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Symbiotoxicity: the ability of environmental stressors to damage healthy microbiome structure and interactions with the host.

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Abstract :

Symbiotoxicity intends to study the impacts of environmental stressors such as pollutants on an overlooked component of organisms' physiology: their microbiome.

Keywords : microbial toxicology, ecotoxicology, emerging pollutants, metal toxicity, mode of action

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It is now accepted that all eukaryotes must be considered as metaorganisms, *i.e.* the close and interdependent association between a host and a collection of symbiotic microorganisms (microbiota) such as bacteria, archaea, small eukaryotes and viruses forming an inseparable functional unit within which pathogenicity is far from being the norm. Symbiosis refers to the close and long-term association and biological interactions between two species. This association can be mutualistic, commensal or parasitic depending on the evolutive outcome for each partner. Functional interactions in metaorganisms contribute to many aspects of host physiology like development, morphogenesis, metabolism, aging, behaviour, pathogen protection and resistance, and maturation of immunity (Esser et al. 2019). Thus, interest for microbiomes has tremendously increased over the past two decades. The microbiome can be considered as a proper organ containing at least the same number of bacterial cells as host cells, and possessing its own genome with millions of unique genes. Research on eukaryotes' microbiome originally derived from environmental microbiome research, *i.e.* microbial ecology. In this field, microbial ecotoxicology recently emerged (Pesce et al. 2020). Indeed, like any other living organism, microorganisms are affected by environmental stressors. Microbial ecotoxicology studies how pollutants alter microbial activities including inhibition and development of adaptive resistance responses; and eventually the consequences up to the community level and the resulting effects on ecosystem health. It is thus legitimate to wonder what consequences an imbalance in the structure or the function of the microbiome, referred

to as dysbiosis, would have on fitness, susceptibility to contaminants, metabolic disorders such as inflammatory responses, and aetiology of diseases in the host. However, this component of the physiology of the organisms remains largely neglected by ecotoxicologists.

Ecotoxicology appeared in the early 1970s. It is defined as the study of the effects of chemical, biological and physical agents on organisms, populations, communities and ecosystems. Since then, ecotoxicology has considerably evolved following the development of new concepts and technologies. Amongst these concepts, the most recent is the exposome concept (Wild 2005) that strives for the consideration and comprehensive characterization of all exposures (chemical, physical, biological, psychological, social and behavioural) leading to stress during the entire life course, through targeted and untargeted approaches. Depending on the targeted cellular structure, cell type or tissue, and the biological processes that are affected, the mode of action and effects of xenobiotics can be described by various disciplines such as genotoxicity, cytotoxicity, neurotoxicity, hepatotoxicity, immunotoxicity or reprotoxicity, for instance. In the same way, "symbiotoxicity" could be used to describe the indirect toxicity to an organism through the disturbance of its microbiome (Figure 1), in terms of healthy composition and/or function of the microbiome, as well as the metabolic interactions between symbiotic partners. This term should not be confused with "toxicomicrobiomics" that describes the effect of microbiome variations on xenobiotics, poisons, and drugs adverse effects.

Historically, gastrointestinal tract was considered as the major microbial niche in eukaryotes and an important route of entry for xenobiotics. Thus, the current literature dealing with symbiotoxicity mostly studies human physiology with a special focus on gut microbiome (Claus et al. 2016). A similar trend is observed in non-model organisms (Duperron et al. 2020), but a larger focus on microbiota associated with other tissues at the interface between the organisms and their environment, such as gills and skin mucus, is needed. A broad variety of pollutants can affect the microbiota and induce dysbiosis, such as PAHs, pesticides, PCBs, metals, persistent organic compounds, and more recently nanoparticles, cyanobacterial toxins and microplastics; encouraging the use of microbiota related endpoints for a better environmental risk assessment. The increasing quantities of antibiotics in the environment due to human medicine and economic activities, and the potential disruption of the microbial populations associated with animal hosts, provides a telling example (Kraemer et al. 2019). One could then wonder how to determine and quantify symbiotoxicity? In the literature, dysbiosis is mostly described by compositional profiling, *i.e.* changes in the abundance of beneficial and/or pathogenic bacterial taxa. Other methods use few targeted taxa. In this case, the development of a dysbiosis index that assigns a symbiotic score to biological samples should be encouraged to study dysbiosis in non-model species. Changes in microbiome

