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Use of Effect Biomarkers for Regulatory Risk Assessment of Chemical Mixtures

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Abstract

General and workers populations are exposed to a wide range of chemicals in their daily lives. Exposures to these chemical mixtures depend on the different environments, routes of exposures (inhalation, skin, and ingestion), and sources. Human Biomonitoring (HBM) is a powerful tool for assessing the uptake of chemicals into the human body in a holistic manner. In this context, effect biomarkers have become an essential part of biomonitoring programs because they reveal adverse effects from chemical exposures also accounting for unknown mixtures effects, the most common human exposure scenario. Effect biomarkers enable us to link chemical exposures to their combined health effects and disease development. This effect biomarker approach implies a needed paradigm shift in regulatory risk assessment from investigating one chemical substance at the time to exposures to chemical mixtures. To date, several relevant effect biomarkers have been validated and some effect biomarkers have been implemented as part of Adverse Outcome Pathway (AOP). The previous multidisciplinary review performed represents a basis for enhancing the identification of relevant effect biomarkers and their mechanistic pathways following the AOP framework. This approach offers a systematic understanding and enables us to bring the use of effect biomarkers and chemical mixture risk assessment into regulatory use by defining mixture thresholds. Guiding principles and examples for defining AOP related effect thresholds for relevant Mode of Actions (MoAs) will be elaborated in an OECD follow up activity with the expert's engagement from more than 25 institutes and organizations.

Keywords: Human biomonitoring; Mixture exposure and risk assessment; Occupational exposure; Mode of action; Adverse outcome pathway

Introduction

The continuous exposures to chemicals and their mixtures can contribute to the development of short-and long-term health effects in general and workers populations. In this context, risk assessment and management of chemicals and their mixtures are a challenging, continuous and dynamic process [1]. Despite the increasing awareness that both regulated and unregulated substances find their way into living organisms and the environment as mixtures, the current regulatory frameworks are still strongly single substance-oriented and is typically enforced based on limit values of a subset of measurable single substances. Due to the possible multiple sources and routes of exposures, Human Biomonitoring (HBM) data is in our view the best approach for assessing actual exposure and risk [2]. An isolated chemical exposure cannot explain the total health burden; which is a rather complex set of factors that jointly contribute to the common reported health effects related with chemical exposures. Effect biomarkers are measurable biochemical, physiological, and behavioral effects, or other alterations within an organism that depending on their magnitude, can be recognized as associated with an established or possible health impairment or disease [3]. Therefore, effect biomarkers can help in identifying early health effects in humans due to low doses exposures, establish dose-response relationships, explore mechanisms and increase the biological plausibility of epidemiological associations. Moreover, many of the effect biomarkers are directly linked to or part of an Adverse Outcome Pathway (AOP). An AOP describes a chain of events at different biological organizational levels that causally connects a molecular initiating event to an adverse health outcome [4,5]. AOPs greatly facilitate the identification of mechanisms shared by several chemicals and thereby highlight and provide supporting evidence for risks of mixture effects 2021, enabling more accurate risk assessment of exposure to chemical mixtures.

Using effect biomarkers offers not only an assessment of exposures, but also direct measure of the effects resulting from a exposure to a mixture, even when not knowing all the chemicals that might be involved in that mixture.

Literature Review

Exposure biomarkers in combination with effect biomarkers, contributes to human health risk assessment by providing information on uptake, bioavailability and bioactivation of chemicals in the human body. Effect biomarkers are therefore a powerful option to measure and directly assess effects from exposures to chemical mixtures in both general and workers populations. This is in line with the priorities of the European Union strategy (2019) 'Towards a Sustainable Chemicals Policy Strategy of the Union'. This strategy aims to ensure that the combination effects of chemicals and the combined exposure of humans to chemicals are properly and consistently addressed in the risk assessment and risk management processes. It also mentions that all relevant sources to chemical exposures should be considered [6]. To understand the observations reported in epidemiological studies, the use of effect biomarkers will facilitate an understanding of the underlying toxic mechanisms that lead to disease occurrences and health impairment [7].

Although effect biomarkers have been widely applied in various environmental health studies in the last decades, they are still considered an emerging approach in the area of risk assessment. An interdisciplinary network of experts from the International Society for Exposure Science-European Chapter (ISES Europe) and the Organization for Economic Co-operation and Development (OECD) Occupational biomonitoring activity of working parties of Hazard and Exposure assessment group sought to overcome this challenge. The ISES Europe and OECD collaboration network mapped the conventional framework of effect biomarkers, and provided recommendations for their systematic use [8]. The current review focused on describing applications of effect biomarkers in risk assessments and management of chemical mixtures.

