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# Environmental risk assessment of combined effects in aquatic ecotoxicology: A discussion paper

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ABSTRACT

Environmental regulatory edicts within the EU, such as the regulatory framework for chemicals REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), the Water Framework Directive (WFD), and the Marine Strategy Framework Directive (MSFD) focus mainly on toxicity assessment of individual chemicals although the effect of contaminant mixtures is a matter of increasing concern. This discussion paper provides an overview of the field of combined effects in aquatic ecotoxicology and addresses some of the major challenges related to assessment of combined effects in connection with environmental risk assessment (ERA) and regulation. Potentials and obstacles related to different experimental, modelling and predictive ERA approaches are described. On-going ERA guideline and manual developments in Europe aiming to incorporate combined effects of contaminants, the use of different experimental approaches for providing combined effect data, the involvement of biomarkers to characterize Mode of Action and toxicity pathways and efforts to identify relevant risk scenarios related to combined effects are discussed.



## 1. Introduction

Organisms in polluted environments are typically exposed to a complex mixture of chemical contaminants and the exposure may sometimes cause toxic effects even though the individual stressors are present at concentrations lower than the No Observable Effect Concentration (NOEC) (Brian et al., 2007; Kortenkamp, 2008; Silva et al., 2002). This phenomenon is known as combined effects, mixture toxicity, joint toxicity or cocktail effects. Because the assessment of chemical toxicity normally is done substance by substance, neglecting potential mixture effects, it is possible that adverse effects of environmental pollutant mixtures are underestimated. Contaminants with similar or different Mode of Action (MoA) can influence each other's toxicity; resulting in an almost unlimited number of possible additive, synergistic or antagonistic combinations. The term MoA can be defined as the series of key processes that begins with the interaction of a chemical contaminant with a target (e.g. receptor) site and proceeds through operational and anatomical changes in an organism that result in sublethal or lethal effects (USEPA, 2000). Due to the large number of potential chemical contaminants and the great complexity of natural systems it is not feasible to perform (eco)toxicity tests for each potential mixture. In addition, non-chemical factors may also act as stressors and add to the complexity of multiple stressor situations (Fig. 1). Therefore, a simplified and robust approach to assess the ecotoxicity of chemical mixtures is needed for use in environmental risk assessment (ERA) and in regulatory toxicology. ERA is defined as procedures by which the likely or actual adverse effects of pollutants and other anthropogenic activities on ecosystems and their components are estimated with a known degree of certainty using scientific methodologies (Depledge and Fossi, 1994). An ERA framework normally includes a certain set of tiered modules as shown below (Fig. 2) and provides a tool for evaluation and management of environmental pollution. The aspects of combined effects have not yet been implemented in ERA in a standardised manner, nor has the combined effect issue become an integrated part of chemical regulation edicts (Kortenkamp et al., 2009). However, an active process aimed for meeting these limitations has been going on for some time.

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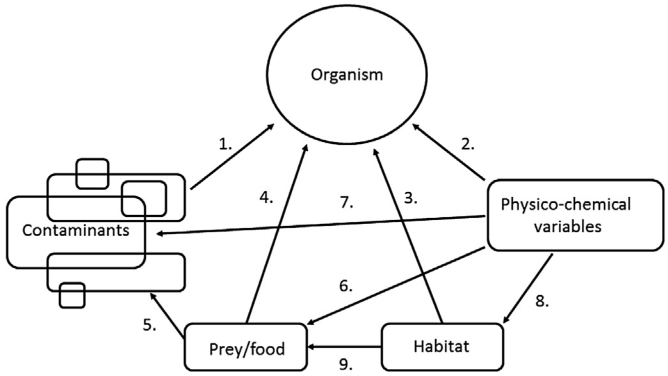


**Fig. 1.** Multiple factors which may affect the organism as stressors. 1: Exposure and effect of contaminants (possible outcomes being additivity/synergism/antagonism). 2: Physicochemical variables (e.g. climatic conditions). 3: Habitat changes. 4: Availability, type and nutritional value of food. 5: The type of food influence type and magnitude of contaminant exposure. 6: Physical variables influence availability of food (e.g. abundance of prey species). 7: Changes in environmental variables influence contaminant bioavailability (e.g. by transport/advection, diffusion, adsorption etc.). 8: Physico-chemical variables also affect the habitat of the organism. 9: The habitat of the organism is also the habitat of its prey organism, thus influencing on type and availability of food.