taxonomic composition are commonly described by changes in alpha diversity indices that measure the overall community heterogeneity or beta diversity that quantifies dissimilarity between communities. In humans, low alpha diversity is known to be associated with unhealthy phenotypes (Wei et al. 2021). However, even though it gives a hint on the occurrence of a symbiotoxic stress, this approach hardly allows the identification of conserved responses amongst hosts species exposed to different stressors and hence, fails to establish clear physiological consequences of dysbiosis in response to xenobiotic exposure. Moreover, due to functional redundancy, as well as significant interindividual variation, it seems counterintuitive to define a healthy microbiome solely by its composition because changes may not be associated with differences in functional processes. Another caveat is that other members of microbiomes like fungi, small eukaryotes and viruses remain overlooked. The ability of the microbiome to perform a set of metabolic functions and to interact with the host sounds more appropriate for the study of symbiotoxicity. To go functional, taxonomic changes must be completed with genes expression, proteins translation and metabolites production in response to xenobiotic exposure. Therefore, symbiotoxicity will surely benefit from the development and increasing accessibility to omics analyses that allow the description of a wide range of effects and mechanisms, at different biological scales, in response to multiple stressors (Duperron et al. 2020; Ebner 2021). This challenging approach that aims at fully integrating microbiome into system biology is being developed in Human health. It certainly constitutes a path to follow in environmental toxicology to provide a holistic picture, and a definition for symbiotoxicity in non-model species too.

In conclusion, with the developing interest in microbiome study, including in ecotoxicology, "symbiotoxicity" already exists effectively. But very little is still known about the symbiotoxic potential of many chemicals. As such, more research is needed to study a neglected link between toxicology and ecosystems health.

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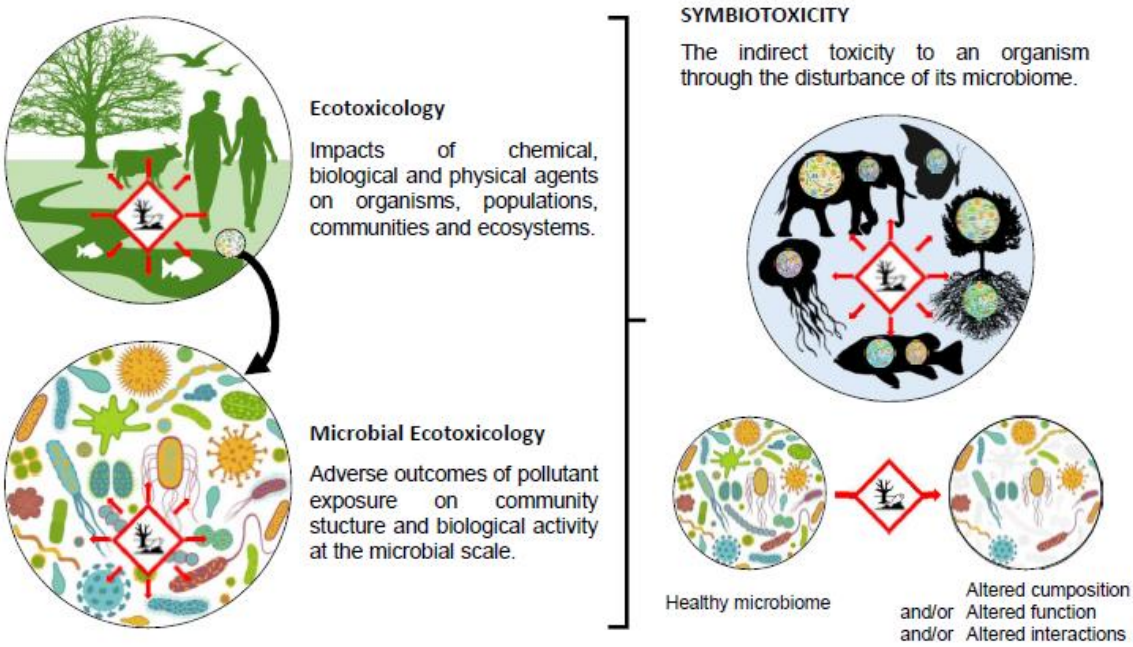

Figure 1 Symbiotoxicity intends to study the impacts of environmental stressors such as pollutants on an overlooked component of organisms' physiology: their microbiome.