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Prioritising research on endocrine disruption in the marine environment: a global perspective

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ABSTRACT

A healthy ocean is a crucial life support system that regulates the global climate, is a source of oxygen and supports major economic activities. A vast and understudied biodiversity from micro- to macro-organisms is integral to ocean health. However, the impact of pollutants that reach the ocean daily is understudied for marine taxa, which are also absent or poorly represented in regulatory test guidelines for chemical hazard assessment. Inspired by the United Nations Decade

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of Ocean Science, which aims to reverse the decline in ocean health, this communication calls for global coordination in building resources for studying the effects of marine pollution. The bibliographic analysis, a collective product of scientists from diverse backgrounds, focused on endocrine-disrupting chemicals (EDCs). In this review, we (*i*) critically analyse the literature on endocrine signalling pathways and high-level physiological impacts of EDCs across 20 representative marine taxa; (*ii*) identify knowledge and regulatory gaps; (*iii*) apply bioinformatics approaches to marine species genomic resources, with relevance for predictions of susceptibility; and (*iv*) provide recommendations of priority actions for different stakeholders. We reveal that the scientific literature on EDCs is biased towards terrestrial and/or freshwater organisms, is limited to a handful of animal taxa, and marine organisms are dramatically underrepresented. Our bibliographic analysis also confirmed that only a small number of (neuro) endocrine pathways are covered for all animals, whilst basic knowledge on endocrine systems/endocrine disruption for most marine invertebrate phyla is minimal. Despite significant gaps in genomic resources for marine animals, endocrine-related protein conservation was evident across more than 500 species from diverse marine taxa, highlighting that they are at risk from EDCs. Despite recent technological advances, translation of existing knowledge into international regulatory test guidelines for chemical hazard assessment and monitoring programs is limited. Furthermore, the current understanding is confounded in part by transposing vertebrate endocrinology onto non-vertebrate taxa. In this context, specific recommendations are provided for all stakeholders, including academia (e.g. to expand knowledge across metazoan taxa and endocrine targets and translate it to New Approach Methodologies and Adverse Outcome Pathways; to increase and improve tools for comparative species-sensitivity distributions and cross-species extrapolations), regulators (e.g. increase awareness of specific risks for the marine environment, prioritise international standardisation of testing methods for marine species and request evidence for absence of endocrine disruption in marine phyla), policy makers (e.g. implement sustained, long-term international marine monitoring programs and increase global co-operation) and the public or non-governmental organisations (e.g. foster public engagement and behaviours that prevent marine chemical pollution; promote citizen science activities; and drive political actions towards protective and restorative marine policies). We hope that this and past reviews can contribute towards meeting ambitious international plans for marine water quality assurance, mitigation of marine pollution impacts and protection of marine biodiversity. The importance of marine biodiversity for climate change mitigation, food security and sustainable ecosystem services calls for urgent, cooperative action.

Key words: adverse outcome pathways, biodiversity, chemical pollution, endocrine-disrupting chemicals, marine organisms, new approach methodologies, next-generation risk assessment, marine, monitoring, ocean health.

CONTENTS

I. INTRODUCTION

The United Nations (UN) Decade of Ocean Science for Sustainable Development (2021–2030) strives for a clean ocean where sources of pollution are identified and reduced or removed by 2030 (Ryabinin *et al.*, 2019). Pollution is one of the top five drivers of biodiversity loss and undermines sustainable development, yet it remains a huge challenge for governments and the international development agenda (Landrigan *et al.*, 2018). The ocean is teeming with life and is essential for planetary health but despite its vastness, it is at risk from multiple physical, chemical and biological threats. The ocean is the ultimate sink for all manmade pollutants, including industrial chemicals, nutrients,

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pharmaceuticals and personal care products, pesticides, radioactive materials, nanomaterials and (micro)plastics, with still unknown consequences (Persson *et al.*, 2022). The UN Convention on the Law of the Sea also requires states to protect the marine environment from all sources of pollution (UNCLOS, 1982). One visible form of pollution, plastics, is now pervasive in the marine environment from the deep sea to the poles (Haward, 2018; Wang, Zhao & Xing, 2021) and their visibility and persistence have sensitised the public and governments leading to the current negotiations for a new international legally binding instrument to tackle plastic pollution. Microplastics can also act as vectors of pollutants, including endocrine disruptors (Caruso, 2019; Ullah *et al.*, 2023), but pollution from synthetic organic chemicals is an insidious and invisible threat (BacktoBlue, 2022). The increasing rate of production and release of larger volumes and numbers of pollutants with diverse hazard and risk potential, exceeds societies' ability to conduct safety-related assessments and monitoring (Persson *et al.*, 2022). It is therefore not surprising that targets such as the UN Sustainable Development Goal (SDG) 12.4, aiming at sound management of chemicals and all waste to reduce, release and minimise environmental and human health impacts by 2020 have not been achieved (UN, 2016; Macias Moy *et al.*, 2022). The lack of an effective global waste management system and the growing human population will further increase pollution, whilst the argument that 'dilution is the solution' no longer holds true, especially for coastal environments around urbanised areas with poor wastewater treatment.

Endocrine-disrupting chemicals (EDCs) are a large class of pollutants that interfere with any aspect of hormone action causing adverse effects (WHO/UNEP, 2012; La Merrill *et al.*, 2020). Diverse, synthetic EDCs continue to emerge and cause concern as they are often biologically active at very low concentrations and may have high environmental persistence, bioaccumulation and biomagnification potential (Metcalfe *et al.*, 2022; EC, 2020; WHO/UNEP, 2012). EDCs are of special concern as they do not only reduce survival but can affect development, behaviour and reproduction, attributes that affect populations and community structures, with significant implications for ecosystem health and services of societal relevance.

Efficient regulatory measures to reduce chemical exposure require, amongst other options, the application of sensitive and reliable test methods. Although a number of standardised assays for EDC testing are available, current approaches are limited to detecting EDCs that can disrupt oestrogen, androgen or thyroid (EAT) signalling along with the steroidogenesis pathway in vertebrates and ecdysteroid (Ec) / juvenile hormone (JH) signalling in ecdysozoan animals. Furthermore, the regulatory tests cover a small number of vertebrate model species: mammals, dominated by rodents, and freshwater animals, dominated by fish and amphibians (OECD, 2018, 2024). This is partly because chemicals known to target vertebrate EAT signalling pathways are ubiquitous and/or persistent in the environment and disruption of these pathways can affect both human and wildlife populations. Examples of negative consequences for human health include infertility, developmental abnormalities, reduced IQ and hormone-related cancers (WHO/UNEP, 2012) – conditions of high societal concern. In addition, research on EAT-disrupting chemicals has benefited from extensive knowledge about receptor structure, function and signalling pathways in vertebrate systems that provided consensus endpoints for test guidelines. Similarly, disruption of Ec and ecdysone receptor (EcR) signalling affects arthropod development, behaviour and population dynamics with unmeasured implications for ecosystems and agriculture (Song *et al.*, 2017). For example, insects are prime targets for biocides designed to disrupt Ec/JH signalling (Malhotra & Basu, 2023; Toyota *et al.*, 2022) with benefits for pest control; however, these biocides are of potential harm for marine arthropods that also rely on these signalling pathways to regulate functions like growth and reproduction.

As research in the EDC field continues to evolve, efforts to understand the consequences for human and environmental health of a broader range of hormones and endocrine pathways are increasingly emphasised, highlighting important knowledge gaps for regulatory decisions (Crane *et al.*, 2022; James, Kroll & Minier, 2023). However, there is also a general need for expanding the taxonomic coverage of regulatory tests to include marine animals, particularly focusing on EDCs since endogenous hormone signalling cascades regulate many, if not all, aspects of animal physiology, determining fitness and population stability.

The presence of vitellogenin, a female-specific, egg yolk protein, in juvenile and male fish has been used extensively as a biomarker of exposure to environmental oestrogens in many aquatic bodies (see review by Hiramatsu *et al.*, 2006), including estuaries (Allen *et al.*, 1999) and even the open sea (Scott *et al.*, 2006). Moreover, history shows that EDCs in the marine environment are a real threat that can affect populations, as exemplified by the developmental abnormalities of marine gastropods that led to population crashes globally due to tributyltin (TBT) exposure, and the predicted extinction of some killer whale (*Orcinus orca*) populations due to polychlorinated biphenyl (PCB) bioaccumulation (Desforges *et al.*, 2018; Bryan *et al.*, 1986). Given the magnitude, complexity and diversity of marine life, global coordinated efforts are required to cover the knowledge gaps and to improve availability and curation of long-term monitoring data.

Identifying the direct molecular targets of hormones/neuro-hormones and the functions they regulate across a broad phylogenetic scale is the basis for identifying the likely impacts of EDCs on fitness and survival of marine species. However, species diversity linked to a multitude of shared and species-specific physiological processes and signalling pathways at a functional level makes risk assessment of EDCs for regulatory purposes a major challenge (Crane *et al.*, 2022; James *et al.*, 2023). Nevertheless, the existing knowledge about endocrine signalling in marine animals can already contribute to setting priority targets. The bibliographic analysis undertaken herein includes the most documented molecular targets and toxicity pathways associated with potential

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endocrine disruption of marine species. A subset of animal taxa representative of marine biodiversity was considered in relation to current regulatory tests/monitoring tools for EDC hazard assessment. Knowledge gaps and challenges, as well as opportunities, are identified and used to establish strategic research priorities and recommendations for regulators, policy makers and the public.

