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Review article

Zooplankton-based adverse outcome pathways: A tool for assessing endocrine disrupting compounds in aquatic environments

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ABSTRACT

Endocrine disrupting compounds (EDCs) pose a significant ecological risk, particularly in aquatic ecosystems. EDCs have become a focal point in ecotoxicology, and their identification and regulation have become a priority. Zooplankton have gained global recognition as bioindicators, benefiting from rigorous standardization and regulatory validation processes. This review aims to provide a comprehensive summary of zooplankton-based adverse outcome pathways (AOPs) with a focus on EDCs as toxicants and the utilisation of freshwater zooplankton as bioindicators in ecotoxicological assessments. This review presents case studies in which zooplankton have been used in the development of AOPs, emphasizing the identification of molecular initiating events (MIEs) and key events (KEs) specific to zooplankton exposed to EDCs. Zooplankton-based AOPs may become an important resource for understanding the intricate processes by which EDCs impair the endocrine system. Furthermore, the data sources, experimental approaches, advantages, and challenges associated with zooplankton-based AOPs are discussed. Zooplankton-based AOPs framework can provide vital tools for consolidating toxicological knowledge into a structured toxicity pathway of EDCs, offering a transformative platform for facilitating enhanced risk assessment and chemical regulation.

1. Introduction

The European Regulation for Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH), which is European Union (EU) legislation applied to chemical substances, has classified endocrine disrupting compounds (EDCs) as substances of very high concern (SVHC). As a result, EDCs have become a focal point in ecotoxicology and their identification and regulation have become a priority. The International Programme on Chemical Safety of the World Health Organisation (WHO-ICPS) has defined EDCs as exogenous substances or mixtures that alter the function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)populations (World Health Organization, 2013). They are various types of chemicals that possess endocrine disrupting properties, including polycyclic aromatic chemicals (e.g. pyrene, anthracene), metals, organometallic chemicals (e.g. cobalt and cadmium), non-halogenated phenolic chemicals (e.g. bisphenol A and nonylphenol), personal care products (e.g. 3-benzylidene camphor), and plasticisers (e.g. bis(2-ethylhexyl)phthalate, dibutyl phthalate) (Fig. S1). The pathways through which EDCs enter the environment primarily involve agricultural activities, residential waste, effluents from sewage treatment plants (STPs), and wastewater treatment plants (WWTPs) (Aris et al., 2020). The most commonly found endocrine-disrupting compounds (EDCs) in wastewater effluents are synthetic oestrogen 17α-ethynylestradiol (EE2), natural hormone 17β-estradiol (E2), alkylphenols, alkylphenol ethoxylates, polybrominated diphenyl ethers, and Bisphenol A (BPA) (Plahuta et al., 2017). Unfortunately, owing to inadequate and inefficient water treatment facilities, EDCs are being released into the environment, inadvertently contaminating water supplies. EDCs have been consistently detected in aquatic ecosystems in various countries including the United States (Jones et al., 2020),

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Abbreviations

Abbreviations	Definition
20E	20-hydroxyecdysone
AOP-KB	AOP Knowledge Base
AOPs	Adverse outcome pathways
BPA	Bisphenol A
BPF	Bisphenol F
BPS	Bisphenol S
CCAP	Crustacean cardioactive peptide
DSX	Doublesex
EcR	Ecdysone receptor
EDCs	Endocrine disrupting compounds
EDSP	Endocrine Disruptor Screening Program
ERA	Environmental risk assessment
ETH	Ecdysis triggering hormone
Ftz-f1	Fushi tarazu factor-1
GST	Glutathione S-transferase
HBB	Haemoglobin
JHA	Juvenile hormone analogues
KEs	Key events
MIEs	Molecular initiating events
OECD	Organisation for Economic Co-operation and Development
PFOS	Perfluorooctane sulfonate
REACH	European Regulation for Registration, Evaluation, Authorisation, and Restriction of Chemicals
US EPA	United States Environmental Protection Agency

Canada (Atkinson et al., 2012), Spain (Gorga et al., 2015), England (Lusher et al., 2017), Italy (Pignotti and Dinelli, 2018), Brazil (Weber et al., 2017), Malaysia (Wee and Aris, 2017), China (Li et al., 2018a,b; Niu and Zhang, 2018), Japan (Yamazaki et al., 2015) and Singapore (You et al., 2015).

