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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 higher trophic levels (fish). Owing to bioaccumulation and biomagnification, zooplankton can become a source of contaminant exposure. The presence of EDCs in aquatic ecosystems leads to adsorption of these chemicals into zooplankton via dietary exposure and absorption across cellular membranes (Chouvelon et al., 2019).

A wide range of concentrations of EDCs with an abundance of well-known EDCs, such as metals, as well as newly emerging EDCs, such as microplastics, have been detected in zooplankton across various regions (Fig. 1 and Table S1). Environmental microplastics have been observed to act as reservoirs for a diverse array of chemicals, including EDCs (Ullah et al., 2023). Upon ingestion by organisms, microplastics have the potential to facilitate the leaching of these chemicals into their systems, with possible indirect effects on their endocrine systems (Zaki and Aris, 2022). Building on this, a previous study by In et al. (2019) further underscored the significance of EDCs in aquatic environments. The findings indicated BPA, Bisphenol F (BPF), and Bisphenol S (BPS) triggered molting, developmental abnormalities, and adverse effects on fecundity in freshwater zooplankton (*Diaphanosoma celebensis*) at concentrations of 6.85 mg L^{-1}, 8.63 mg L^{-1}, and 28.67 mg L^{-1}, respectively. Similarly, Navis et al. (2018) investigated the effects of fenoxycarb on *D. magna* and observed an increase in resting eggs (ephippia) and sexual switching from females to males at an exposure concentration of 0.7 μg L^{-1}. Furthermore, significant effects ($p < 0.001$) on both reproductive and mortality parameters were observed in *Brachionus calyciflorus* and *Brachionus havanaensis* exposed to ibuprofen concentrations exceeding 12.5 mg L^{-1} (González-Pérez et al., 2016). Additionally, Perfluorooctane sulfonate (PFOS) causes several adverse effects in *D. magna*, including changes in heartbeat, reproductive performance, and biochemical function during chronic exposure to 8 mg L^{-1} (Xu et al., 2017).

The mechanisms and modes of action of EDCs primarily involve nuclear receptors (NRs) (Toporova and Balaguer, 2020). EDCs disrupt the endocrine system, particularly hormone signalling, by antagonising the modes of action and mechanisms of endogenous hormones (Rezg et al., 2022). Generally, EDCs exhibit two distinct modes of action when affecting zooplankton which are agonistic and antagonistic effects (Maqbool et al., 2016; Wee and Aris, 2017). Agonistic effects occur when EDCs imitate the actions of natural hormones such as oestrogens or androgens within the endocrine systems of zooplankton. This can trigger the activation of specific receptors, potentially eliciting responses parallel to those induced by natural hormones (Lambert et al., 2021). For instance, EDCs with oestrogenic properties may provoke feminisation of male zooplankton, resulting in alterations in their reproductive behaviour, physiology, and morphology (Cho et al., 2022). In contrast, the antagonistic effects of EDCs involve substances that obstruct or disrupt regular hormonal signalling pathways in zooplankton. These substances are often referred to as anti-oestrogens or anti-androgens. Antagonistic EDCs can competitively bind hormone receptors, thereby preventing the binding of natural hormones. This interference can lead to diminished or modified hormonal responses, potentially resulting in adverse effects on the reproductive and developmental processes of zooplankton (Guarnotta et al., 2022).

Exposure to EDCs can initiate a cascade of molecular events in zooplankton, ultimately leading to perturbations in their endocrine systems. EDCs, such as bisphenol analogues, have been found to increase the activity of antioxidant enzymes, including total antioxidant capacity, superoxide dismutase, glutathione peroxidase, peroxidase, and catalase (Ullah et al., 2017). This increase in antioxidant enzyme activity suggests that the antioxidant defences of zooplankton may become overwhelmed by excessive ROS levels, disrupting the balance of the antioxidant system within cells and leading to oxidative damage such as mitochondrial damage (Samanta et al., 2020).

Moreover, EDC exposure has been linked to disturbances at the organ organisation level, such as cardiac disorders, in cladoceran species. These effects can manifest through diverse mechanisms, including modifications of the transcriptome, protein expression, and DNA methylation (Qiu et al., 2019). A study conducted by Razak et al. (2022b) demonstrated that acute exposure to BPA at concentrations as low as 10 μg L^{-1} resulted in chronotropic impairment, as evidenced by changes in the expression of haemoglobin (HBB) and glutathione

