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Invited article

# Significance of adverse outcome pathways in biomarker-based environmental risk assessment in aquatic organisms

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ABSTRACT

In environmental risk assessments (ERA), biomarkers have been widely used as an early warning signal of environmental contamination. However, biomarker responses have limitation due to its low relevance to adverse outcomes (*e.g.*, fluctuations in community structure, decreases in population size, and other similar ecobiologically relevant indicators of community structure and function). To mitigate these limitations, the concept of adverse outcome pathways (AOPs) was developed. An AOP is an analytical, sequentially progressive pathway that links a molecular initiating event (MIE) to an adverse outcome. Recently, AOPs have been recognized as a potential informational tool by which the implications of molecular biomarkers in ERA can be better understood. To demonstrate the utility of AOPs in biomarker-based ERA, here we discuss a series of three different biological repercussions caused by exposure to benzo(*a*)pyrene (B*a*P), silver nanoparticles (AgNPs), and selenium (Se). Using mainly aquatic invertebrates and selected vertebrates as model species, we focus on the development of the AOP concept. Aquatic organisms are suitable bioindicator species whose entire lifespans can be observed over a short period; moreover, these species can be studied on the molecular and population levels. Also, interspecific differences between aquatic organisms are important to consider in an AOP framework, since these differences are an integral part of the natural environment. The development of an environmental pollutant-mediated AOP may enable a better understanding of the effects of environmental pollutants in different scenarios in the diverse community of an ecosystem.



## Introduction

The aquatic environment is continuously loaded with diverse xenobiotics such as organic compounds, heavy metals, nanoparticles, and a host of other organic and inorganic chemical pollutants. Aquatic organisms are increasingly being exposed to chemicals released from a wide spectrum of sources during all stages of their life cycles. Moreover, multi-generational effects of chemicals have even been observed (Van der Oost et al., 2003; Ankley et al., 2010; Hutchinson et al., 2013) (Fig. 1). A variety of toxic effect endpoints such as immunotoxicity, neurotoxicity,

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reproductive toxicity, cancer, and death of aquatic wildlife are closely linked with the significant adverse impact of chemicals on the aquatic ecosystem (Adams, 2002). To protect aquatic environmental health and integrity, several countries have enforced specific regulations in the last two decades that restrict the loading of chemicals into the aquatic environment. These regulations have had a significantly positive effect on the level of environmental pollution, especially for aquatic pollutants such as nonylphenol, tributyltin (TBT), and terbutryn (Díez et al., 2002; Quednow and Püttmann, 2009). Pieces of legislation such as the Food Quality Protection Act (FQPA) and the Registration, Evaluation and Authorization of Chemicals (REACH) regulations are also impactful in that they increase awareness of the potential risk of the growing number of chemicals and the need to minimize or control this risk (Ankley et al., 2010; Caldwell et al., 2014).

Environmental risk assessment (ERA) is an important tool for examining the adverse effects of chemicals on various biological responses in target and nontarget species (Van der Oost et al., 2003). In the 20th century, ecological risk assessors have studied the effects of environmental pollutants on the individual, population, community, and ecosystem levels (Choi, 2005; Villeneuve and Garcia-Reyero, 2011; OECD, 2012). For example, the sediment quality assessment triad was conceived as an effect-based approach for ecological/environmental risk assessment. This triad covers sediment chemistry, *in situ* studies (*e.g.*, research on the benthic organism community), and bioassays (toxicity tests) (Chapman, 1986; Chapman, 1996; Chapman and McDonald, 2005). In general, bioassays include direct measurements of adverse outcomes *in vivo* (*e.g.*, mortality and failure to grow or reproduce). However, these kinds of approaches are costly, time-consuming, and unfocused. Moreover, conclusions are often derived from many assumptions and several arbitrary uncertainty factors have been found to influence the outcomes. Additionally, extrapolation from these data is not sufficient to determine interspecific differences or to discriminate controlled tests from uncontrolled real environmental situations (Villeneuve and Garcia-Reyero, 2011). In conventional ERA, it is often insufficient to assess non-lethal effects of low concentrations of pollutants and to detect early biological responses (Van der Oost et al., 2003; Maier et al., 2004; Choi, 2005).