Hormones are chemical messengers that have a central role in maintaining homeostasis in animals, and can be proteins, peptides, steroids, amino acid derivatives and gases. The action of hormones is triggered when they bind to specific receptors, which are found primarily in the plasma membrane or nucleus of responsive cells (Belfiore & Leroith 2018). At a molecular level, hormones can act through different mechanisms across animal taxa but the activation of nuclear receptors (NRs) and G-protein coupled receptor superfamilies (GPCRs) are the best documented, if not the primary mediators of hormone action, making them also prime molecular targets of EDCs including EAT-disruptors and TBT (Balaguer, Delfosse & Bourguet, 2019; Cardoso & Larhammar, 2014; Castro *et al.*, 2007; Escriva, Bertrand & Laudet, 2004; Lagadic *et al.*, 2018; Périan & Vanacker, 2020).

NRs are diverse and variable between different animal clades (i.e. from less than 20 in cnidarians to more than 200 in nematodes), with one third being 'orphans' as they have no identified endogenous ligand (Papageorgiou *et al.*, 2021) – see Table 1 for a list of members of the NR superfamily that are known to be susceptible to modulation by EDCs (Tan *et al.*, 2021). NRs are ligand-activated transcription factors that have been found in all extant metazoan taxa and share a common evolutionary history and similar sequence features at a protein level. The NR superfamily is divided into nine subfamilies (NR0–NR7 and two DNA-binding domain NRs), seven of which display the canonical protein architecture of a single ligand-binding and a single DNA-binding domain (Miglioli *et al.*, 2021). Subfamily 2, containing retinoid X receptors (RXRs), represents the ancestral clade of the superfamily (Holzer, Markov & Laudet, 2017a; Bridgham *et al.*, 2010) and RXR is not only the earliest NR, but also displays remarkably well-conserved ligand binding domains across metazoans. Given the biological importance, likelihood of chemical binding and the well-documented negative effects elicited in marine organisms by organotin compounds (Castro *et al.*, 2007; Nishikawa *et al.*, 2004) it is surprising that no international tests targeting vertebrate or invertebrate RXR are available (OECD, 2018, 2024).

The same is true for peroxisome proliferator-activated receptors (PPARs), another major class of NRs that are key regulators of adipogenesis, following dimerisation with the RXR (Capitao *et al.*, 2018). RXR and PPAR signalling often involves formation of heterodimers with other NRs. In addition, ToxCast™ (a suite of high-throughput *in vitro* assays) for PPARγ and RXRα does not correlate well with laboratory measurements of PPARγ and RXRα activity, precluding the identification of many obesogenic chemicals (Janesick *et al.*, 2016). However, these challenges should not be a deterrent for the development of suitable assays where the pathways can be elucidated.

GPCRs form the largest family of plasma membrane receptors and are central regulators mediating endocrine signalling and regulating physiological functions related to growth, differentiation, metabolism, reproduction or general homeostasis, in both vertebrates and invertebrates (Cardoso & Larhammar, 2014). Most research has focused on the identification of GPCR ligands across metazoans, with many receptors still to be 'de-orphanised', and on their functions defined in human diseases (Cardoso & Larhammar, 2014; Rask-Andersen, Masuram & Schiöth, 2014). Several studies have reported the disruption of signalling for some GPCRs by EDCs including oestrogens, plastic chemicals and other pollutants (Barton *et al.*, 2018; McPartland *et al.*, 2024; Périan & Vanacker, 2020; Rask-Andersen *et al.*, 2014; Thomas *et al.*, 2007; Zapater *et al.*, 2024), but most were based on mammalian or fish receptors. GPCR signalling pathways, their physiological roles and potential disruption are just starting to be unravelled in some invertebrate taxa such as terrestrial insects (Liu *et al.*, 2021), and marine echinoderms such as sea cucumbers and starfish (Roberts *et al.*, 2017; Yuan *et al.*, 2023). Thus, given their relevance in endocrine regulation and potential for disruption, we include GPCRs in our bibliometric analysis carried out across marine taxa to identify knowledge gaps.

Finally, our analysis also included the signalling (and disruption) of the highly reactive gasotransmitter mediator nitric oxide (NO). This is an endocrine mediator of emerging interest (Bahadoran *et al.*, 2020) as it is involved in numerous physiological processes in vertebrates and invertebrates including embryonic development, metamorphosis, reproduction, immune defence, neurotransmission and cardiovascular homeostasis (Bahadoran *et al.*, 2020; Elphick, Green & O'Shea, 1993; Jacklet, 1997; Locascio *et al.*, 2023; Liu *et al.*, 2018; Ueda *et al.*, 2016) and its production is also regulated by hormones and neurotransmitters (Locascio *et al.*, 2023). However, only a few reports exist on the disruption of NO pathways by pollutants (e.g. Xu *et al.*, 2013), highlighting a key gap for future research and justifying the inclusion of NO signalling in this analysis.

II. METHODS

Two sessions of the Model-EDC workshop were held under the auspices of a Euromarine Foresight Workshop and network funding project. The workshops took place online in November 2021 and as a face-to-face satellite meeting of the 30th Conference of European Comparative Endocrinologists (September 2022) in Faro, Portugal (Pinto *et al.*, 2025). An international network of 83 participants specialised in comparative and integrative physiology and endocrinology discussed the status and priorities for EDC screening in the

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Table 1. Members of the nuclear receptor (NR) superfamily that are susceptible to modulation by endocrine-disrupting chemicals (EDCs), based on Tan *et al.* (2021). Non-vertebrate NR subfamilies and receptors are indicated with #. Physiological ligands stem from *in vivo* vertebrate data, whilst empty cells highlight receptors for which the physiological ligand is yet to be identified or whose orphan state is currently disputed. Best documented biological functions are summarised as reviewed in Miglioli *et al.* (2021, 2024) and references therein. For simplicity, all NRs are referenced in the table according to the designation defined by the Nuclear Receptors Nomenclature Committee (NRNC).

Subfamily	Group	Name	NRNC name	Abbreviation	Physiological ligand	Best-documented biological functions
1	**A**	Thyroid hormone receptor	NR1A1-2	Thyroid hormone receptor, THR	T3[a]	Growth and metamorphosis
	B	Retinoic acid receptor	NR1B1-3	Retinoic acid receptor, RAR	All-trans-RA[b]	Neurogenesis and axial patterning
	C	Peroxisome proliferator-activated receptor	NR1C1-3	Peroxisome proliferator-activated receptor, PPAR	Fatty acids, prostaglandins	Lipid metabolism
	H #	Liver X receptor-like	NR1H1	Ecdysone receptor, EcR	Ecdysteroids	Growth, moulting and reproduction
	I	Vitamin D receptor-like	NR1I1	Vitamin D receptor, VDR	Vitamin D	Detoxification responses to xenobiotics
			NR1I2	Pregnane X receptor, PXR	Xenobiotics	
			NR1I3	Constitutive androstane receptor, CAR	Androstane	
	J #		NR1J1	HR96		
2	**B**	Retinoid X receptor	NR2B1-3	RXR		Heterodimeric partner to THR, RAR, PPAR, liver X and vitamin D-like receptors
			NR2B4	*USP*		
3	**A**	Oestrogen receptor	NR3A1,2	Oestrogen receptor, ER	Oestradiol	Reproduction, stress response, metabolism, immune function, electrolyte homeostasis, growth and development
	B	Oestrogen-related receptor	NR3B1-3	Oestrogen-related receptor, ERR		
	C	Steroid receptor/ ketosteroid receptors	NR3C1	Glucocorticoid receptor, GR	Cortisol	
			NR3C2	Mineralcorticoid receptor, MR	Aldosterone	
			NR3C3	Progesterone receptor, PR	Progesterone	
			NR3C4	Androgen receptor, AR	Testosterone	
	D #	Oestrogen-like receptor in Protostomia	NR3D	Oestrogen receptor-like, ER-like		Potentially involved in reproductive functions and proliferation of primordial germ cells
	E #	Oestrogen-like receptor in Cnidaria	NR3E	Oestrogen receptor-like, ER-like		

[a]Triiodothyronine.
[b]Retinoic acid.

marine environment (see online Supporting Information, Table S1 for a list of the questions discussed). Following this preliminary analysis, the core Model-EDC network Working Group created the first draft of this review in September 2022, and subsequent drafts benefited from contributions of additional international experts during 2023–2024.

Bibliographic searches of peer-reviewed articles in *PubMed* were used to review the current knowledge about endocrine functions and disruption in marine organisms. Global search queries are provided in the legend to Fig. 1. Searches with these queries were also performed using the *Web of Science* and resulted in similar conclusions and trends as those presented and discussed for *PubMed* (results not shown). Knowledge regarding the best-documented molecular targets and adverse biological effects of chemicals with endocrine-active properties was evaluated by experts for 20 taxa representative of marine biodiversity (based on the World Register of Marine Species database; WoRMS, 2023a). The results are presented in Fig. 2 and Table S2.