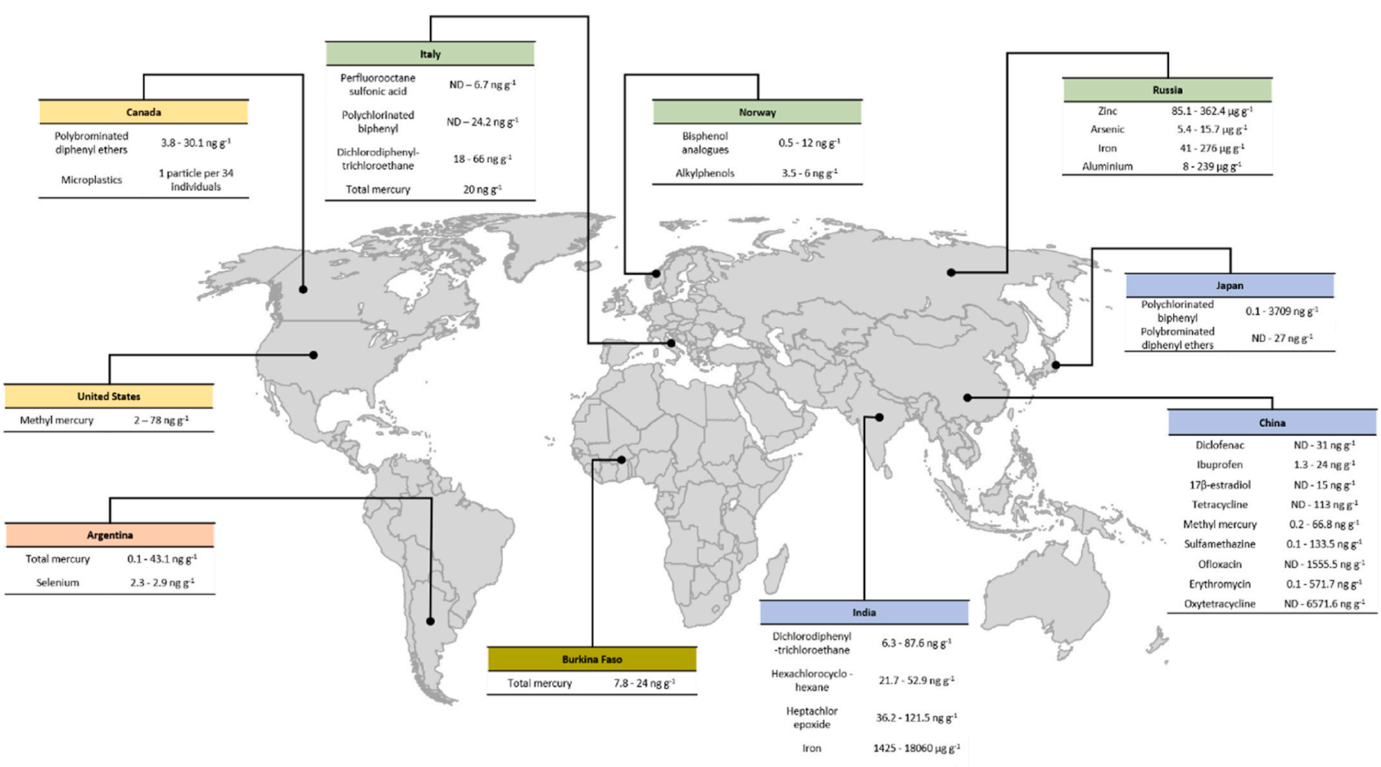

Fig. 1. Worldwide range of EDCs concentrations detected in zooplankton. ND; Non detected.

S-transferase (GST) genes in *Moina micrura*. Similarly, a prior investigation noted that exposure to EDCs resulted in the suppression of the heart rate and feeding activity in *D. magna*. (Fekete-Kertész et al., 2020).

A distinctive trait utilised in zooplankton as a bioindicator is its capability for moulting and sex switching, which makes it particularly sensitive to EDCs adverse effects at the individual organisational level. EDCs have the ability to function as anti-ecdysteroid compounds by binding to ecdysteroid receptors or synergising with endogenous juvenoid hormones, specifically methyl farnesoate, resulting in a delay in the moulting process (Li et al., 2018a,b). Consequently, disruption or delay in the normal moulting process may lead to reduced reproductive rates and smaller individual sizes in cladocerans exposed to EDCs. Most zooplankton species employ parthenogenesis as their primary reproductive strategy, allowing them to produce a large number of parthenogenetic offspring under favourable environmental conditions. However, in response to poor environmental conditions such as the presence of EDCs in water, zooplankton switch to sexual reproduction (Azuraidi et al., 2013). Parthenogenetic females transition to produce male offspring, which then mate with adult females during sexual reproduction (Mikulski and Grzesiuk, 2020; Zhang et al., 2016b). This adaptive response leads to the production of embryos encased in protective shells or gamogenetic resting eggs (ephippia), which enable survival under harsh environmental conditions (Holm et al., 2018). Several critical genes, including doublesex (DSX) and juvenile hormone analogues (JHA), have been identified as key regulators of reproductive switching across various zooplankton species, including *Ceriodaphnia*, *Moina, Bosmina*, and *Oxyurella* (Nong et al., 2017; Toyota et al., 2021; Wuerz et al., 2019).

Regulatory agencies acknowledge the significance of considering lower trophic organisms in risk assessments to ensure the comprehensive evaluation and protection of aquatic ecosystems (Cozigou et al., 2015; Doke and Dhawale, 2015). The European Union (EU) has established the Technical Guidance Document (TGD) to facilitate the assessment of hazards posed by chemical substances to human health and the environment (European Commission Joint Research Centre, 2003) (Fig. S3). This framework recommends the inclusion of three trophic levels, which is primary producers (algae, phytoplankton, seaweed), primary consumers (zooplankton, mollusks), and secondary consumers (fish), as biological markers to increase confidence in the chemical and risk assessment of regulatory decisions.