The effects of toxicants begin at the molecular level and then progress to the biochemical, subcellular, cellular, tissue, organ, individual, and population levels (Van der Oost et al., 2003). Thus, a precise understanding of the effects of toxicants on the molecular or biochemical level can provide valuable early warning signals, as opposed to higher level adverse effects that occur later in this chain of progression. Early detection of sublethal effects would be useful to highlight pollution in need of remediation before catastrophic effects occur. Detection of these sublethal events is also useful for monitoring the recovery site after management has been implemented (Van der Oost et al., 2003; Berninger et al., 2014). High-throughput technologies such as transcriptomics, proteomics, and metabolomics have helped us understand the modes of action of many toxins on the individual level (Hook, 2010). However, the biological response observed on the suborganism level does not provide reliable results in the context of environmental risk assessment, since the response on the suborganism level is based on an extensive volume of biological information controlled by physiological compensatory responses and repair pathways (De Kruijf, 1991; Choi, 2005). Thus, these studies have been received with some skepticism, since they do not take the environment into account. Moreover, exposed organisms potentially interact within their own population and with other populations, such as competitors, predators, and prey. Exposed organisms also interact with biotic and abiotic factors of their environment (Kramer et al., 2011). Therefore, it is important to have a linkage framework on the subindividual level by which the response can be connected to potential adverse outcomes (*e.g.*, population, ecological levels). Such a framework highlights the usefulness of biomarkers in mapping the risk of chemical exposure on all the biological levels at which a chemical is likely to act.

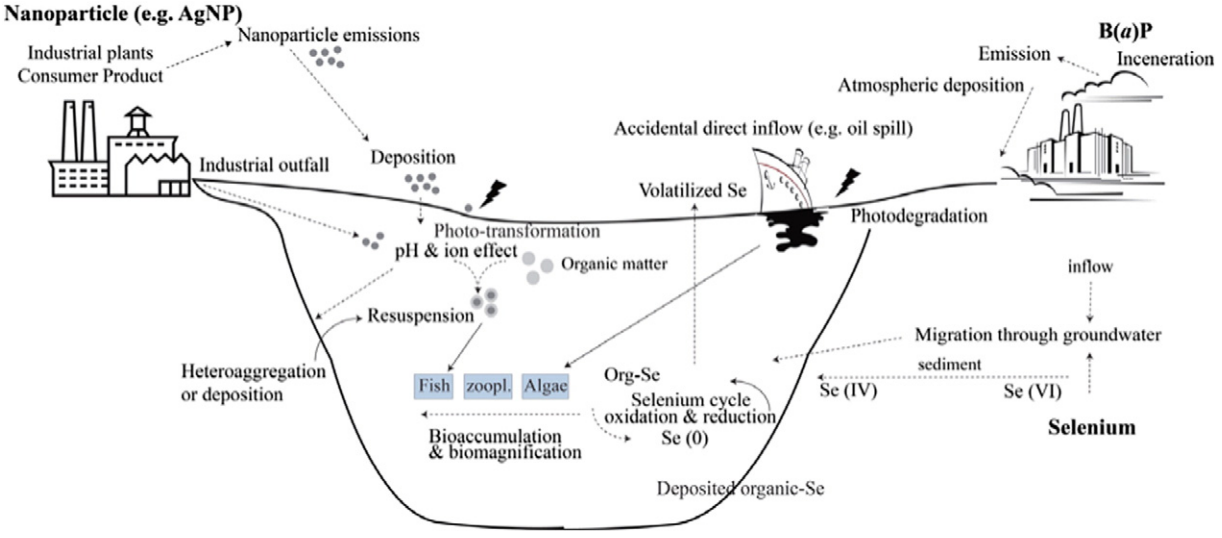


**Fig. 1 – Fates of nanoparticles, B[*a*]P, and Se in the aquatic environment.**