PubMed searches established the presence/absence of selected molecular targets and the available evidence for endocrine disruption in each taxon. The abstracts obtained using the initial search strings (provided in Appendix S1) were manually curated by reading all abstracts when <50 articles were located, or by using additional search strings optimised per taxon to eliminate duplicates and false positives (mainly due to publications on freshwater species) – see Appendix S1 for all taxon-specific search strings. Taxon

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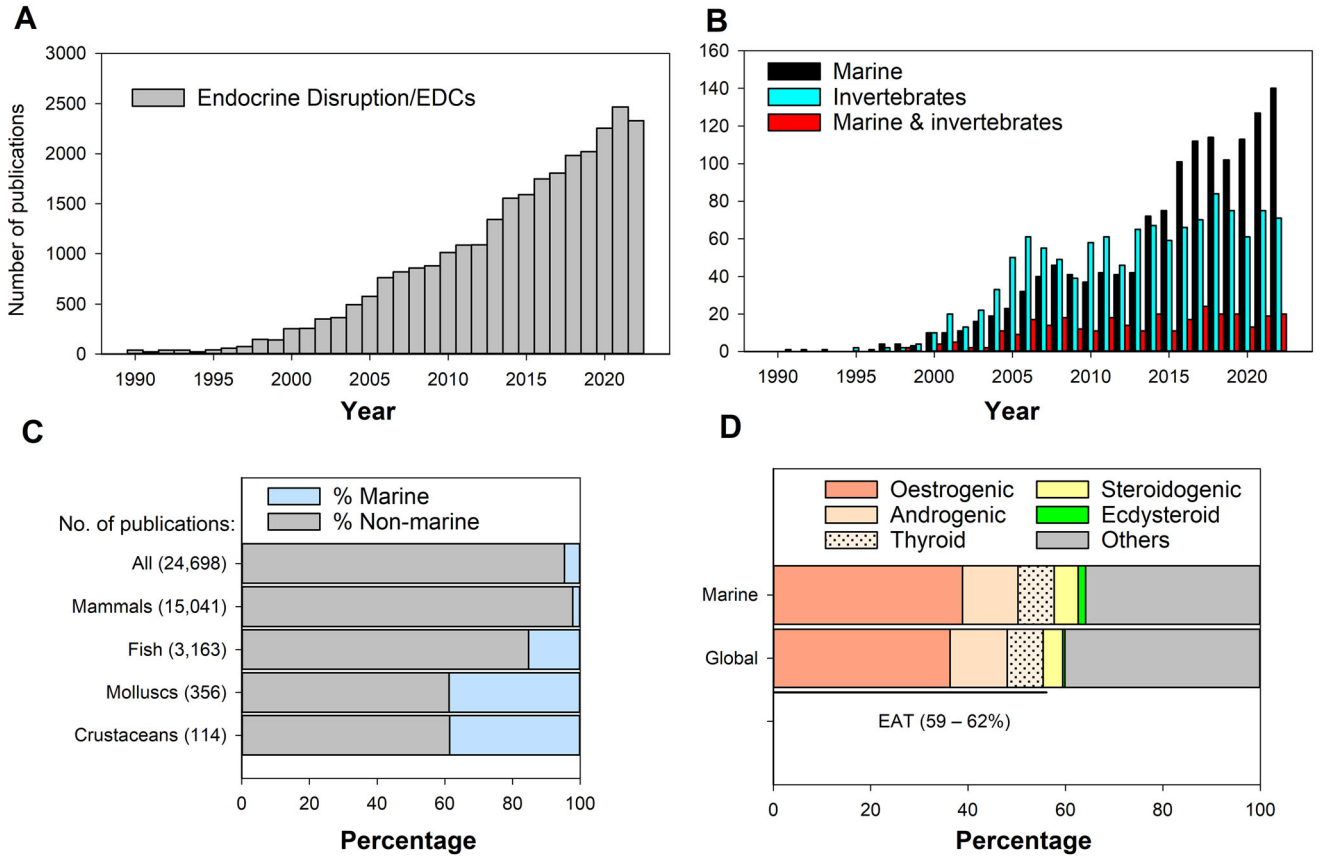

Fig. 1. Evolution of the number of publications on endocrine disruption (ED) or endocrine-disrupting chemicals (EDCs) over 32 years (1990–2022), their distribution according to groups of animals, whether they are marine, and the main endocrine disruption modalities targeted. (A) Results from the global EDC keyword-based query (*'Endocrine disrupt*' OR 'EDC'*) in *PubMed*. (B) Number of *PubMed* publications obtained by adding to the query *AND marine* (black bars), *AND invertebrates* (blue bars) or *AND marine AND invertebrates* (red bars). (C) Horizontal bar 'All' represents the total number of *PubMed* articles until 2022 obtained using the global query (*'Endocrine disrupt*' OR 'EDC'*); light blue represents the proportion of these articles for marine organisms, identified by adding *AND marine*. Additional subdivisions of 'All' articles by category of animal was obtained by adding *AND* (*mammal OR mammalian OR mammals*) for 'Mammals'; *AND fish* for 'Fish'; *AND* (*bivalv* OR gastropod* OR cephalopod* OR mussel OR snail*) for 'Molluscs'; and adding *AND* (*amphipod* OR decapod* OR copepod**) for 'Crustaceans'. (D) The proportion of 'All' endocrine disruption papers that referred to specific oestrogen, androgen and thyroid (EAT)-mediated signalling mechanisms (Martyniuk *et al.*, 2022) were retrieved by adding *AND Oestrogen**, adding *AND androgen** or adding *AND thyroid*, according to the specific search. Steroidogenesis disruption papers were included by adding AND steroidogenic*. Publications related to invertebrate-specific steroids were identified by adding *AND Ecdys**.

search results are categorised in Fig. 2 and Table S2 based on the number of relevant articles identified: 1 (1–10 articles), 2 (11–50 articles); 3 (51–100 articles) and 4 (>100 articles). Search results were visualised with SigmaPlot14 (SYSTAT) using bar plots for the biodiversity and bibliography results. For simplicity, the term 'endocrine' (chemical signals in the form of hormones produced in glands, which travel in the bloodstream and control distant cells or organs) was used throughout the searches and herein to represent endocrine, paracrine, autocrine and neuroendocrine actions (Crane *et al.*, 2022; Waye & Trudeau, 2011).

To evaluate the utility of bioinformatics approaches for the extrapolation of toxicity knowledge based on conservation of endocrine-relevant targets in marine species, an initial screening was conducted with the United States Environmental Protection Agency (US-EPA) 'Sequence Alignment to Predict Across Species Susceptibility' tool, SeqAPASS v7.0 (LaLone *et al.*, 2016; US-EPA, 2024a). This tool was created to evaluate protein conservation across species by gathering evidence through protein sequence and structural alignments. For SeqAPASS Level 1, a primary amino acid sequence comparison was completed for 18 proteins (limited to the focus of this analysis) using human as the query species, except for the EcR where the fruit fly *Drosophila melanogaster* was used as the query species (Table 2). The full report outputs from SeqAPASS, which included all species with protein sequences that aligned to the query species protein, were compared using the WoRMS database Taxon Match Tool

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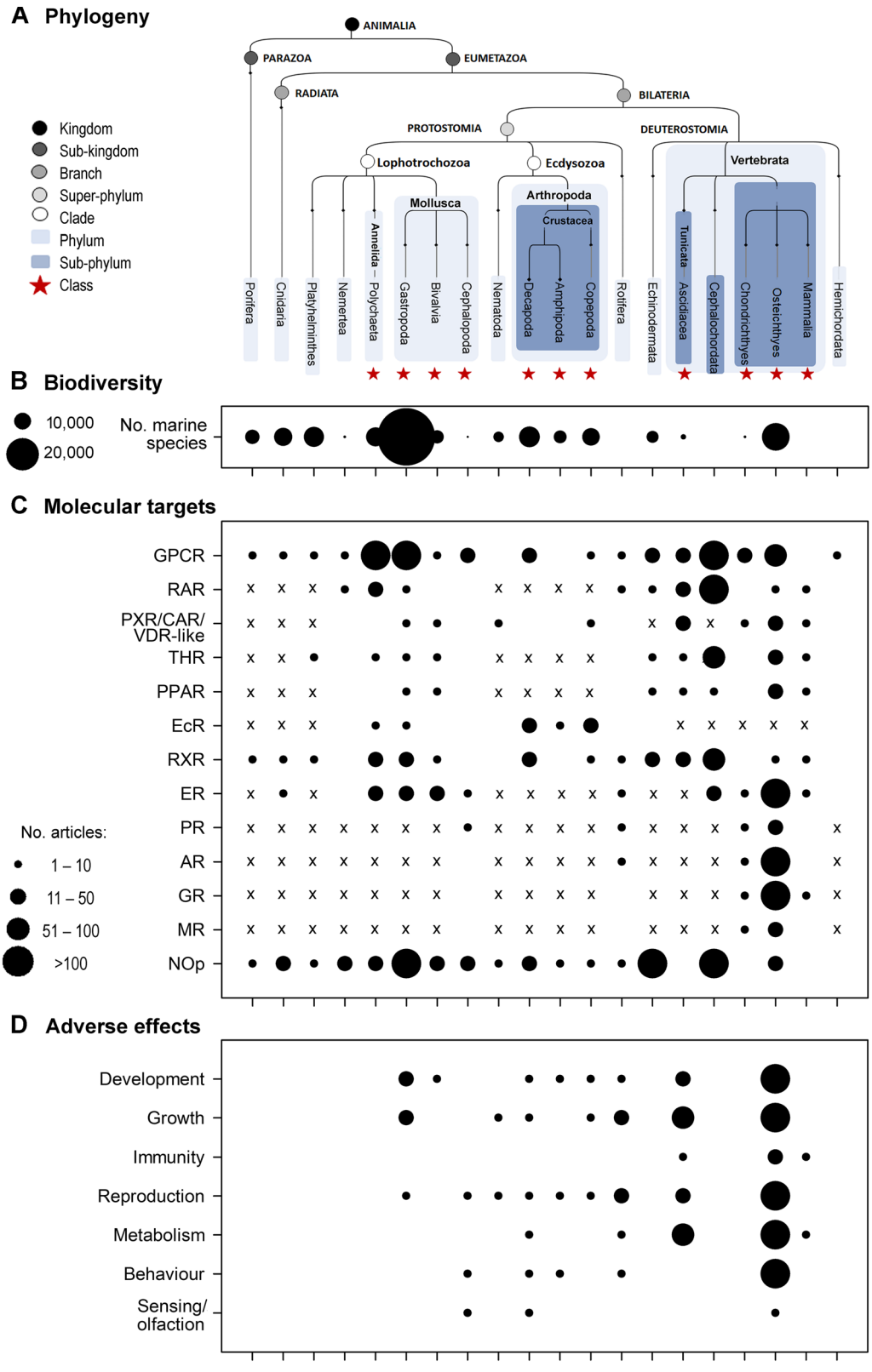

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(WoRMS, 2023b) to identify marine species specifically (Tables S2 and S3).