3. Adverse outcome pathway (AOP) framework

Contamination of freshwater with EDCs is expected to increase the risk of adverse effects on aquatic organisms. Consequently, monitoring the levels of EDC contaminants in freshwater bodies, including rivers, lakes, and water reservoirs, has become a common practice for conducting risk assessments (Čelić et al., 2020; He and Aga, 2019; Li et al., 2018a,b; Wee et al., 2020). However, monitoring approaches have been shown to be time-consuming for effective decision making in mitigating EDC contamination. Therefore, a preventive risk-based approach, known as environmental risk assessment (ERA), has been established to identify, analyse, and estimate the probability of potential consequences that may have negative effects on aquatic organisms, public health, and the environment (Agathokleous et al., 2019; Van den Berg et al., 2019).

Despite years of ecotoxicology research on EDCs, the available data remain insufficient to support the chemical and risk assessment processes. For instance, Rämö et al. (2018) encountered obstacles in their ecotoxicological risk study of 19 pesticide compounds because of the absence of toxicity data for seven pesticides in the literature and public databases. Similarly, a study by Razak et al. (2022b) revealed that the risk assessment for BPS could not be conducted compared to BPA and BPF owing to insufficient toxicity testing. Furthermore, a previous study by Zhang et al. (2017) highlighted the inadequate ecotoxicity data available for pharmaceutical compounds, such as metoprolol, atenolol, and carbamazepine, thereby hindering accurate risk assessments for algae, invertebrates, and fish. Comprehensive evaluation of risk assessment and its impacts on aquatic ecosystems and human well-being necessitates precise reports on exposure, dose-response relationships, and hazards associated with each specific chemical (Berggren et al., 2015).

Nevertheless, conventional risk assessments focus primarily on the adverse effect endpoints of EDCs without analysing the underlying mechanisms of toxicants (Futran Fuhrman et al., 2015). Additionally, conventional assessments fail to recognize the complexity of the specific mechanistic responses of organisms, including interactions between cells and tissues, tissues and organs, organs and individuals, and individuals and populations (Archer et al., 2017). Although the ERA offers valuable insights into adverse outcomes, it is often difficult to reproduce, interpret, and account for numerous sources of uncertainty (Razak et al., 2021; Skinner et al., 2016). Ecological risk assessors require rapid, precise, cost-effective, and animal-based approaches to evaluate a large number of EDCs within a limited timeframe. Furthermore, it is essential to establish effective and practical methods for translating mechanistic data into regulatory endpoints for ecological risk assessment, a task that cannot be accomplished using conventional risk assessment.

Thus, the AOP framework was established to integrate multidisciplinary approaches from the fields of toxicology, biology, and computer science while also incorporating extensive experimental data from multiple organisational levels (Triebskorn et al., 2015; Yozzo et al., 2013). As a result, AOPs offer distinct benefits in the utilisation of diverse data types, extending beyond the ultimate effect data obtained from animal toxicity studies to enhance the understanding of chemical hazards (Angrish et al., 2018). AOPs align with OECD guidelines, and the OECD takes further steps to elucidate the AOP framework, advocating the amalgamation of multiple methodologies for risk assessment and applications in ecotoxicology. (Brockmeier et al., 2017; Garcia-Reyero and Murphy, 2018; Groh et al., 2015a; Gutsell and Russell, 2013; Lee et al., 2015).

The AOP framework facilitates pathway development by extrapolating data from one model species by revising species-specific dose responses, such as binding affinity and activation of a receptor, while also addressing economic considerations by reducing costs, labour requirements, and time for ecotoxicity testing (Conolly et al., 2017; Perkins et al., 2019). Additionally, the AOP framework satisfies ethical concerns by replacing vertebrate animal testing with lower taxonomic organisms (Wieczerzak et al., 2016). The introduction of the AOP framework brought about significant novelty by incorporating a sequence of key events (KEs) within the biological systems. Furthermore, these KEs can be experimentally verified and interconnected through Key Event Relationships (KERs), which describe the causal connections between upstream and downstream events (Groh et al., 2015b; Villeneuve et al., 2014). The implementation of an AOP allows for a systematic progressive pathway that connects each specific KE to the eventual adverse outcomes (Tollefsen et al., 2014). In addition, molecular initiating events (MIE) have been identified as crucial interactions that trigger adverse outcomes in organisms. MIE plays an essential role in the development of AOPs as it represents the first KE, enabling the identification of mechanistic pathways within organisms.

Furthermore, an actual AOP was established in a mixed network based on convergent, divergent, and bow tie topologies, as multiple key events interact and influence each other (Fig. S4). (Knapen et al., 2018). Convergent topology focuses on several MIEs that may be linked to similar adverse effects, whereas divergent topologies emphasise specific MIEs that are linked to several adverse effects. The combination of convergent and divergent topologies creates a bowtie topology, signifying an integrative biological pathway for potential adverse outcomes (Blackburn et al., 2015; Docea et al., 2017; Institute of Environment and Health, 2012).

