness of the dose addition assumption and to derive the relative toxicity of chemicals. Results from in-vitro testing are then compared with data from animal studies. Although in-vitro assays already allow generation of new hazard data on yet-untested chemicals, their results need to be extrapolated from internal exposure concentrations to external doses before being used in mixture risk assessment. For in vitro to in vivo extrapolation (IVIVE) substance-specific kinetic models have been developed.

EuroMix has delivered an open web-based data and model platform for exposure, hazard and risk assessment. The modular system includes in silico modelling, dose-response modelling of in vitro test and in vivo results, the derivation of relative potency factors, an IVIVE modelling approach and the combination of hazard characterisations with dietary and non-dietary exposure assessments into margins of exposure. Eleven European Member States performed dietary exposure assessments using EuroMix data and models. Case studies addressing multiple exposure routes of bisphenols and pesticides, a comparison with human biomonitoring data and a feasibility study on simultaneous exposure to pesticides, additives and contaminants regulated under different regulatory sectors will be further explored. Stakeholders have been successfully trained on the EuroMix models.

For better or worse, chemicals have become an integrant part of our lives. And while there is still much we don't know about the consequences of this ubiquity on our health, EuroMix is certainly making headway. A EuroMix follow-up initiative, as part of the EFSA Risk Assessment Agenda, is currently under discussion aiming to apply the EuroMix test approach and risk models to other toxic endpoints and/or relevant combination of chemicals.



EuroMix has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 633172



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SESSION 1: Joint forces tackling chemical mixtures - Key results and conclusions from EDC-MixRisk and EuroMix

### **EDC-MixRisk highlights and key messages**

Åke Bergman<sup>1</sup>, Carl-Gustaf Bornehag<sup>2,3</sup>, Joëlle Rüegg<sup>1</sup>, Chris Gennings<sup>3</sup>, the EDC-MixRisk consortium.

(1) Karolinska Institutet, Stockholm, Sweden (2) Karlstad University, Sweden (3) Icahn School of Medicine at Mount Sinai, New York, USA

#### **ABSTRACT:**

A healthy endocrine system is essential for our ability to reproduce and develop. Endocrine disrupting chemicals (EDCs) are linked to serious health problems such as diabetes, obesity, neurodevelopmental disorders and reproductive problems. The fact that we are exposed to complex mixtures of EDCs is of particular concern. EDC-MixRisk is an EU Horizon 2020 research project that has developed a novel whole mixture approach that is based on 1) identifying EDCs in mixtures (so called bad actors) associated with adverse health outcomes in epidemiological studies, 2) preparing artificial mixtures of the bad actors and testing them in different experimental settings, and 3) using the experimental data for mixture risk assessment. This proof-of-concept will enable more systematic integration of epidemiological and experimental evidence into mixture risk assessment strategies. In our presentation, we will highlight the key results and conclusions of this project and how they compare to other testing and risk assessment approaches. We will also present the future needs identified based on the EDC-MixRisk outcome.



EDC-MixRisk project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 634880.



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### **EFSA PERSPECTIVE**

Jean Lou C M Dorne: European Food Safety Authority, Scientific Committee and Emerging Risks Unit, Parma, Italy

Abstract:

The scientific Committee of EFSA has recently adopted after public consultation a guidance document on harmonised risk assessment methods of combined exposure to multiple chemicals "chemical mixtures" for human health, animal health and ecological risk assessment. EFSA is currently implementing these methods in the areas of human and animal health for regulated compounds (i.e. pesticides), feed additives and contaminants as well as in the ecological area particularly for bee health. In parallel, EFSA is developing a set of open source tools and models to support biologically-based risk assessment of mixtures.

The Horizon 2020 projects EDC-MixRisk and EuroMix have investigated the impact of chemical mixtures on human health particularly for pesticides and contaminants. The approach taken for EDC-MixRisk included experimental testing strategies such as *in vivo*, *in vitro* and *in silico* methods for endocrine disrupters and epidemiological studies in an integrated manner while also considering health risks and societal impact. The EuroMix project has developed *in vivo*, *in vitro* and *in silico* methods and integrated all results and models in a toolbox to support human exposure, hazard and risk assessment of mixtures using component-based approaches.

Considerations of these research activities from an EFSA perspective are given with regards to methodologies and human risk assessment of combined exposure to multiple pesticides and contaminants.