These data represent a foundation for extrapolating potential molecular targets of EDCs in existing frameworks [i.e. adverse outcome pathways (AOPs) and other new approach methodologies (NAMs)] to marine species that have available sequence information. AOPs are a useful means to overcome the complexity of biological processes. Originally developed for chemicals (Ankley *et al.*, 2010), the concept is gaining attention for a diverse group of hazards (Clerbaux *et al.*, 2024). AOPs are not only useful as a framework that organises knowledge to allow grouping of chemicals with the same molecular initiating event (MIE, see Section III.3.*b* and Fig. 3), but they can be a source of ideas for developing novel markers for chemical hazard assessment. NAMs can either be non-animal methods or methods that reduce and refine the use of animals and include quantitative structure–activity relationship predictions, high-throughput screening bioassays, −omics applications, cell cultures, organoids, microphysiological systems or machine learning models and artificial intelligence, and they are increasingly recognised as an indispensable component of modern toxicology (Schmeisser *et al.*, 2023). In summary, our bioinformatic approach can help identify which marine species and relevant taxonomic groups are absent or underrepresented in genomic resources, and therefore in need of sequencing and annotation efforts.

III. RESULTS AND DISCUSSION

(1) Available knowledge and identified gaps

A large body of literature on endocrine disruption and EDCs has accumulated in the last three decades with a total of 24,698 articles identified in *PubMed* (Fig. 1A), of which 14% were review papers. However, this number dramatically decreased when the key words 'marine', 'invertebrates' or 'marine and invertebrates' were included (Fig. 1B). Less than 300 articles were retrieved for the latter combination corresponding to *ca.* 18 articles annually in the last 10 years. Key word searches for specific marine taxa did not increase the number of publications retrieved (data not shown) and hence, the results were assumed to be a robust representation of relative research effort. Additional searches selecting specific groups of animals highlighted that only 2% of the papers on endocrine disruption/EDCs on mammals and 15% on fish include the term 'marine' in the full article (Fig. 1C). Interestingly, approximately 40% of articles on molluscs and crustacean species were 'marine'. This may reflect the importance and abundance of these phyla in marine environments (Knigge, LeBlanc & Ford, 2021; Ford & LeBlanc, 2020), as collectively they account for >40% of all marine species (Fig. 2B; WoRMS, 2023a). It may also reflect the numerous reports on the devastating effects of TBT that led to global population crashes of marine gastropods (Matthiessen & Gibbs, 1998). Finally, in either total or marine-restricted searches, *ca.* 60% of the papers referred to the EAT and steroidogenesis disruption modalities (Fig. 1D), with only 0.5–1.5% of papers referencing ecdysteroids (LaFont, 2000; Crane *et al.*, 2022), revealing a strong bias towards typical vertebrate mechanisms.

To estimate better the knowledge concerning endocrine disruption in 20 vertebrate and invertebrate taxa that include a high number of marine species (Fig. 2 and Table S2), detailed searches were performed for common molecular targets of EDCs including selected NRs (Table 1), GPCRs and NO.

This bibliometric analysis (Fig. 2) revealed a poor relationship between the number of publications and representation of taxon within marine biodiversity. Assessment of molecular targets across clades such as nemerteans, cephalopods, nematodes, rotifers, echinoderms and hemichordates (Fig. 2C) revealed major knowledge gaps, extensive variation in the presence or absence of several members of the NR superfamily, as well as on the information about EDCs. Significantly, information about endocrine disruption and major NRs shown to be impacted by environmental chemicals [e.g. pregnane X receptor/constitutive androstane receptor and vitamin D receptor-like (PXR/CAR/VDR-like) and RXR], having developmental functions in bilaterians [i.e. retinoic acid receptor (RAR), thyroid hormone receptor (THR)] or involved in endocrine signalling in specific groups such as the Ecdysozoa [i.e. EcR (Cruzeiro *et al.*, 2016;

(Figure legend continued from previous page.)
Fig. 2. Phylogenetic relationships of the main marine animal taxa considered (A), compared to their biodiversity (B) and knowledge about their endocrine system and disruption (C, D). In B, the number of marine species for each taxon retrieved from the World Register of Marine Species database (WoRMS, 2023*a*) is represented by size-proportional bubbles. Available knowledge for the molecular targets (C) and adverse biological effects (D) is represented as size-proportional bubbles according to the number of articles published until January 2023 (corresponding to categories 0–4 defined in Section II and summarised in Table S2). All key words and search strings used in the *PubMed* searches are provided in Appendix S1. All initial searches of taxa were manually curated by experts as described in Section II. When there was published evidence for a predicted absence of a signalling pathway, this is indicated by an x in C and in Table S2. AR, androgen receptor; EcR, ecdysone receptor; ER, oestrogen receptor; GPCR, G-protein coupled receptor; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; NOp, nitric oxide pathway; PPAR, peroxisome proliferator-activated receptor; PR, progesterone receptor; PXR/CAR/VDR-like, pregnane X receptor/constitutive androstane receptor/vitamin D receptor-like; RAR, retinoic acid receptor; RXR, retinoid X receptor; THR, thyroid hormone receptor.

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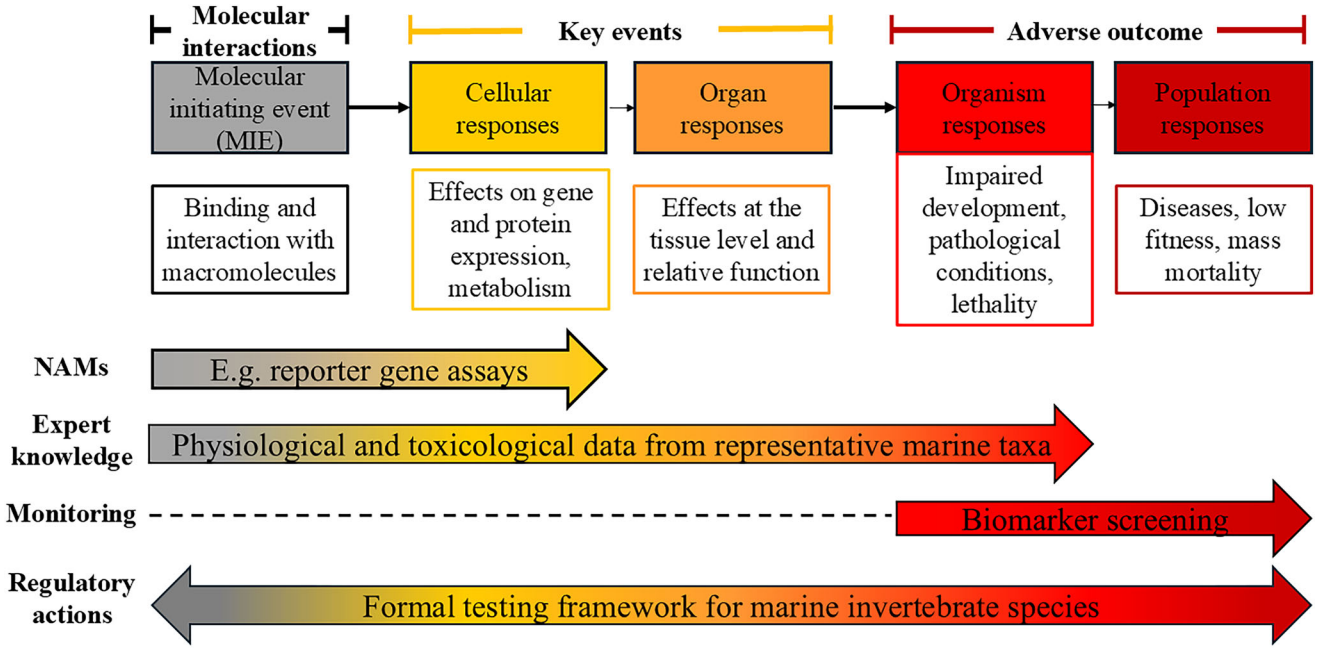

Fig. 3. Scheme representing the adverse outcome pathways (AOP) framework components, with reference to other activities that collectively can improve understanding of risk to marine animals. NAM, new approach methodology.

Miglioli *et al.*, 2021; Delfosse *et al.*, 2021; Ruivo *et al.*, 2021)] is lacking for several marine taxa (Fig. 2C), especially in invertebrate species.

A surprising aspect was the relatively low number of publications found associating GPCRs with endocrine disruption for most taxa. GPCRs are the largest membrane receptor family, mediating the action of many endocrine factors in diverse taxa, and are targets linked to increasingly important diseases in humans, e.g. obesity, metabolic syndrome, diabetes (Cardoso & Larhammar, 2014; Rask-Andersen *et al.*, 2014); however, no data exists for these conditions in marine wildlife. Finally, no literature on the potential impacts of EDCs on either GPCRs or the NO pathway (NOp) in marine mammals was found whilst very few publications exist on NO and endocrine disruption in marine cartilaginous (Chondrichthyes) or bony (Osteichthyes) fish.