In the fields of toxicology and risk assessment, the development of AOPs has emerged as a powerful tool to elucidate the mechanisms by which chemicals induce adverse effects in living organisms. AOPs provide a structured framework to connect MIEs with ultimate adverse outcomes, facilitating the understanding of toxicity pathways. This understanding of toxicity pathways has been significantly enhanced through innovative tools such as sequence alignment to predict across-species susceptibility (SeqAPASS) (seqapass.epa.gov/seqapass/). SeqAPASS leverages protein sequence conservation to predict similar MIEs in nontarget species (LaLone et al., 2016). This approach has allowed for the identification of shared responses across diverse classes of species, including Malacostraca (crabs and prawns), arachnids (scorpions and spiders), Priapulida (marine worms), Chilopoda (centipedes), and Insecta (insects), when exposed to specific chemicals. The results obtained using SeqAPASS underscore the utility of AOPs for predicting toxic responses through interspecies extrapolation. This not only advances the understanding of chemical risks to various organisms but also enhances the accuracy and efficiency of regulatory assessments.

International test guidelines have increasingly incorporated the AOP framework as a valuable tool for systematic evaluation and organisation of chemical or drug toxicity data. Concurrently, there has been a noticeable shift in recent years towards the widespread adoption of New Approach Methodologies (NAMs). These approaches are designed to discern the mechanisms of toxicity while simultaneously reducing reliance on animal testing (O'Rourke et al., 2023). NAMs involve the utilisation of less complex organisms and integration of novel and holistic techniques. These techniques include the use of quantitative structure-activity relationship (QSAR) predictions, high-throughput screening (HTS) bioassays, omics applications, cell cultures, organoids, microphysiological systems (MPS), machine learning models, and artificial intelligence (AI) (Schmeisser et al., 2023). Organisations such as the United States Environmental Protection Agency (US EPA) and ECHA advocate the use of NAMs in identifying endocrine disruptors. (ECHA, 2016; US EPA, 2023). AOPs were initially conceived with the primary purpose of bolstering the implementation of NAMs in the evaluation of chemical safety and risk assessments.

Moreover, the National Institutes of Health (NIH) in the United States has recommended the construction of assessment methodologies for ecotoxicological testing using animal models based on the principles of Replacement, Reduction, and Refinement (Russell and Burch, 1959). In line with this replacement strategy, alternative computerised analysis programs have been established to regulate emerging chemicals instead of relying on animal models. This strategy promotes the utilisation of cells and tissues, emphasizing the substitution of higher-taxonomic-rank animals (such as mammals and primates) with lower-taxonomic-rank animals (such as invertebrates) (Hamm et al., 2017). The "Reduction" strategy aims to minimise the number of animals used per test by avoiding unnecessary replication in each assessment process. Furthermore, the implementation of efficient and precise experimental designs as part of the "Refinement" strategy helps reduce the suffering of test animals. The OECD has incorporated the principles of 3Rs (Replacement, Reduction, and Refinement) in the development of the AOP framework, resulting in a 53% reduction in animal use, equivalent to approximately 150,000 rats, in both regulatory and toxicity testing (Törnqvist et al., 2014).

US EPA, REACH, Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), and OECD are actively engaged in advancing the adoption of AOPs as a more effective and ethical approach for assessing the risks associated with EDCs (Andersen and Krewski, 2009; Barton-Maclaren et al., 2022; Farhat and Kennedy, 2019; Villeneuve et al., 2014). The US EPA created the Endocrine Disruptor Screening Program (EDSP) to develop ecotoxicological assessments specifically for EDCs using the AOP framework (Browne et al., 2017; Garcia-Reyero and Murphy, 2018; Manibusan and Touart, 2017; Matthiessen et al., 2018). The EDSP employs a two-tiered screening and testing strategy to evaluate thousands of EDCs for potential adverse effects on wildlife and humans (Collier et al., 2016). Consequently, numerous molecular and apical endpoints have been identified through EDSP, as well as the EPA's Toxcast program and Tox21 (US EPA, 2011).

3.1. Utilisation of zooplankton in AOP development

Current investigations of EDC in zooplankton-based AOP illuminate the complex interactions between pivotal events and their resulting adverse effects. Despite notable advancements, it is essential to recognize that there are still underlying mechanisms that require further exploration. Currently, there are only two (2) full description of AOP-Wiki deposited for EDC prototypical stressors in zooplankton, particularly Daphnia spp. One AOP delineating juvenile hormone receptor agonism resulted in the induction of male offspring and subsequent population decline in *D. magna* and *D. pulex* (https://aopwiki.org/aops/201). Another AOP centred on ecdysone receptor (EcR) agonism, leading to mortality associated with incomplete ecdysis in *D. magna* (https://aopwiki.org/aops/4). There are several potential studies of zooplankton-based AOPs towards EDCs utilizing freshwater zooplankton as a bioindicator that can be deposited in the AOP-wiki, as tabulated in Table 1.