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### **EDC-MIXRISK AND EUROMIX IMPLICATIONS FOR THE FUTURE - PERSPECTIVES FROM AN OECD VIEWPOINT**

Eeva Leinala<sup>1</sup> (1) Organisation for Economic Cooperation and Development

Abstract:

The Organisation for Economic Cooperation and Development (OECD) recently published a document on Considerations for Assessing Combined Exposures to Multiple Chemicals<sup>i</sup>. The approaches in both EDC-MixRisk and EuroMix align with these considerations. The OECD also works to advance the use of in silico and in vitro methods, inclusion of mechanistic thinking (e.g. use of Adverse Outcome Pathways) and Integrated Approaches to Testing and Assessment that also apply new approach methodologies. The two H2020 initiatives provide examples of how to combine various types of data to build a case for the need for and support the results of assessment of risk to combined exposures. Linking epidemiological or in vivo results to in vitro approaches, harnessing biomonitoring and use data to inform co-exposure, examining modelling information in the context of measured data, building grouping rationales based on mechanistic thinking ...

Reflecting on discussions at the OECD, the main risk assessment methods are in place for assessment of mixtures, however there is a need for further examples of the use of these methods in different information contexts. Also, for the uptake of new methods (e.g. new in vitro methods), there is a clear expression from regulators for transparency and clarity on what information new methods are providing, their domain of applicability and the interpretation of results. Tools are available to aid in a transition between research and regulatory use<sup>ii,iii,iv</sup>.

<sup>i</sup> OECD (2018), Considerations for Assessing the Risks of Combined Exposure to Multiple Chemicals, Series on Testing and Assessment No. 296, ENV/JM/MONO(2018)37, OECD, Paris. <http://www.oecd.org/chemicalsafety/risk-assessment/considerations-for-assessing-the-risks-of-combined-exposure-to-multiple-chemicals.pdf>

<sup>ii</sup> OECD (2014), Guidance Document for Describing Non-Guideline In Vitro Test Methods, Series on Testing & Assessment No. 211. ENV/JM/MONO(2014)35, OECD, Paris.

<sup>iii</sup> OECD (2016), Guidance Document on the Reporting of Defined Approaches to Be Used within Integrated Approaches to Testing and Assessment, Series on Testing and Assessment No. 255, ENV/JM/MONO(2016)28, OECD, Paris.

<sup>iv</sup> OECD (2016), Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to Be Used within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation, Series on Testing and Assessment No. 256, ENV/JM/MONO(2016)29, OECD, Paris.



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### **PERSPECTIVES FROM THREE EUROPEAN COMMISSION DGs**

Stephanie K Bopp<sup>1</sup>, Laura Fabrizi<sup>2</sup>, Peter Korytar<sup>3</sup>

(1) European Commission DG Joint Research Centre (2) European Commission DG Health and Food Safety (3) European Commission DG Environment

The European Commission has worked in the area of chemical mixtures over the last decade (The State of the Art report on Chemical Mixtures (2009), the Opinion of the non-food Scientific Committees (2011) and the Commission Communication on Chemical Mixtures (2012)). The Communication identified data and knowledge gaps and called for an improved understanding of the exposure to chemical mixtures, the toxic effects, modes of action and potential interactions of chemicals, as well as identification of specific mixtures to be addressed with priority. It also called for follow up actions by Horizon 2020 projects.

On endocrine disruptors, the European Union legislation foresees strict regulatory measures to protect the human health and the environment: they are identified and regulated under REACH Regulation and regulatory criteria for their identification in the sector of biocides and pesticides were adopted for the 1st time worldwide, including scientific guidance for their implementation. The Communication “Towards a comprehensive EU framework on endocrine disruptors (2018)” presents a strategy to address endocrine disruptors comprehensively and acknowledges data gaps in understanding combined exposure to those and other substances.

Both projects, EuroMix and EDC-MixRisk contributed to fill some of these gaps by providing a toolbox for exposure, hazard and risk assessment, making progress on integration of epidemiological and experimental data for improved strategies for mixture risk assessment, considering societal impact. The link of the projects with ongoing initiatives in pesticide cumulative risk assessment, endocrine disruptors and overall methodology to address chemical mixtures will be discussed from a policy related perspective.