Towards zero pollution: Knowledge gaps and future research needs concerning endocrine disruptors (EDs) – EURION contribution

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INTRODUCTION

The function and regulation of the endocrine system in humans and other species is of high biological complexity, including advanced feedback signalling and mechanistic interactions between different endocrine axes to sustain homeostasis. Chemicals as well as chemical mixtures can affect the endocrine system through multiple pathways which are equally complex and often intertwined. This can result in a disruption of the endocrine balance and cause adverse developmental, reproductive and other pathophysiological effects. Most current research on single chemicals and mixtures focuses on the effects on specific endocrine axes and mechanisms of action, to the detriment of the real-life complexity of effects at organism level. Furthermore, there is still a substantial lack of information about the toxicological and biological aspects of chemicals interfering with the endocrine axes. The European Cluster to Improve Identification of Endocrine Disruptors, EURION, has identified a number of crucial future research needs concerning endocrine disruptors.

METHODOLOGY

With regard to the methodological aspects, it is important to support inter-and transdisciplinary research. The (experimental) models should follow state-of-the-art development incorporating biologically relevant details and interactions between systems. The role of sex, microbiota, individual susceptibility (incl. genetic pre-disposition, existing disease condition), diet variability (fibre intake, etc.), chemical intake, timing of exposure and potential resilience-adding factors should be addressed properly as these points are crucial to be able to move from animal testing to protective animal-free toxicity testing of human relevance. Moreover, non-mammalian species (e.g. fish and amphibians, incl. embryonic stages) and invertebrates can be used to predict effects or raise concerns about potential effects in humans or vice versa. This will enable more effective use of data across human health and environmental hazard assessments. Furthermore, computational toxicology and artificial intelligence (e.g. machine learning) approaches should be afforded a greater role in order to predict effects.

RESULTS

Future research needs are summarised as follows:

1) Better understanding of the effects of chemicals and chemical mixtures on the underlying mechanistic crosstalk between endocrine axes, endocrine pathways and other key biological systems;

2) Studying the impact of EDs on target organs and physiological barriers, such as the placenta, the blood-brain barrier, intestinal, pulmonary and immune cells as well as their interaction with microbiota;

3) Developing advanced human 3D cell culture models able to more closely recapitulate in-vitro human biology for testing the effects; 4) Investigating biological effects of realistic mixtures for a more detailed understanding of the endocrine effectome; 5) Assessing the occurrence and relevance of multi- and transgenerationally inherited effects. The mechanistic underpinnings of such effects, their persistence over generations, and their contribution to the effectome;

6) Developing Adverse Outcome Pathways (AOPs), quantitative AOPs and AOP networks to support identification of EDs and better use of data that make it possible to link endocrine activity and adverse effects.

DISCUSSION

These fundamental knowledge gaps should be addressed to ensure that the hazard and risk assessment of chemicals protects human health and the environment. Ultimately, this new knowledge should be used to elaborate on testing strategies for identifying hazards in the future. The research needs are closely linked to the aims of the Chemicals Strategy for Sustainability which highlights the protection of consumers and workers from the most harmful substances, including endocrine disruptors. The strategy aims to identify endocrine disruptors more effectively and emphasises considerations for vulnerable populations and combination effects of chemicals, in line with the research needs outlined here. Importantly, further research in this field would also contribute to the aims of the Zero Pollution Action Plan and the UN's Sustainable Development Goals. The research needs are based on two focus meeting discussions between the EURION Coordinators' group members during the summer of 2021. The research needs were circulated among the group and elaborated on the basis of the co-authors' input and comments made during the process. The projects have received funding from the Horizon 2020 framework programme.