The inclusion of zooplankton in various toxicity guidelines substantiates their suitability as representatives of the AOP framework, as several advantages have been identified in using zooplankton as a biological marker in AOP development (Garcia-Reyero and Murphy, 2018). First, zooplankton are highly sensitive to perturbations in aquatic ecosystems and exhibit rapid responses to environmental changes, including the presence of EDCs (Cajaraville et al., 2016). Secondly, toxicants can undergo biomagnification from lower to higher trophic levels within organisms, making zooplankton an important indicator because of their position in the middle of the food web (Yan Zhang et al., 2016a). Third, the short life cycle and large offspring production of zooplankton allows for multigenerational studies with minimal resources and shorter time frames (Dahms et al., 2016). Additionally, the use of zooplankton as a model organism can reduce the laboratory size and testing area by 50% compared to fish or other animal models. Fourth, the transparent carapace of zooplankton enables the analysis of internal organs such as the heart, gut, and eggs in the brood chamber (Razak et al., 2022b). Fifth, omics analyses of zooplankton provide valuable information for establishing mechanistic pathways, elucidating the molecular processes involved, and extending our understanding from the molecular level to the individual level. (Ravindran et al., 2019). Sixth, only a small amount of RNA derived from zooplankton is required to analyse differential gene expression (DEG). For instance, the whole body of three (3) *Daphnia magna* specimens was sufficient for RNA extraction prior to omics analysis (Houde et al., 2015). Finally, zooplankton exhibit a significant number of overlapping genes with humans, surpassing other consecutive invertebrates (Colbourne et al., 2012). The freshwater cladoceran Daphnia magna, which shares 56% similarity in gene sequences with humans, plays a crucial role in the establishment of regulatory standards by various government authorities, including the OECD, US EPA, and Environment Agency of Japan (Shaw et al., 2008).

Consequently, numerous test guidelines have been established for zooplankton, including acute (24 or 48 h) and chronic toxicity tests in both water samples and sediments (Organization for Economic Co-operation and Development, 2004; International Organisation for Standardisation, 2012; American Society for Testing and Materials, 2020). Subsequently, *D. magna* (a cladoceran), *Tigriopus japonicus* (a copepod), *Brachionus koreanus* (a rotifer), and Paracyclopina nana (a copepod) have achieved global recognition as bioindicators for risk assessment because of their intensive standardisation and regulatory validation (Hwang et al., 2010; Kim et al., 2013; Rhee et al., 2013).

Moreover, the advent of AOP has brought about fast, cost-effective, and robust tools that allow for the correlation of molecular profiles with conventional endpoints (mortality, reproduction, and growth) in ecotoxicity and chemical risk assessment (Ellis-Hutchings et al., 2018). This new era of scientific discovery has opened up possibilities for mapping biological pathways. AOPs provide a means of understanding the interconnectedness of these pathways, unravelling a vast network

Table 1
The potential study of zooplankton-based AOP towards EDCs using freshwater zooplankton as a bioindicator.

