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Review

Human exposure to chemical mixtures: Challenges for the integration of toxicology with epidemiology data in risk assessment

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ABSTRACT

Little is known about the potential adverse effects from longterm exposure to complex mixtures at low doses, close to health-based reference values. Traditional chemical-specific risk assessment based on animal testing may be insufficient and the lack of toxicological studies on chemical mixtures remains a major regulatory challenge. Hence, new methodologies on cumulative risk assessment are being developed but still present major limitations. Evaluation of chemical mixture effects requires an integrated and systematic approach and close collaboration across different scientific fields, particularly toxicology, epidemiology, exposure science, risk assessment and statistics for a proper integration of data from all these disciplines. Well designed and conducted epidemiological studies can take advantage of this new paradigm and can provide insight to support the correlation between humans low-dose exposures and diseases, thus avoiding the uncertainty associated with extrapolation across species. In this regard, human epidemiology studies may play a significant role in the new vision of toxicity testing. However, this type of information has not been fully considered in risk assessment, mainly due to the inherent limitations of epidemiologic studies. An integrated approach of *in vivo*, *in vitro* and *in silico* data, together with systematic reviews or meta-analysis of high quality epidemiological studies will improve the robustness of risk assessment of chemical mixtures and will provide a stronger basis for regulatory decisions. The ultimate goal is that experimental and mechanistic data can lend support and biological plausibility to the human epidemiological observations.

Contents

1. Exposure to chemical mixtures

The presence of chemical mixtures in the food or the environment constitutes a major health challenge deserving due attention. The scientific community has shown a great interest in assessing,

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and if possible quantifying, how combined exposures to chemicals may affect the human health (Tsatsakis et al., 2016, 2017). As shown by human biomonitoring studies, populations (including children) from distinct geographic areas are exposed to a large number of chemicals throughout their lives, with these exposures occurring at intermittent and inconsistent doses instead of at a consistent rate and dose magnitude (Nachman et al., 2011). Although not all these exposures are potentially harmful, information is needed on how to regulate and screen chemical mixtures since they might threaten the human health. Regulatory requirements for risk assessment of these mixtures are rare, except for intentional mixtures such as formulated products. Until now, little is known about the adverse effects from long-term exposure to complex mixtures at low doses, close to regulatory reference values in humans (health-based guidance values) and animals (NOAELs, used as points of departure used for derivation of guidance values). By studying the toxicity of chemical mixtures, instead of their individual constituents, it may be possible to clarify their potential role in the development of chronic diseases, particularly those with long latency periods. If so, tailored public health interventions could be implemented to prevent the potential impact of these exposures (Taylor et al., 2016; Tsatsakis et al., 2016).

2. Testing the safety of chemical mixtures for cumulative risk assessment

Prior to market entry, chemicals such as pesticides and biocides undergo a process of scientific assessment to ensure their safety for humans, animals and the environment. Despite a comprehensive and rigorous battery of regulatory toxicological studies to evaluate the safety of individual chemicals, there are growing concerns about their potential long-term effects and the appropriateness of experimental models to adequately predict human health risks. A number of methodologies have been developed for assessing the combined effects of chemicals on humans and the environment, and the most widely used for human risk assessment are based on the framework proposed by the WHO/IPCS (Meek et al., 2011), which provides tiered approaches for screening level assessments and further refinements.

Nowadays, the international scientific community as well as international regulatory authorities have started to realise the need for a cumulative risk assessment and new methodologies are being developed (EFSA, 2013a; US-EPA, 2006). In particular, EFSA started to give special attention to cumulative risks from exposure to pesticides that produce common adverse outcomes on the same target organ/system (EFSA, 2013b). However, the lack of data from toxicological studies investigating chemical mixtures represents one of the major regulatory challenges. In the European Union, the Regulation on the classification, labelling and packaging (CLP) of substances and mixtures (Regulation (EC) No. 1272/2008) transferred the responsibility of performing animal testing of commercial mixtures to industry as a last resort to prove a toxicological hazard; however, no regulatory provision has been taken for non-commercial artificial mixtures that represent the real scenario of real life exposure.