EDCs have various effects on aquatic organisms at different trophic levels, including algae (Czarny et al., 2019; Mao et al., 2017), phytoplankton (M'rabet et al., 2019), zooplankton (In et al., 2019; Shaw et al., 2008; Zhou et al., 2020) and fish (Rämö et al., 2018; Tinguely et al., 2021; Zhang et al., 2017). EDCs can disrupt normal functioning of the endocrine system in aquatic organisms, including hormone synthesis, secretion, transport, and receptor signalling, thereby causing endocrine-related disorders (Gore et al., 2015). Aquatic vertebrate endocrine systems (fish and amphibians) involve specific nuclear receptors located within the cell that directly influence gene expression (Baker and Lathe, 2018). Examples of vertebrate-specific nuclear receptors are the oestrogen, androgen, and thyroid hormone receptors. Similar to vertebrates, aquatic invertebrates (mollusks and zooplankton) possess steroid hormone receptors (Crane et al., 2022; Cuvillier-Hot and Lenoir, 2020). However, Invertebrates have diverse and often diffuse mechanisms for hormone reception. They may involve G-protein-coupled receptors and other receptor types located on the cell surface, influencing second messenger systems and cascades (Mojib and Kubanek, 2020). The involvement of various hormones and receptors in different taxonomic groups makes them either sensitive or vulnerable to distinct types of EDCs.

The effects of EDCs at the molecular level may be passed on to a higher organisational level. For example, EDCs can interfere with reproductive and developmental processes in aquatic organisms, leading to reduced fertility, altered sex ratios, impaired growth, and developmental abnormalities (Razak et al., 2023; Windsor et al., 2018). EDCs can disrupt the balance and function of aquatic food webs by affecting the reproductive success and survival of key species, leading to cascading effects at higher trophic levels (Hong et al., 2020; Ismail et al., 2020; Radwan et al., 2020; Razak et al., 2022a). Consequently, the impact of EDCs can extend beyond individual organisms to affect the entire aquatic ecosystem. EDC-induced disruptions in population dynamics, community structure, and ecosystem processes can have long-term consequences for ecosystem health and resilience (Hawkins et al., 1993).

In 2012, the Organisation for Economic Co-operation and Development (OECD) initiated a new program focused on the development of Adverse Outcome Pathways (AOP). The purpose of AOP is to gather, incorporate, and integrate ecotoxicological data through pathway assessment to elucidate adverse outcomes (Adeleye et al., 2015; Ankley et al., 2010; Burden et al., 2015). The intention was to capture scientific knowledge and evidence supporting a causal relationship between the perturbation of a biological pathway or system and the occurrence of adverse effects. The primary goal was to promote the increased utilisation of mechanistics-based data in regulatory decision making (Coady et al., 2019). This involves assessing the relevance of changes observed at the molecular, cellular, and biochemical levels of an organisation when making decisions related to individual health and/or population effects (Villeneuve et al., 2014).

AOPs have been recognised as valuable tools in regulatory frameworks for assessing and managing risks associated with EDCs. For example, the European Chemicals Agency (ECHA) utilises AOPs to inform decision making under the REACH regulation (Escher et al., 2017). Thus, the AOP Knowledge Base (AOP-KB), which includes AOP-Wiki, Effectopedia, and AOP Xplorer, introduced in 2014 to serve as a centralised repository for collecting and organising mechanistic information (Carusi et al., 2018). The AOP-KB and AOP Forum (https://aopwiki.org/forums/index.php) also offer excellent platforms for discussing OECD guidance on the development and utilisation of AOPs (Pollesch et al., 2019).

In recent years, significant efforts have been made to integrate the AOP framework into risk assessment and ecotoxicology (Fig. S2). There has been a noticeable increase in research focus and the number of publications combining AOP and risk assessment, with toxicology being the primary subject area, followed by environmental sciences and biochemistry. Moreover, the increase in AOP-Wiki content reflects the increased emphasis on AOP development, which now comprises 916 biological events leading to adverse effects, making it a significant resource for risk assessment (Martens et al., 2018). This review aims to provide a comprehensive summary of recent concepts and scientific advancements for risk assessors and toxicologists seeking to integrate AOP with current ecotoxicity and risk assessment practices. This review focuses on EDCs and the utilisation of freshwater zooplankton as bioindicators in ecotoxicological assessments.

2. Zooplankton as aquatic organism model species

Presently, zooplankton have emerged as the most suitable and informative aquatic biological markers because of their ecological significance, accessibility, and well-defined test protocols that encompass comprehensive information on hormonal systems (Silva-Briano, 2015; Wagner et al., 2017). The utilisation of zooplankton is essential because of their position in the middle of the food web, serving as a warning system for perturbations in aquatic ecosystems (Niedrist and Füreder, 2017). Moreover, zooplankton play a vital role in providing ecosystem services such as nutrient cycling, carbon sequestration, and water purification (López-Valcárcel et al., 2021). Disruptions caused by EDCs in zooplankton populations and their functional traits can have far-reaching effects on ecosystem services. In the aquatic food chain, zooplankton serves as a medium for energy transfer and the transport of organic matter from primary producers (algae and phytoplankton) to