Species	Prototypical Stressor	Molecular Endpoints (MIE/KEs)	Apical Endpoints (Adverse Outcome)	References
Rotifers				
Brachionus koreanus	Benzo(a)pyrene	Glutathione S-transferase (GST), glutathione reductase (GR), sulfotransferase (SULT), glutathione (GSH), glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), heat shock proteins (HSP), oxidative stress-related protein	Mortality, growth rate	Kim et al. (2013)
Brachionus koreanus	Acetaminophen, trimethoprim, carbamazepine, oxytetracycline, sulfamethoxazole, atenolol	Acetylcholinesterase (AchE)	NA	Rhee et al. (2013)
Brachionus koreanus	Triclosan and triclocarban	Detoxification proteins (e.g., CYPs), antioxidant proteins (e.g., GST-sigma, Cu/ZnSOD, CAT), heat shock proteins (HSPs)	Mortality, population growth, lifespan, fecundity	Han et al. (2016)
Brachionus koreanus	Methylmercury (MeHg)	Extracellular signal-regulated kinase (p-ERK), jun amino-terminal kinases (p-JNK), glutathione (GSH), glutathione S-transferase (GST), glutathione reductase (GR), glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT),	Growth retardation, fecundity, mortality	Lee et al. (2017)
Cladocerans				
Daphnia magna	Isoprenaline, propranolol	β-adrenergic receptor (β-AR), C-type lectins, carboxypeptidase B, chymotrypsin BI precursor, carboxylesterase, putative serine protease, trypsin serine protease, UDP-glucorosonyltransferase 2A1, Zinc carboxypeptidase	Heart rate, size, contraction capacity	Jeong et al. (2018a)
Daphnia magna	Bisphenol A (BPA), lignin-derived bisphenol	Superoxide dismutase (SOD), Acetylcholinesterase (AChE), α-glucosidase (α-Glu), catalase (CAT), glutathione s-transferase (GST)	Growth, molting, reproduction, dry weight,	Li et al. (2018a,b)
Daphnia magna	4-Chloroaniline, yohimbine, nadolol, cyproheptadine, propranolol	Metabolite profiling	Swimming behaviour, heart rate	Jeong et al. (2018b)
Daphnia magna	20-Hydroxyecdysone	Ecdysone receptor (EcR), nuclear receptor E75B (E75B) gene, Fushi tarazu factor-1 (Ftz-f1) gene, ecdysis triggering hormone, crustacean cardioactive peptide (CCAP), ecdysis motoneuron bursts, excitatory postsynaptic potential	Incomplete ecdysis, mortality	Song et al. (2017b)
Daphnia magna	Microplastics	Heat shock protein (HSP60, HSP70), glutathione-S-transferases (GST), sarco (endo)plasmic reticulum calcium ATPase (SERCA), actin (Act), alpha tubulin (aTub),	Mortality, reproduction, morphological (body length, width and tail spine length)	Imhof et al. (2017)
Daphnia magna	20-hydroxyecdysone	Ecdysone receptor (EcR), neverland (nvd) and shade (shd), Cytochrome (Cyp18a1), EcR recruits ultraspiracle (USP)	Molting, reproductive cycle	Sumiya et al. (2014)
Daphnia magna	Chlorpyrifos, malathion, carbofuran	Acetylcholinesterase (AChE), carboxylesterase (CbE)	Mortality	Russom et al. (2014)
Daphnia magna	Propranolol, diazepam, carbamazepine, fluoxetine	Serotonin receptors, dopamine receptors, epinephrine receptors, γ-aminobutyric acid (GABA) receptors	Locomotor activity	Simão et al. (2019)
Daphnia magna, Ceriodaphnia dubia	Benzalkonium chloride (BAC)	DNA damage	Reproduction	Lavorgna et al. (2016)
Daphnia pulex-pulicaria	Copper (Cu), nickel (Ni)	Metabolite profiling	Reproduction	Taylor et al. (2016)
Daphnia pulex	Nanoplastics	Rapamycin (mTOR), Forkhead box transcription factors (FOXO), Janus kinase (JAK)/signal transducer and activator of transcription (STAT) and proteomics analysis	Reproduction and growth	Liu et al. (2021)
Daphnia magna	Copper oxide (CuO), zinc oxide (ZnO)	Glutathione-S-transferase (GST), oxidized glutathione (GSSG), thiobarbituric acid reacting substances (TBARS), metal-lothionein (MT)	NA	Mwaanga et al. (2014)
Daphnia magna	Acetaminophen, chlorpromazine, diclofenac, propranolol	Cholinesterases (ChEs), catalase (CAT), glutathione-S-transferases (GSTs), glutathione-peroxidase (GPx)	NA	Oliveira et al. (2015)
Daphnia magna	Diclofenac	Ecdysone receptor (EcR), P-glycoprotein (P-gp), cytochrome (CYP360A8 and CYP314), glutathione s-transferase (GST), vitellogenin (VTG), hormone receptor (HR96)	Survival, growth rate, reproduction	Liu et al. (2017)
Daphnia magna	20-Hydroxyecdysone	Ecdysone receptor (EcR), chitobiase enzyme	Molting frequency, survival	Song et al. (2017a)
Copepods				
Paracyclopina nana	Arsenic (As), cadmium (Cd), copper (Cu)	Vitellogenin genes (Vg1 and Vg2)	NA	Hwang et al. (2010)
Paracyclopina nana	polystyrene microbeads	Mitogen-activated protein kinase (MAPK), nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)	Growth rate, fecundity	Jeong et al. (2017)
Paracyclopina nana	Methylmercury (MeHg)	Extracellular signal-regulated kinase (p-ERK), jun amino-terminal kinases (p-JNK), glutathione (GSH), glutathione S-transferase (GST), glutathione reductase (GR), and glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT),	Growth retardation, fecundity, mortality	Lee et al. (2017)
Tigriopus japonicus	Triclosan	Cytochrome (CYP3026A3 and CYP3037A1), glutathione s-transferase (GST-D, GST-O, GST-S), glutathione peroxidase, superoxide dismutase (SODs)	Fecundity	Park et al. (2017)

that defines the workings of biology. Diverse ranges of available endpoints across different organisations, which can be effectively employed by utilizing zooplankton in the development of AOP (Fig. S5) (Asselman et al., 2019, 2018; Chen et al., 2019, 2021; Han et al., 2017; Jensen et al., 2016; Jeong et al., 2017, 2018b; Karatzas et al., 2020; H. Y. Kim et al., 2017b; Lavorgna et al., 2016; Liu et al., 2021; Simão et al., 2019; Taylor et al., 2017, 2016). In a previous study, Song et al. (2017a,b) developed a comprehensive AOP for EcR agonism, with the MIE showing incomplete ecdysis, ultimately resulting in mortality (Song et al., 2017b) (Fig. 2). The complete development of AOP involved in chemico, in vitro, and in vivo analyses across different organisational levels of zooplankton (*D. magna*).