Exposure scenarios simulating real life is a complex issue because exposure to multiple chemicals may lead to a web of interactions with a wide array of underlying mechanisms that ultimately may result in diverse health outcomes (Fig. 1). In this respect, linear −monomodal, but also nonlinear, effects can be seen in the range of low and/or high concentrations of exposures (Hernández et al., 2013a). Special concerns are related to different types of toxicity, such as neurotoxicity (Baltazar et al., 2014; Dardiotis et al., 2013; Zaganas et al., 2013), cardiotoxicity (Posnack, 2014; Zafiropoulos et al., 2014), nephrotoxicity (Vardavas et al., 2016), genotoxicity (Stivaktakis et al., 2016; Tsitsimpikou et al., 2013), hepatotoxicity (Hernández et al., 2013b) and endocrine disruption (Bergman et al., 2013; Ihde et al., 2015; Mrema et al., 2013).

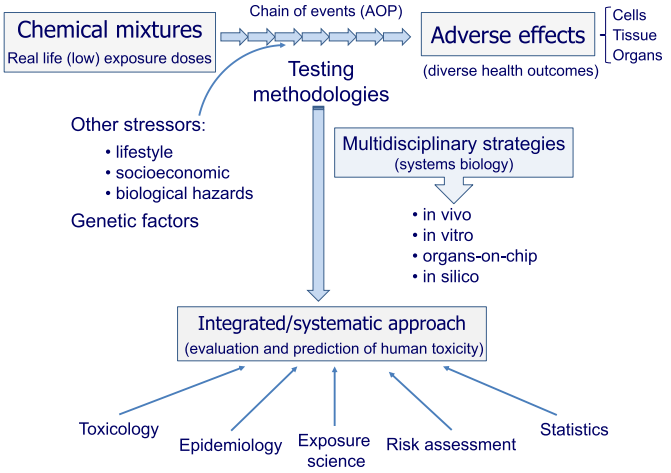

Fig. 1. Multiple hazard approach for long-term health outcomes and integrated approach of multiple lines of evidence for toxicity testing and prediction (AOP: adverse outcome pathways).

Evaluation of chemical mixture effects is considered a multifactorial task that needs an integrated and systematic approach not only for long-term scenarios but often for acute or subchronic exposures. The need for a new experimental methodology for mixture testing is intended to answer to multiple questions on health concerns related to exposure to low realistic doses that raised the attention of researchers in the field (Tsatsakis et al., 2016; Tsatsakis and Lash, 2017).

Prior papers (Docea et al., 2016; Tsatsakis et al., 2017) reported animal protocols to evaluate the cumulative toxicity of different chemical mixtures by using realistic doses following long term exposure. These experimental methodologies have the ambition to provide at one strike multi-answers to multi-questions, e.g. to study long term toxicity of non-commercial chemical mixtures consisting of common everyday life chemicals (pesticides, food additives, components of lifestyle products) at low and realistic dose levels around the human regulatory limits with the simultaneous investigation of several key endpoints like target organ toxicity and non-organ directed toxicity such as genotoxicity, endocrine disruption and oxidative stress.

Understanding exposure to real-world concentrations of chemical mixtures and their associated health effects require close collaboration across different scientific fields, particularly toxicology, epidemiology, exposure science, risk assessment and statistics for a proper integration of data from each of these disciplines (Carlin et al., 2013) (Fig. 1). Besides, there is a need to develop novel statistical approaches for the evaluation and prediction of effects associated with exposure to chemical mixtures (Taylor et al., 2016; Tsatsakis et al., 2016). However, the joint action of multiple environmental exposures is not limited to chemicals since other stressors may act also as determinants of diseases (e.g., socioeconomic status, risky behaviours including lifestyle, biological agents, etc.).

If the hypothesis of an increased hazard from cumulative exposure to chemicals around regulatory reference levels were shown to be true, this will encourage public authorities and the scientific community to shift from the single-compound risk assessment to the era of cumulative risk assessment. The next step in cumulative risk assessment will be to evaluate whether any type