Critical appraisal of currently available guidance on human risk assessment from combined exposure to multiple chemicals

Main author: Dimitra Nikolopoulou (Benaki Phytopathological Institute (BPI))

Co-authors: Dimitra Nikolopoulou, Kyriaki Machera, Katerina Kyriakopoulou, Chris Anagnostopoulos, Evangelia Ntzani

INTRODUCTION

The consumption of fruits, vegetables and foods of animal origin typically leads to consumer exposure to pesticide residues, which are present in food as a consequence of the plant protection practices applied. The current international practice is to assess the risk to the consumer from exposure to each chemical separately, although studies on the monitoring of pesticide residues in food indicate that the consumer is exposed to a combination of chemical compounds. Therefore, the need for internationally harmonised risk assessment approaches from combined exposure to multiple chemicals has been identified by the scientific community.

We undertook a critical appraisal of key guidance (EFSA, ECHA, EPA, WHO, OECD) and pivotal literature thereon for consumer risk assessment from dietary exposure to mixtures of chemicals and discussed challenges relating to their implementation.

METHODOLOGY

As for single chemicals, the cumulative risk assessment (CRA) process for chemical mixtures entails the steps of problem formulation, hazard identification and characterisation, exposure assessment and risk characterisation including uncertainty analysis. Nevertheless, the complexity of each step increases in the case of chemical mixtures due to the large number of chemicals potentially involved and their different toxicological profiles, as well as the different sources, pathways and routes of human exposure. Moreover, the current grouping of chemicals for component-based CRA focuses on a single regulatory sector, whist reality is more complex. For example, in the area of dietary CRA, combined exposure may be expected from regulated products (e.g. pesticides), contaminants in the food and feed chain including environmental contaminants (e.g. brominated flame retardants), chemical substances resulting from food and/or feed processing and natural toxins produced as undesirable substances in food and feed, fungi

and other microorganisms (e.g. mycotoxins). In this work, we compared and contrasted the guidance documents under appraisal using the aforementioned RA attributes.

RESULTS

Available methodologies stress that the conditions related to CRA need to be defined upfront. An iterative, structured approach consisting of a rigorous assessment of the continuously updated reliable evidence for co-exposure and/or the common target organ or system, and a prioritisation of chemicals, considering hazard and exposure data, in order to identify risk drivers is proposed by EFSA.

Currently, the grouping of priority chemicals during component-based CRA is hazard-driven, following a standard process (Adverse Outcome Pathway, Mode of Action (MoA), Weight of Evidence, Uncertainty Analysis) and identifying the NOAEL/BMD of the specific effect for consideration in risk characterisation. Admittedly, when this level of detailed knowledge is less robust, different grouping options are discussed by different guidance documents such as common adverse outcome (toxic effect) on target organ, structural similarity, and common metabolites.

In the exposure assessment, probabilistic modelling including an uncertainty analysis is preferred for cumulative risk assessment as opposed to deterministic approaches which are applied for single chemicals.

DISCUSSION

The development of scientific approaches for assessing combined exposure to multiple chemicals in humans has been a key research priority in most regulatory agencies over the past few years. Implementation-wise, examples of recent CRA efforts come from the US EPA on organophosphates, N-methyl carbamates, chloracetanilides, triazines, and pyrethrins/pyrethroids and from EFSA on pesticides with acute and chronic effects on the nervous system or chronic effects on the thyroid. Although the principle of dose addition has been widely accepted, based on scientific evidence, for low levels of exposure (e.g. to pesticide residues through diet) to chemicals with the same toxic effect regardless of MoA, chemical interactions (synergism, antagonism, potentiation) should be considered in uncertainty analyses and in order to trigger further scientific research. The availability of reliable and sufficient exposure and hazard data, including detailed MoA analyses, remains a continuous challenge in CRA and is critical for defining and revising problem formulation and for prioritising risk assessments to ensure the protection of human health.