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Review article

From the exposome to mechanistic understanding of chemical-induced adverse effects

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ABSTRACT

The exposome encompasses an individual's exposure to exogenous chemicals, as well as endogenous chemicals that are produced or altered in response to external stressors. While the exposome concept has been established for human health, its principles can be extended to include broader ecological issues. The assessment of exposure is tightly interlinked with hazard assessment. Here, we explore if mechanistic understanding of the causal links between exposure and adverse effects on human health and the environment can be improved by integrating the exposome approach with the adverse outcome pathway (AOP) concept that structures and organizes the sequence of biological events from an initial molecular interaction of a chemical with a biological target to an adverse outcome. Complementing exposome research with the AOP concept may facilitate a mechanistic understanding of stress-induced adverse effects, examine the relative contributions from various components of the exposome, determine the primary risk drivers in complex mixtures, and promote an integrative assessment of chemical risks for both human and environmental health.

Abbreviations: AEP, Aggregate exposure pathway; AO, Adverse outcome; AOP, adverse outcome pathway; EWAS, exposome-wide association studies; KE, key event; HTS, high throughput screening; MIE, molecular initiating event; TD, toxicodynamic; TK, toxicokinetic.

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Contents

1. Introduction

The exposome expands our perception of lifetime exposure because it integrates exogenous chemicals with genetic and external factors that generate chemicals inside the body and thereby may pose threats to human health (Miller and Jones, 2014; Rappaport and Smith, 2010; Wild, 2012). The external contribution to the human exposome is determined by environmental exposure, also termed the eco-exposome (Lioy and Smith, 2013), such as exposure via air, food, water, dust, and use of consumer products (Fig. 1). Apart from environmental pollutants and their biotransformation products, the exposome includes endogenous metabolites and markers of the adaptive cellular stress responses, as well as chemicals that are generated in response to psychosocial stress and lifestyle factors. These joint exposures can be related to adverse health effects via exposome-wide association studies (EWAS; Rappaport, 2012) without attempting to identify mechanistic causes (Fig. 1). Importantly, these associations capture the joint effect of many stressors acting in concert, which invokes mixture effects not only in chemical space of exogenous and endogenous compounds, but also mixtures in time, including the time dependence of effects. The exposome has thus been advocated as a key to cumulative risk assessment (Smith et al., 2015).

During the last decade, the exposome approach has mainly been considered in epidemiology, while the complementary concept of Adverse Outcome Pathways (AOP) has emerged in (eco)toxicology (Ankley et al., 2010). The AOP concept links the exposure of chemicals to their cellular concentrations and molecular initiating events (MIE), through network/pathway disturbances and key events (KE) to responses at the cellular, organ, organism and, finally, population and ecosystem levels (Fig. 1). The AOP concept aims to enhance the utility of

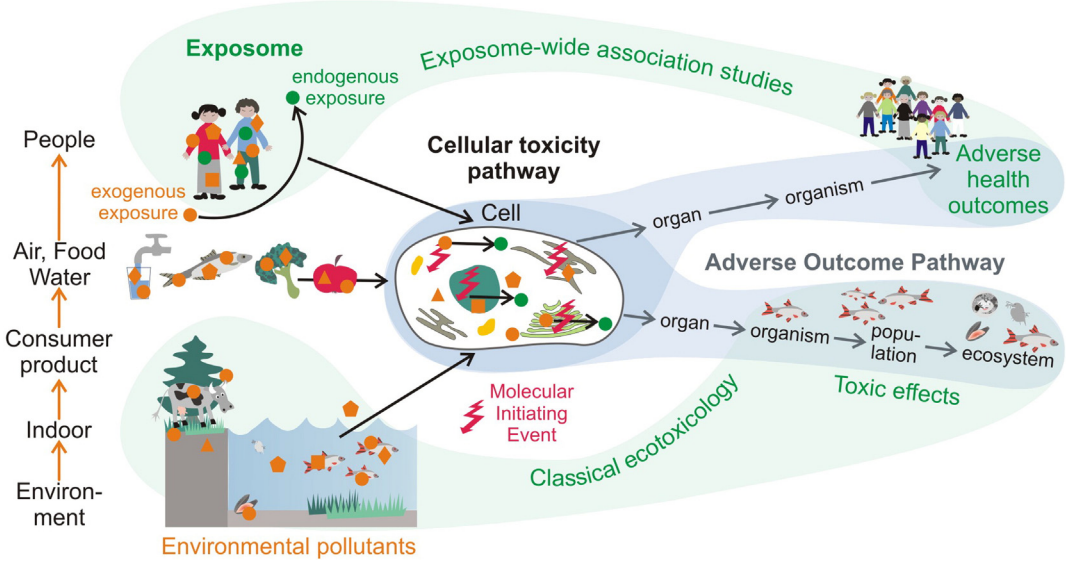

Fig. 1. Multiple chemical exposures of the environment and their link via environmental media and the food chain to human exposure. Any type of exogenous chemical exposure will change the endogenous exposure, both of which will elicit effects on cellular toxicity pathways. The cellular level might serve as integrator to understand both, the pathways to adverse health outcomes as well as to ecosystem-level effects.

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