Analysis of knowledge gaps on potential adverse biological outcomes of EDCs in marine species revealed that available information is skewed towards vertebrate clades (Fig. 2D), where identification of adverse effects is presumably linked to a better comprehension of their endocrine axes and biological functions. Conversely, knowledge concerning marine invertebrates is very limited (Fig. 2D) probably due to gaps in basic understanding of invertebrate endocrinology, receptors and biological functions, which hampers the identification of molecular targets and the assessment of the endocrine toxicity of chemicals (Cuvillier-Hot & Lenoir, 2020; Castro & Santos, 2014; Miglioli *et al.*, 2021; Crane *et al.*, 2022; Ford & LeBlanc, 2020).

It is important to underline that the presence of receptor orthologues in different animal clades does not necessarily imply conserved ligand-binding and activation or a homologous function. For instance, oestrogen-like receptors in invertebrates have little or no response to cognate vertebrate ligands, including steroidal oestrogens such as 17β-oestradiol (Bridgham *et al.*, 2014; Keay & Thornton, 2009). This also appears to be the case for other NRs including THR, RAR and PPAR (Miglioli *et al.*, 2021; Holzer, Roux & Laudet, 2017b; Gutierrez-Mazariegos, Schubert & Laudet, 2014; Capitao *et al.*, 2018). It is, therefore, important to highlight that cross-species extrapolations on endocrine targets should be addressed within the appropriate phylogenetic and evolutionary context and should be supported by relevant genomic and functional data. Certainly, available knowledge on exposure, adsorption, distribution, metabolism, and elimination, along with life history and life stage must be integrated to provide a more complete description of pathway perturbation leading to adverse impacts across taxa (Crane *et al.*, 2022; Santos *et al.*, 2018).

Bioinformatics evaluation of protein conservation for 18 EDC-relevant targets using SeqAPASS and comparison to the WoRMs database (Tables 2, S3 and S4) retrieved 513 unique marine species from 69 unique taxonomic groups. The largest number of marine species mapped to SeqAPASS sequence results were vertebrates, with Mammals, Aves and Actinopterygii having 40 or more species per taxonomic group that aligned in SeqAPASS (Table S4). Chondrichthyes, Malacostraca, Gastropoda, Bivalvia, Hexanauplia, Anthozoa, Cephalopoda, and Polychaeta had between 10 and 27 species with sequences that aligned in the SeqAPASS results.

Of the 69 classes of marine organisms, 30 had only one species identified in the SeqAPASS results. The results of

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Table 2. Summary of SeqAPASS results identifying the number of marine species with relevant protein sequence information (for details, see Tables S3 and S4). SeqAPASS results were collected from the Level 1 Full Reports (primary amino acid sequence alignments) and provide an initial evaluation of the number of marine species yielding sequence results in each data set. Further evaluation of Level 1 Primary reports and additional levels of analysis will need to be conducted for extrapolation purposes.

Protein target	SeqAPASS query accession	SeqAPASS Level 1 output
		Marine/total number of species
Probable G-protein coupled receptor (GPCR) 19	NP_006134.2	296/1368
Retinoic acid receptor (RAR) alpha isoform 1	NP_001138773.1	328/1432
Pregnane X receptor (PXR)	O75469.1	323/1476
Constitutive androstane receptor (CAR)	Q14994.2	323/1342
Vitamin D (1,25- dihydroxyvitamin D3) receptor (VDR)	BAH02291.1	324/1511
Thyroid hormone receptor alpha (THRα)	P10827.1	330/1473
Thyroid hormone receptor beta (THRβ)	P10828.2	324/1457
Peroxisome proliferator-activated receptor alpha (PPARα)	NP_005027.2	342/1475
Peroxisome proliferator-activated receptor delta (PPARδ)	Q03181.1	342/1497
Peroxisome proliferator-activated receptor gamma (PPARγ) isoform 2	NP_056953.2	341/1495
Ecdysone receptor (EcR) isoform G	NP_0001163061.1	349/1615
Retinoid X receptor (RXR) alpha	P19793.1	318/1438
Oestrogen receptor 1 (ER1) isoform	NP_000116.2	370/1495
Progesterone receptor (PR)	AAA6008.1	367/1513
Androgen receptor (AR)	AAI32976.1	358/1591
Glucocorticoid receptor (GR)	P04150.1	367/1575
Mineralocorticoid receptor (MR)	P08235.2	358/1521
Nitric oxide synthase (NOS) inducible	NP_000616.3	304/1938

the SeqAPASS evaluation demonstrated that genomic resources need to be expanded to provide greater species coverage, although as outlined above, sequence similarity does not necessarily reflect ligand-binding capacity or function so further evaluation will be required. Conservation of function should also be determined alongside sequencing information to allow prediction of susceptibility to chemicals.

(2) Current status of endocrine-disrupting chemicals (EDCs) testing and the importance of marine species

Aquatic taxonomic diversity is represented in current regulatory testing for non-specific toxicity for both vertebrate and invertebrate species. However, except for two recommended seawater species in the fish early-life stage toxicity test, Organisation for Economic Co-operation and Development (OECD) Test Guideline 210 (Table 3), all other aquatic test species are freshwater species. EDC-specific test guidelines are based on the endocrine pathways of freshwater fish and amphibians. Although some chronic test guidelines with invertebrate species consider reproduction, any observed effects can be specifically associated with an endocrine mode of action (Table 3). Furthermore, the fish models typically used for regulatory purposes (zebrafish, *Danio rerio*; Japanese medaka, *Oryzias latipes*; or fathead minnow, *Pimephales promelas*) are tested under laboratory conditions designed to promote continuous, repeated spawning for assessing potential reproductive effects of chemicals. This character, while convenient for testing, does not reflect the diversity of fish reproductive strategies (Murua & Saborido-Rey, 2003; Mcbride *et al.*, 2015; Patzner, 2008), nor cover the positive feedback loops between sex steroids and gonadotropins documented in fish species that spawn annually or once in their lifetime (Antonopoulou *et al.*, 1999; Shao *et al.*, 2015).

From a conceptual perspective, there are compelling reasons to expand EDC testing to include greater representation of different taxa from the marine biosphere. Reasons include:

(1) The ocean has great ecological and economic importance, as it regulates climate and planetary cycles and provides important food and economic pillars in many countries (the Blue Economy), while holding a huge, yet underestimated biodiversity (MBON, 2023; Tara Ocean Foundation, 2023; Ryabinin *et al.*, 2019; Lee, Noh & Khim, 2020).
(2) The ocean remains the main sink for wastewater (80% of which is discarded raw worldwide) and hence is accumulating pollutants (Persson *et al.*, 2022; Ryabinin *et al.*, 2019; Ajala *et al.*, 2022).
(3) Chemical properties that affect bioavailability, toxicokinetics or persistence may differ between freshwater and seawater environments, e.g. due to different ionic compositions or pH (Leung *et al.*, 2001).
(4) There is evolutionary evidence that freshwater colonisation by marine species was accompanied by genomic and physiological divergence, which may affect the relative sensitivity of marine animals to chemicals (Horn & Anderson, 2020; Liu *et al.*, 2019; Morris, Lenski & Zinser, 2012; Aguirre *et al.*, 2022; Leung *et al.*, 2001; Mearns *et al.*, 2015; Del Signore *et al.*, 2016).

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Table 3. Summary of the OECD (Organisation for Economic Co-operation and Development) chronic test guidelines (TGs) for environmental chemical hazard and endocrine disruption assessment in aquatic animals (OECD, 2018, 2024). TG titles are provided as well as the recommended aquatic test species divided into freshwater (FW) or seawater (SW) species.

OECD TG	Test guideline (TG) title	Recommended FW species	Recommended SW species	Endocrine endpoints
210	Fish, Early-Life Stage Toxicity Test	Rainbow trout (*Oncorhynchus mykiss*), fathead minnow (*Pimephales promelas*), zebrafish (*Danio rerio*), Japanese rice fish or medaka (*Oryzias latipes*)	Sheepshead minnow (*Cyprinodon variegatus*), silverside (*Menidia* sp.)	No
211	*Daphnia magna* Reproduction Test	Crustacean (*Daphnia magna*)	No	Partially[a]
212	Fish, Short-term Toxicity Test on Embryo and Sac-fry Stages	Rainbow trout (*O. mykiss*), fathead minnow (*P. promelas*), zebrafish (*D. rerio*), Japanese medaka (*O. latipes*), common carp (*Cyprinus carpio*)	No	No
215	Fish, Juvenile Growth Test	Rainbow trout (*O. mykiss*)	No	No
218	Sediment-Water Chironomid Toxicity Using Spiked Sediment	Insect (*Chironomus riparius*, *Chironomus dilutus*)	No	No
219	Sediment-Water Chironomid Toxicity Using Spiked Water	Insect (*C. riparius*, *C. dilutus*)	No	No
225	Sediment-Water Lumbriculus Toxicity Test Using Spiked Sediment	Annelid (*Lumbriculus variegatus*)	No	No
229	Fish Short-term Reproduction Assay	Fathead minnow (*P. promelas*), zebrafish (*D. rerio*), Japanese medaka (*O. latipes*)	No	Yes
230	21-day Fish Assay	Fathead minnow (*P. promelas*), zebrafish (*D. rerio*), Japanese medaka (*O. latipes*)	No	Yes
231	Amphibian Metamorphosis Assay (AMA)	Amphibian (*Xenopus laevis*)	No	Yes
233	Sediment-Water Chironomid Life-Cycle Toxicity Test Using Spiked Water/Sediment	Insect (*C. riparius*, *C. dilutus*)	No	No
234	Fish Sexual Development Test	Zebrafish (*D. rerio*), Japanese medaka (*O. latipes*), three-spined stickleback (*Gasterostreus aculeatus*)	No	Yes
240	Medaka Extended One Generation Reproduction Test (MEOGRT)	Medaka (*O. latipes*)	No	Yes
241	The Larval Amphibian Growth and Development Assay (LAGDA)	Amphibian (*X. laevis*)	No	Yes
242	*Potamopyrgus antipodarum* Reproduction Test	Mollusc (*Potamopyrgus antipodarum*)	No	No
243	*Lymnaea stagnalis* Reproduction Test	Mollusc (*Lymnaea stagnalis*)	No	No
248	Xenopus Eleutheroembryonic Thyroid Assay (XETA)	Amphibian (*X. laevis*)	No	Yes
250	EASZY assay: Detection of Endocrine Active Substances, acting through oestrogen receptors, using transgenic tg(cyp19a1b:GFP) Zebrafish embrYos	Zebrafish (*D. rerio*)	No	Yes
251	Rapid Androgen Disruption Activity Reporter (RADAR) assay	Japanese medaka (*O. latipes*)	No	Yes
252	Rapid Estrogen Activity *In Vitro* (REACTIV) assay	Japanese medaka (*O. latipes*)	No	Yes
253	Short-term juvenile hormone activity screening assay (JHASA) using *Daphnia magna*	Crustacean (*D. magna*)	No	Yes