In this paper, the status in the field of combined effects is discussed, with emphasis on issues related to aquatic environments. Although research on combined effects has gained impetus recently many major gaps of knowledge remain; such as: which environmental pollutants (classes and specific structures) are likely to contribute most significantly to combined effects? What are the predominant cause–effect relationships and MoAs involved? Which non-chemical factors are relevant? In which phyla does combined effects occur at environmentally realistic conditions and how pronounced are species-differences in susceptibility? And how can issues of combined effects become implemented in ERA and environmental regulation? The discussion will be oriented around the following set of ecotoxicological problem formulations:

1) Which biological species/organization level do we aim to protect (individual, population community, ecosystem keystone species)?
2) Which endpoints/effects do we consider being relevant (e.g. the regulatory endpoints)?
3) Which compounds do we expect to encounter (from monitoring data)?
4) Which compounds are likely to cause effects (based on persistence, bioaccumulation/biomagnification, and toxicity (PBT) criteria)?
5) Which assemblies of compounds are likely to cause combined effects (given possibly relevant MoA and effect endpoints)?

## 2. Anthropogenic contaminant stresses relevant to combined effects

Pesticides have received much attention as possible combined toxicity stressors in different aquatic environments (Relyea, 2009; Rodney et al., 2013; Verbruggen and Van den Brink, 2010). The term *pesticide* refers to any (toxic) substance used for the purpose of combating a pest organism. Some pesticides (in particular the organohalogens) are highly persistent in the environment and according to the Stockholm convention on POPs are as many as 9 of the 12 most environmentally hazardous organic chemicals pesticides. Certain animal classes, such as the amphibians, are thought to be particularly sensitive to the combined toxicity of pesticide mixtures, e.g. Hayes et al. (2006). It is a concern that the significant decline recorded in amphibian populations in many agriculturally dominated regions around the world is, at least partly, caused by the adverse effect of pesticide mixtures.

The so-called persistent organic pollutants (POPs) including polychlorinated biphenyls (PCBs) and polybrominated flame retardants and many other substance classes, constitute a diverse class that is considered as relevant in connection with mixture toxicity phenomena, especially in ecological top-predators such as seals, cetaceans, otters and birds of prey, as well as in humans. In some populations of top-predatory animals, significant reductions

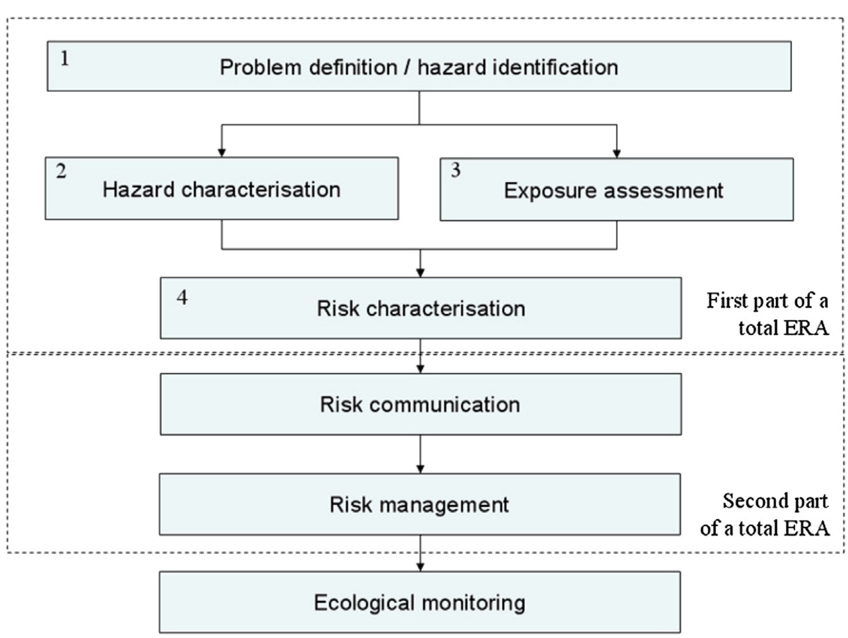


**Fig. 2.** Conceptual overview of the main components of an Environmental Risk Assessment (ERA) framework. Such frameworks are widely used to organize the processes of assessment and management of chemical pollution.