Discussion

Several effect biomarkers, especially for use in occupational settings, are validated and/or qualified scientifically. Promising novel effect biomarkers are emerging for biomonitoring of the general population. The results the ongoing OECD activity in Occupational Biomonitoring indicate that a large number of validated effect biomarkers can already be used to address mixture effects, relevant health effect endpoints, and Mode of Actions (MoAs) in humans. We found a strong link to the growing AOP knowledge for most of the recommended effect biomarkers. The key messages and perspectives from this multidisciplinary review effort are outlined below [9].

Key messages and perspectives

- Effect biomarkers are the only option available for addressing known and unknown mixture effects from chemical exposures, but are rarely applied.
- Several relevant effect biomarkers are validated and offer a direct assessment of the overall risks of health effects.
- Our multidisciplinary review represents a starting point for enhancing the identification of relevant effect biomarkers and their mechanistic pathways following the Adverse Outcome Pathway (AOP) framework.
- Effect biomarkers can serve as early warning systems in risk assessment and to define intervention priorities when planning risk management.
- Availability of high-quality, validated, high- throughput analytical methods is crucial to ensure that the biomarker data obtained from studies are accurate and precise.
- Biological effect threshold levels can and need to be derived based on mechanistic knowledge coming from the AOP framework to implement the use effect biomarkers in risk assessment of chemical mixtures.

Conclusion

Exposure and effect biomarkers can be used to assess exposures and risks from known and unknown chemical mixtures from different sources. Efforts are being dedicated to prioritizing molecular and biochemical effect biomarkers. The potential applications of effect biomarkers are many folds: Effect biomarkers can serve to provide a causal link in exposure-health outcome associations with a particular MoAs. The fact that different MoA result in different patterns of metabolite changes may help to identify MoAs of new compounds and their mixtures and to interpret these changes in term of metabolic pathways. A further potential area of application, which has so far not received much attention, is the use of effect biomarkers within the regulatory risk assessment of chemical mixtures. Effect biomarkers need to be reliable, robust, and provide an understanding of exposure and effect in the human body. In addition, for effect biomarkers to be used in regulatory risk assessments for chemical mixtures, biological effect thresholds need to be developed. These need to be specific for each effect biomarker and based on AOP knowledge. These thresholds need to be related to concentrations/levels of well-understood, prototypical stressors (focusing on chemicals), that produce the MoA effect. Furthermore, effect biomarker studies have yet to comply with a harmonized framework for data generation to improve their robustness and reliability. Overall, from a risk management perspective, effect biomarkers need to undergo both internal and external validation processes before they can be accepted use in the regulatory risk assessment. New techniques such as in silicon methods (e.g. QSAR, physiologically based kinetic and dynamic (PBK/D) modeling) as well as 'omics' data will aid this process. Moreover, HBM studies with different study designs, particularly prospective cohorts, are needed worldwide to pursue the discovery of effect biomarkers. A systematic understanding of both the relevance and interpretation of effect biomarker data may lead to an increased protection for general population and workers.

Outlook and next steps

A network of experts from US-EPA, Swiss SCAHT, LNS in Luxembourg and several other institutions recommend developing guiding principles for derivation of mixture threshold levels and their use within OECD Working Parties on Hazard & Exposure Assessment (WPHA/WPEA) and OECD Extended Advisory Group on Molecular Screening and Toxicgenomics (EAGMST). In this scope, an interdisciplinary follow-up activity

was adopted recently: Using Adverse Outcome Pathways (AOP) to address combined exposures to chemicals with relevant effect biomarkers. This activity is foreseen to start in summer 2022 with several experts involved from 25 institutions/organizations and intends to complement the missing pieces to facilitate an integrative regulatory use of effect biomarkers for mixture risk assessment.

Acknowledgment

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Disclaimer

The publication was generated as a joint activity of European chapter of International Society for Exposure Science (ISES Europe) including experts of an OECD Occupational Biomonitoring activity effect [1] biomonitoring subtask. As the OECD work is in progress, any text that refers to opinions or recommendations about the OECD work is considered preliminary and as the opinions of the co-authors. The OECD expert group development of draft guidance documents is on-going and will be subject to review and endorsement under the processes of the OECD committee structure. This can lead to changes in the approaches and recommendations documented based on further OECD discussions.

Conflicts of Interest

There are no conflicts of interest.

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