[a]Only if the optional endpoint on sex ratio is included.

In addition, due to differences in life-history traits it can be very challenging to extrapolate the effects of EDCs from freshwater to marine species. Even in situations where comparative effect predictions may be appropriate, the lack of data about basic endocrinology for marine species makes extrapolations uncertain (Del Signore *et al.*, 2016; US-EPA, 2023; Wheeler *et al.*, 2002; MEDIN, 2021). Finally, 16 out of the 34 animal phyla that exist on our planet are exclusively marine (e.g. Echinodermata, Tunicata, Sipuncula, Ctenophora), 16 are common to marine and freshwater

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environments, one phylum is exclusively freshwater (Micrognathozoa) and one is predominantly terrestrial (Onychophora), although there are marine fossil records (Templado *et al.*, 2010).

The regulatory community should therefore embrace the challenge, and marine organisms should be prioritised for the development of laboratory models for representative phyla and life stages (Rosner *et al.*, 2023) that can be used for screening and testing of chemicals on different endocrine modalities. Relevant stakeholders should consider the long-term need for international test method validation and generate opportunities for the global community to work together on accelerating the development of assays to cover the current gaps, their standardisation and validation through the OECD.

Practical and technical challenges include access to well-characterised reference species and good quality marine water. Landmark research infrastructures such as the European Marine Biological Resource Center (EMBRC) in the European Research Infrastructure Consortium roadmap (ERIC, 2022; Piña *et al.*, 2018) are national and international assets that could be a vehicle for establishing screening capability across Europe, standardisation and methods for EDC testing, and production of 'open' data that could be used for regulatory decisions. Ultimately, to safeguard ocean health, a coordinated global agenda is needed for EDC assessment and should be supported and driven by regulatory and societal mandates.

(3) New developments

While evaluation of possible endocrine-mediated effects of chemicals should ideally encompass the universe of biological pathways, endpoints and species, including marine organisms, an important reality is that resources are limited. Further, societal pressures to decrease current levels of animal use for toxicological testing are a pragmatic (and understandable) obstacle to expand EDC tests (Capela *et al.*, 2020). These challenges have been acknowledged both by scientists and regulatory authorities (Scholz *et al.*, 2013; Lilienblum *et al.*, 2008). Consequently, in recent years, there has been an emphasis on the development and implementation of NAMs to assess human health and the ecological risks of EDCs in a more resource-effective and timely manner. NAMs include a variety of methods covering bioinformatics, *in vitro* and *in vivo* tools (for non-sentient animals, or life stages or animals of lower sentience) as well as genomic techniques (Schmeisser *et al.*, 2023; Capela *et al.*, 2020). In the following sections, the case is made for how the strategic use of NAMs, together with increased knowledge about the effects of endocrine disruption in representative marine species, can better address the effects of EDCs in the environment.

(*a*) *Genomic resources, bioinformatic tools and high-throughput testing*

Since sequencing of the first animal whole genome 25 years ago, technological advances have accelerated the availability of genomic resources (Hotaling, Kelley & Frandsen, 2021). Today, there are numerous projects aimed at expanding genomic sequences to cover global biodiversity rather than focusing on canonical models or economically relevant species. Current initiatives in Europe include the Darwin Tree of Life project (WSI, 2023) aiming to sequence the genomes of 70,000 species in Britain and Ireland; the European Reference Genome Atlas (ERGA, 2023) and the recently launched ATLASea initiative to sequence the genome of 4,500 marine species in French waters (CNRS, 2022; ATLASea, 2023).

The anticipated explosion of genomic resources will facilitate comparisons of endocrine pathways in representative marine organisms, allowing predictions of their cross-species conservation (or divergence) and help define putative molecular targets or pathways in the different taxa/species. For example, a comparative analysis of the chemical defensome (the collection of genes and pathways involved in organismal responses to chemical stressors) was conducted across five teleost model species (two freshwater, two estuarine and one marine), revealing that although the majority of these genes have been retained in teleost genomes over millions of years, there are notable differences among species (Eide *et al.*, 2021). Such comparisons can contribute to focus research efforts on relevant endocrine pathways while identifying and acknowledging potential non-homology of systems and functions among taxa/species, and the presence of currently unknown invertebrate endocrine systems. An excellent example of the latter was a study by Fonseca *et al.* (2023), where the evolution of the NRs was reviewed from a chemical susceptibility viewpoint.

These new resources provide a great opportunity for the chemical risk assessment community, exemplified by the recent formation of the International Consortium to Advance Cross-Species Extrapolation in Regulation, ICACSER (LaLone *et al.*, 2021; SETAC, 2022). Currently ICACSER is working on the development of joint case studies to demonstrate applications, strengths, and weaknesses of combined bioinformatics approaches. Among publicly available web-based bioinformatic tools currently explored by ICACSER, a more mature tool currently integrated in regulatory use is the US-EPA SeqAPASS discussed above (LaLone *et al.*, 2016; US-EPA, 2024a). Extrapolation of existing toxicity knowledge and data from model organisms to other species has been the focus of previous publications although marine organisms were not specifically highlighted (Vliet *et al.*, 2023; Ankley *et al.*, 2016; LaLone *et al.*, 2018). Further, in the context of the AOP framework, some publications described how SeqAPASS data can be used to expand the descriptions of the taxonomic domain of applicability (Jensen, Blatz & LaLone, 2023; Haigis *et al.*, 2023) beyond the model organism typically described when collecting empirical evidence for building AOPs (see Section III.3.*b*).

Bioinformatics, artificial intelligence and machine learning have the potential to expand new approaches relative to EDC screening if adequate knowledge and data are available. Increasing the number of sequenced marine genomes and working towards quality annotation of those

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genomes is an important step towards improving and enhancing bioinformatic approaches to address challenges in extrapolation relative to chemical safety evaluations for the protection of marine life. The research community could be a vehicle for targeted prioritisation of cornerstone species for sequencing, filling knowledge gaps for marine phyla (as identified in Fig. 2). This should be followed by analyses from a phylogenetic and biological perspective, integrating functional data and large-scale chemical screening, as recently shown by trials in jellyfish, octopus and ascidians (Takeda, Kon & Quiroga Artigas, 2018; Wang *et al.*, 2022; Kawada *et al.*, 2022; Satake, Osugi & Shiraishi, 2023).

Various types of *in vitro* assays can address data gaps in the effects of EDCs on marine species. Several mammalian-based *in vitro* systems with a high-throughput format have been proposed to overcome testing backlogs that exist for many thousands of chemicals in commerce that might affect endocrine pathways in humans – for example in the US-EPA Endocrine Disruptor Screening Program (2024b). Although most of these assays are derived from mammalian systems (e.g. McPartland *et al.*, 2024), they typically focus on key MIEs such as receptor binding and activation, inhibition of steroidogenic enzymes or binding to transport proteins, that can be quite well conserved, at least across vertebrates (LaLone *et al.*, 2018). In these instances, screening data from existing high-throughput assays may translate directly to assessing potential EDC risks in ecologically relevant taxa including, potentially, some marine species (e.g. Vliet *et al.*, 2023; Ankley *et al.*, 2016; Haigis *et al.*, 2023). Of course, substantial differences might exist in molecular targets of EDCs in mammalian *versus* non-mammalian species, such as the absence of PXR in both cod and stickleback genomes with important implications for xenobiotic detoxification and clearance (Eide *et al.*, 2018). Other differences may necessitate the development of alternative *in vitro* assays with relevant taxon/pathway-specific targets (Villeneuve *et al.*, 2019). As an example, a multiplexed high-throughput-reporter assay was developed using receptor constructs from representative mammalian, avian, reptile, amphibian, and fish species for assessing the potential effects of chemicals that interact with the EAT and PPARγ receptors (Medvedev *et al.*, 2020).