The principal and mechanistic information of AOPs can be obtained by leveraging fundamental biological knowledge of the MIE. For instance, the insecticide tebufenozide (TEB) is a potent nonsteroidal EcR agonist that plays a crucial role in regulating reproduction, development, and mortality. Exposure of crustaceans, such as *D. magna*, to this insecticide disrupts the moulting process, leading to the failure to shed old exoskeletons, thereby indicating the interaction with the EcR agonist as the relevant MIE (Sumiya et al., 2014). Thus, the development of the AOP framework begins with a comprehensive understanding of the role of EcR agonists in regulating the moulting process. The hormone, 20-hydroxyecdysone (20E), an ecdysteroid hormone, controls metamorphosis and moulting in zooplankton. During the intermolt stage, there was a significant increase in the concentration of this hormone, followed by a rapid decrease before the next moulting cycle, which was essential for successful moulting. Zooplankton exposed to toxicants experience incomplete ecdysis, as the old exoskeletons cannot be shed properly during the molting process. Consequently, adverse effects caused by moulting abnormalities disrupt the feeding rate of organisms, ultimately leading to an increased mortality rate.

The exponential increase in the production of newly synthesised EDCs poses a significant challenge for regulatory organisations conducting ecotoxicological and chemical assessments. The development of the AOP framework has successfully addressed the inclusion of emerging contaminants such as microplastics and nanoplastics (Jaikumar et al., 2019; Kim et al., 2017a,b; Liu et al., 2022; Razak et al., 2023). Microplastics and nanoplastics can absorb and serve as carriers of EDC substances, including bisphenols, phthalates, polybrominated diphenyl ethers, polychlorinated biphenyls, organotins, perfluorinated compounds, dioxins, polycyclic aromatic hydrocarbons, and heavy metals (Ullah et al., 2023). These compounds are frequently employed as additives in plastic manufacturing. For instance, a recent study employed the copepod *Paracyclopina nana* as a bioindicator to identify MIE triggered by microplastic-induced oxidative stress, specifically involving the extracellular signal-regulated kinase (ERK) and Jun N-terminal kinase (JNK) pathways (Jeong et al., 2017). In addition to molecular endpoints, standard apical endpoints such as growth rate and reproduction have been incorporated into the development of AOP networks. Jaikumar et al. (2019) revealed the mechanistic pathway through which microbeads induce oxidative stress, leading to cellular damage and a decrease in the growth rate and reproduction of organisms. Conversely, another study reported contrasting results regarding the effects of microplastic exposure on the cladoceran *D. magna* (Imhof et al., 2017). Imhof et al. (2017) concluded that microplastics had subtle and inconsistent effects on *D. magna* at both molecular and individual levels. However, the potential effects of microplastic toxicity on *D. magna* and other zooplankton cannot be ruled out, as they may vary depending on the shape, size, age, and type of microplastic.

4. Challenges and future directions

Several potential data and knowledge gaps exist in the field of zooplankton-based AOPs for EDCs. Zooplankton encompass a diverse array of species, and not all species may react to EDCs in a uniform manner. Consequently, it is imperative to understand the species-specific variability. Numerous investigations concerning zooplankton and EDCs have concentrated on short-term acute effects, leaving long-term and chronic effects that have not been sufficiently elucidated. Under real environmental conditions, zooplankton encounter myriad stressors, including temperature fluctuations, nutrient pollution, and a complex mixture of EDCs. Thus, further research is needed to unravel the interactions and synergistic effects of EDCs and other stressors. Moreover, it is of paramount importance to determine whether exposure to EDCs in one generation of zooplankton can engender transgenerational effects in the succeeding generations.

Moreover, It is of utmost importance to pinpoint precise areas where data gaps are evident in zooplankton-based AOPs for EDCs. These gaps