One priority for marine invertebrate species is to investigate the consequences of Ec/EcR signalling pathway disruption, since there is relatively little research or testing outside terrestrial and freshwater arthropods (Crane *et al.*, 2022; Knigge *et al.*, 2021; Sumiya *et al.*, 2014; Toyota *et al.*, 2021; DeFur, 1999). Although the scope of our analysis was NRs, other transcription factors outside the NR superfamily are also key players for endocrine signalling. A key pathway for marine arthropods is the JH/methyl farnesoate (MF) signalling pathway, and a recently identified Methoprene-tolerant (Met) protein, which belongs to the basic-helix–loop–helix/Per-Arnt-Sim (bHLH/PAS) family of transcription factors, was proposed to be a JH/MF receptor in crabs (Liu *et al.*, 2016; Li *et al.*, 2021). Interestingly, the aryl hydrocarbon receptor, a major regulator of xenobiotic metabolism in vertebrates, is also a member of the bHLH/PAS family of transcription factors. Since JHs and Ecs regulate many physiological functions in arthropods, understanding the crosstalk between these signalling pathways is a priority, and has been partially elucidated by reporter assay systems (Jones *et al.*, 2012; Kayukawa *et al.*, 2016, 2017). Marine crustaceans represent the largest biomass of all life on Earth (Ghosh, 2021), but their sensitivity to chemical toxicity is not well studied. Although *Daphnia magna* is commonly used for chemical hazard assessment, the endpoints used in the daphnid test guidelines (Table 3) only provide information on generic developmental endpoints, i.e. growth, moulting or metamorphosis (OECD, 2024, 2018), but generally lack mechanistic detail. An exception is the recently approved Short-Term Juvenile Hormone Activity Screening Assay (OECD, 2024) (see Table 3). *In silico* screening methods as well as other NAMs (e.g. reporter gene assays) developed in different crustacean species (Chan, Chu & Chan, 2019; De Wilde *et al.*, 2013; Song *et al.*, 2017; Mellor *et al.*, 2020; Verhaegen *et al.*, 2010; Toyota *et al.*, 2022) could form the basis of AOPs that establish a direct link between molecular interactions and biological effects from cell to population (Section III.3.*b*).

Another approach that could enhance the assessment of EDCs in marine vertebrates and invertebrates is high-throughput transcriptomics. Studies in mammalian systems have shown that derivation of effect concentrations based on concentration–response modelling of global gene expression, following short-term (1–4 days) exposure, can provide protective toxicity benchmarks predictive of those from much longer-term tests (Thomas *et al.*, 2019). These types of analyses can identify endocrine pathways affected by test chemicals in species of concern and their application has already been explored in ecological hazard assessment using the model oestrogen 17α-ethynylestradiol (e.g. Pagé-Larivière, Crump & O'Brien, 2019; Alcaraz *et al.*, 2021). While high-throughput transcriptomics is unlikely wholly to replace more costly long-term *in vivo* assays for generating effects benchmarks, the approach can address knowledge gaps for data-poor species, including marine organisms, for which genomic data exist. This is of particular relevance for an AOP-based approach (see Section III.3.*b*) covering molecular and morphological endpoints (Fig. 3) to identify the causal link between endocrine activity and adversity of a chemical that is required from a regulatory perspective.

(*b*) *Adverse outcome pathways (AOPs)*

The AOP concept can be useful for organising and integrating disparate toxicological data, including information from NAMs (and NAMs can also aid the development of AOPs), into a framework that enhances the communication of scientific knowledge and supports regulatory decision making (Ankley *et al.*, 2010; Clerbaux *et al.*, 2024). AOPs involve the assembly of scientifically plausible biological pathways that start from a MIE and proceed through various key events at cellular or tissue levels and culminate in adverse

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outcomes in individuals and populations (Fig. 3). As such, AOPs support the use of NAM-derived data (typically molecular and biochemical responses) combined with apical endpoints to make toxicological inferences relevant to risk assessors and regulators.

An open-access knowledge base, the AOP-Wiki (2023; https://aopwiki.org/), provides current AOP status and promotes the collaborative development of AOPs. Many AOPs currently available in the AOP-Wiki database are specific to endocrine-mediated pathways, especially for EAT signalling and steroidogenesis in vertebrates. Some of these endocrine-oriented AOPs are applicable mostly to mammalian species and together with SeqAPASS results provide essential information for marine mammals.

There are also around 20 AOPs relevant to endocrine-mediated responses in fish, although these can be limited to particular life stages. Many of the fish-oriented AOPs concern the potential effects of chemicals on oestrogen or androgen signalling and refer to adult exposure rather than developing animals, although recent efforts have been made to address this limitation (Ankley *et al.*, 2023).

Another shortcoming of the current library of endocrine AOPs in fish is a lack of baseline data concerning their relevance to the life-history traits of marine species. Nonetheless, many components of existing AOPs such as the MIEs and early key events should be applicable to a wide range of fish species, even if actual adverse outcomes at the organismal and population levels potentially differ.

There is also a general absence of AOPs relevant to key endocrine pathways in invertebrate species, although some have been developed recently; for example, Schmid, Song & Tollefsen (2021) describe an AOP focused on chemical disruption of chitin synthesis in arthropods (AOP360). Similarly, there is one AOP for the EcR (AOP4), for which there is much evidence for its applicability in all insects but only moderate evidence for crustaceans, the latter based on the freshwater species *D. magna*. By contrast, there are no invertebrate AOPs specific to the well-conserved RXR, a key NR for a large proportion of the marine metazoan clades as represented in Fig. 2, with high environmental relevance due to TBT toxicity (Castro *et al.*, 2007; Nakanishi, 2008; Lagadic *et al.*, 2018).

AOPs for thyroid hormone system disruption are far better characterised for most vertebrate species, especially mammals (Haigis *et al.*, 2023). However, they require further elucidation for invertebrate taxa that appear to have a functional THR (Morthorst *et al.*, 2023) (Fig. 2), especially marine invertebrates, due to sequence differences as well as the abundance of iodine in their environment.

(c) *Expert knowledge*

The anticipated generation of genomic resources and data-mining tools will need to be organised in a coherent and plausible biological way if it is to be useful for regulatory decisions. This is the conceptual basis of the AOP framework, and it is critical that experts in comparative physiology and endocrinology are involved. A practical illustration of the need for expert interpretation is given by TBT, as it acts on more than one molecular target with different consequences for different taxa (Lagadic *et al.*, 2018). TBT can affect vertebrate reproduction by inhibiting the action of aromatase, a key enzyme in steroid 17β-oestradiol synthesis, or affect invertebrate (gastropod) reproduction by interacting with RXR (Fodor *et al.*, 2020, 2022; McAllister & Kime, 2003; Lesoway & Henry, 2021; Nakanishi, 2008; Castro *et al.*, 2007; Fonseca *et al.*, 2020). Although the androgen receptor (AR) and certain steroidogenic enzymes are absent from the genome of invertebrate species, TBT toxicity causing penis formation (imposex) in female marine snails was assumed for over 25 years to be an effect of excess testosterone *via* inhibition of aromatase. This highlights the need to improve organisation of endocrine knowledge for marine invertebrates and build targeted resources for chemical risk assessment, including toxicokinetic and toxicodynamic data from multiple species, meaningfully to protect and prevent biodiversity loss and to educate all stakeholders.

Generating AOPs for the effects of EDCs on marine species is not an easy task due to the uncertainty generated by the largely undescribed endocrinology of most marine phyla (as indicated by the bibliographic analysis presented in Fig. 2). This prevents an adequate understanding of toxicodynamic interactions between pollutants and animals and thus creates uncertainties in relation to chemical management and regulation, especially for suspected EDCs. Nevertheless, the AOP framework (Ankley *et al.*, 2010; AOP-Wiki, 2023) is an excellent conceptual means to organise and structure existing (and future) knowledge of endocrine systems in representative species of marine taxa, and to promote a move away from assumptions based on vertebrate models.

The advances in sequencing and bioinformatics are also excellent tools for understanding the diversity of the endocrine system from an evolutionary perspective and to guide regulatory decisions in the current data-poor environment. As resources and tools are increasing rapidly, what remains to be established is a biologically plausible sequence of events at the endocrine level that can lead to population-level effects. A harmonised approach covering novel methods (e.g. high-throughput transcriptomics or *in vitro* approaches), which provide a mechanistic understanding of the endocrine activity of potential EDCs, combined with traditional endpoints that allow assessment of adversity, is required to achieve this goal. This is where a slightly different community, comparative endocrinologists, not traditionally engaged with regulatory toxicology, must be co-mobilised. Finally, another essential discipline for understanding impact and assessing risk from EDCs is Ecology; life-history traits and ecological interactions are critical for linking adversity at an individual level to population-level impacts (Fig. 3), with the aim of reducing the impacts of chemical pollution on biodiversity loss (Sylvester *et al.*, 2023).

(4) The importance of monitoring

Science has always been fuelled by human curiosity. Observation of the world and a keen desire to understand it have

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generated questions and reflections that are constantly advancing knowledge. In this context, it is surprising that limited attention is paid to marine monitoring, despite ambitious international goals aiming at ocean protection (Ryabinin *et al.*, 2019; Lamy *et al.*, 2020; UN, 2016). To our knowledge, there is no co-ordinated global effort that collects information about the state of different parts of the ocean, as highlighted in the Ocean Decade Vision 2030 White Paper for Challenge 1, to 'Understand and Beat Marine Pollution' (Hatje *et al.*, 2024). Some regional efforts using harmonised methods and indicators do exist, but these are limited in the chemicals and wildlife indicators that they monitor. The OSPAR (Oslo and Paris Convention for the Protection of the Marine Environment of the North-East Atlantic), for example, has common indicators to assess trends in imposex in gastropods as well as organotins, PCBs and polybrominated diphenyl esters in environmental samples across the northeast Atlantic. It is also developing a new candidate indicator for assessing the status and trends of persistent chemicals in marine mammals (Pinzone *et al.*, 2023). Other international conventions and councils such as HELCOM (the Baltic Marine Environment Protection Commission), MED POL (Programme for the Assessment and Control of Marine Pollution in the Mediterranean) and ICES (International Council for the Exploration of the Sea) are also running monitoring programs, but these are too few to cover significant parts of our ocean and they provide limited information on potential impacts in time and space.