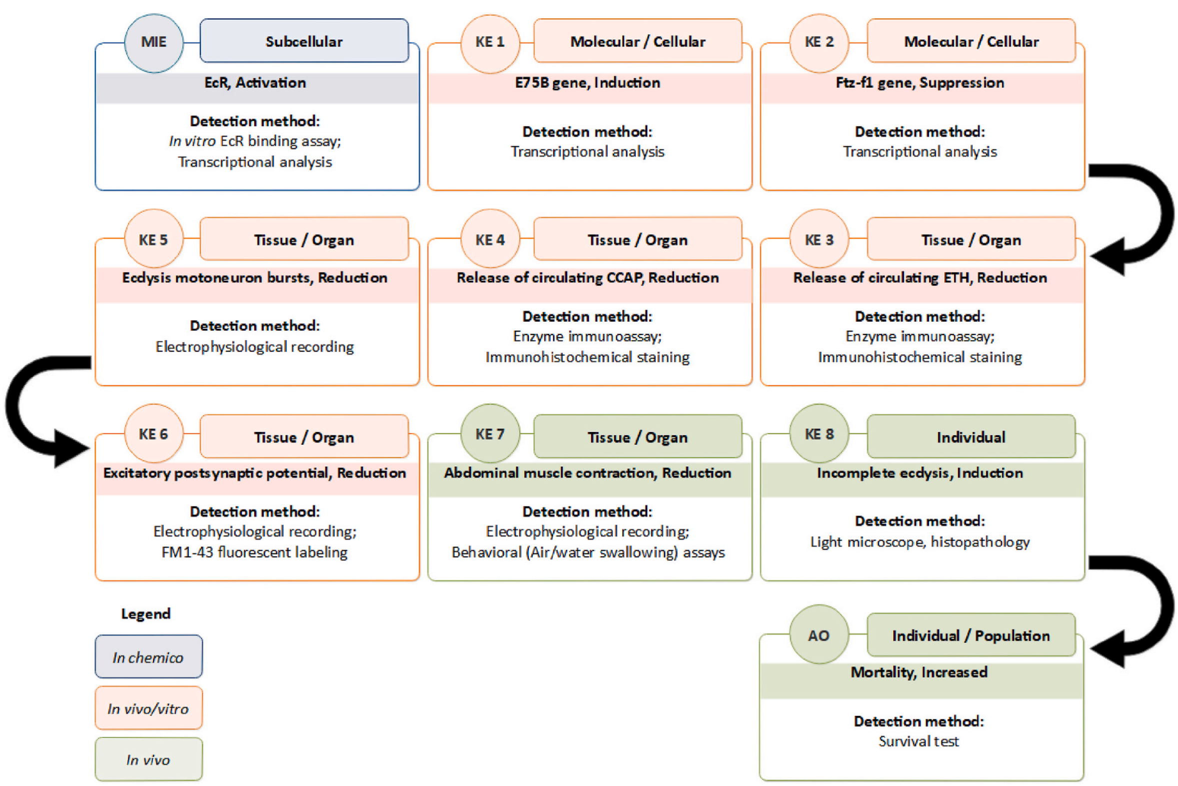

Fig. 2. Development of the complete AOP framework for EcR agonism as the MIE, resulting in incomplete ecdysis and mortality in *D. magna*.

may encompass the absence of toxicity data for specific EDCs, inadequacies in exposure information, and deficiencies in mechanistic understanding of how these compounds affect zooplankton. Once these data gaps are identified, it becomes imperative to prioritise research efforts aimed at filling them. Moreover, it is essential to fully utilise emerging research areas such as the integration of genomics, transcriptomics, and computational modelling. Integration of transcriptomic data with other omics data can facilitate the identification of key molecular events and establish linkages between molecular changes and adverse outcomes. Whole-genome sequencing can offer valuable insights into the genetic composition of zooplankton species and facilitate the identification of genes that play crucial roles in their responses to EDCs. Furthermore, transcriptomic approaches, such as RNA sequencing (RNA-seq), enable the comprehensive analysis of gene expression patterns in response to EDC exposure. By examining changes in gene expression profiles, researchers can identify specific pathways and biological processes affected by EDCs.

However, reliable and validated methods for zooplankton-based AOPs are scarce. Consequently, there is a pressing need to assess and enhance methodologies employed to bolster the robustness and credibility of zooplankton-based AOPs. This evaluation should encompass the optimisation of experimental designs, standardisation of protocols, and improvement of both the sensitivity and reliability of analytical techniques. By addressing these methodological concerns, researchers can markedly increase the precision and reproducibility of AOP studies.

Relevant international organisations should engage in discussions and establish arrangements to expedite the application of AOPs. This includes the dissemination of knowledge among scientists, risk assessors, regulators, governments, legislative bodies, and the private sector. As emphasised in the 2030 Agenda for Sustainable Development (SDG), commitment and collaboration between developed and developing countries are imperative. This partnership is crucial for advancing the transformation and enhancement of global endeavours to achieve sustainable production and consumption, including the responsible management of natural resources and urgent provision of safe access to clean drinking water to safeguard human health. Based on findings and discussions from previous literature, the Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis was conducted to identify gaps and conclude on the application of zooplankton-based AOPs, as depicted in Fig. 3.

5. Conclusion

In the domain of aquatic toxicology, the introduction of zooplankton-based AOPs represents a transformative approach for comprehensively assessing the impact of EDCs on aquatic ecosystems. This innovative tool seamlessly integrates causal events across various biological levels in zooplankton, enhancing the capacity to detect and evaluate EDC effects. A thorough analysis of both the advantages and limitations associated with the use of zooplankton-based AOPs to assess the impact of EDCs will provide valuable guidance to scientists, regulatory bodies, and authorities. This assessment is essential for shaping the fundamental principles and evidence-based frameworks within the fields of toxicology and risk assessment. This review has highlighted numerous studies that have employed zooplankton as a crucial biological marker for EDC exposure while implementing the AOP framework. Additionally, this review has highlighted collaborative efforts within several international guidelines advocating for the synergy of AOPs and zooplankton in the multifaceted landscape of EDC. The zooplankton-based AOPs framework can provide vital tools for consolidating

Fig. 3. SWOT analysis for the utilisation of zooplankton in the adverse outcome pathway.

toxicological knowledge into a structured toxicity pathway, offering a transformative platform for facilitating enhanced risk assessment and chemical regulation. to secure a more sustainable future for aquatic ecosystems.

CRediT authorship contribution statement

Muhammad Raznisyafiq Razak: Writing – original draft, Visualization. **Sze Yee Wee:** Writing – review & editing. **Fatimah Md Yusoff:** Writing – review & editing. **Zetty Norhana Balia Yusof:** Writing – review & editing. **Ahmad Zaharin Aris:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.119045.

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