There is particularly limited data from the global south where capacity building and technical support is required to increase monitoring efforts (Hatje *et al.*, 2024). Under the UN Ocean Decade's Vision 2030 there is an ambition to establish a global network of sentinel stations to monitor marine pollution operated by a network of regional laboratory hubs that support data generation, technology transfer and capacity building by 2030. This intends to provide long-term data to enable evaluation of temporal trends and to understand the effectiveness of control and remediation actions (Hatje *et al.*, 2024). The associated priority chemical list for global monitoring should consider which EDCs should be included. The European Union has an important framework at its disposal due to the Water and Marine Strategy Framework Directives (WFD and MSFD, respectively), but given that marine monitoring programmes are not compulsory, the efforts of the member states to achieve a good environmental status have been scattered, uneven and are still incomplete in terms of monitoring, reporting and EDC effect assessment (Tornero, Boschetti & Hanke, 2018; Vasilakopoulos *et al.*, 2022; James *et al.*, 2023). This is despite the availability of several biomarkers to monitor adverse effects, including some specific for EDCs, which are key in integrating chemical and biological assessments of contaminant impacts in marine environments (Vasilakopoulos *et al.*, 2022; Tornero *et al.*, 2018; Lyons *et al.*, 2017; Kanwischer *et al.*, 2022; Hylland *et al.*, 2017; SGIMC, 2011; Vethaak *et al.*, 2017; Rohr, Salice & Nisbet, 2016; Marigomez *et al.*, 2006).

IV. RECOMMENDATIONS

As a result of our critical review and the gaps and priorities identified in the Model-EDC network and workshop series that underpinned it, a list of generic and specific stakeholder recommendations was produced, and is summarised in Fig. 4.

V. CONCLUSIONS

(1) For marine systems, (*i*) a significant body of knowledge (albeit incomplete regarding species diversity and signalling pathways other than EAT modalities and steroidogenesis) is available for a minority of taxa, i.e. mostly fish; (*ii*) the basic endocrine and endocrine disruption knowledge for most invertebrate taxa is minimal; and (*iii*) the research effort to mine existing information in comparative endocrinology to guide the development of international test guidelines for effective markers for testing and monitoring programs is extremely low and uncoordinated.

(2) The absence of EDC tests for species representative of marine ecosystem diversity is a concern and of critical importance for achieving UN sustainable development goals such as life under water, food security, climate change mitigation and improving the Blue Economy in general.

(3) SeqAPASS and other bioinformatics approaches could be used to define the biologically plausible taxonomic domain of applicability for the MIEs and early key events of existing AOPs, with a focus on marine organisms. Conservation of biological pathways relevant to more apical outcomes may need further definition for these species; however, such extrapolation methods can inform focused testing to fill knowledge gaps and ensure efficient use of limited resources.

(4) The AOP framework is a sensible means of organising and enhancing knowledge of (neuro) endocrine pathways, reducing limitations relative to the taxonomic domain of applicability. Sequencing and computational tools are indispensable for identifying convergent and divergent endocrine pathways and coupled with an evolutionary and physiological perspective, can guide regulatory decisions in the current data-poor environment. Such molecular analyses should always be combined with analyses at higher levels of biological organisation (see Fig. 3) to demonstrate the translation to population-relevant effects.

(5) In terms of priorities in addressing knowledge gaps, we hope that this and previous reviews (Fig. 4; Crane *et al.*, 2022; Santos *et al.*, 2018; Langlois *et al.*, 2022; Martyniuk *et al.*, 2022; Rosner *et al.*, 2023; Ford & LeBlanc, 2020; Coady *et al.*, 2017) contribute towards expanding and organising existing knowledge in a meaningful way for chemical hazard characterisation, avoiding past mistakes caused by superficial interpretations of the evidence. For example, highly conserved molecular targets for disruption of endocrine signalling include GPCRs and the NO pathway

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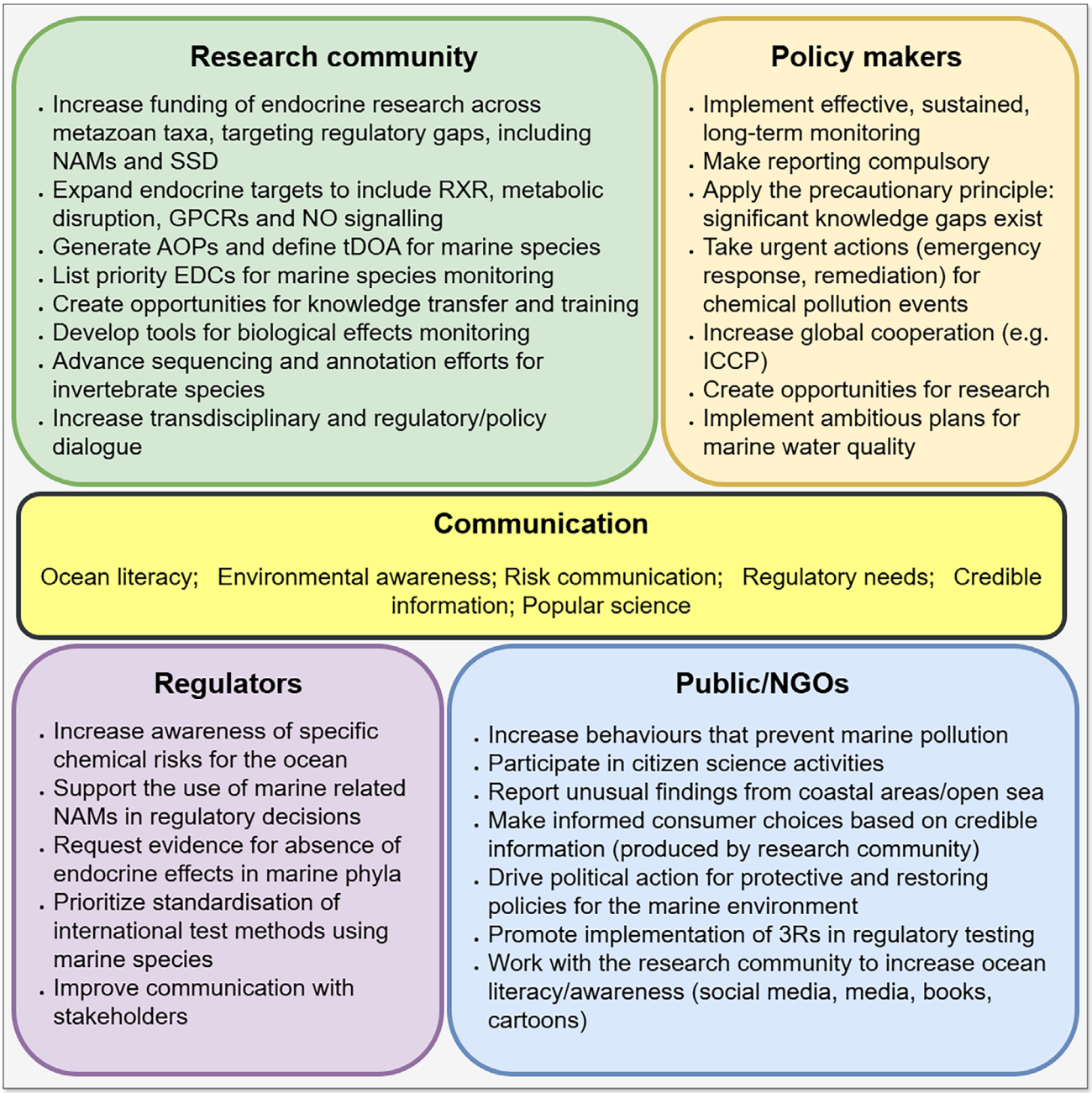

Fig. 4. Actions recommended for stakeholders, and the major priorities and approaches identified by the Model-EDC network, to monitor and protect marine life from endocrine-disrupting chemicals (EDCs). AOP, adverse outcome pathway; GPCR, G-protein coupled receptor; ICCP, Intergovernmental Panel on Climate Change; NAM, new approach methodology; NGO, non-governmental organisation; NO, nitric oxide; RXR, retinoid X receptor; SSD, Species Sensitivity Distribution; tDOA, taxonomic domain of applicability; 3Rs, Reduce, Reuse and Recycle principles.

(Fig. 2), both of which are completely absent from current test guidelines or those under development.

(6) Until some critical knowledge gaps are closed along with the misconceptions they caused in the past, vigilant monitoring programmes and the application of the precautionary principle in regulatory chemical management is essential. The UN Decade of Ocean Science for Sustainable Development (2021–2030) having identified marine pollution as a key challenge for our oceans, provides an additional impetus for an international co-ordinated action to fill in the identified knowledge gaps and to create tools for protecting marine life from pollution from EDCs.

(7) The high biodiversity that the ocean harbours, the unique and sensitive nature of marine life and the

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dependence of terrestrial life forms on the ocean must overcome practical issues and take priority for greater protection of the marine biosphere from the effects of pollutants, which inevitably end up and accumulate in the ocean.

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VIII. SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Questions posed to each working group (Testing or Monitoring working groups) in the workshop Model-EDC editions 1 and 2 (see Section II for more details).
Table S2. Summary of bibliographic search results used to create Fig. 2 concerning knowledge on the best-documented molecular targets and adverse biological effects of endocrine-active compounds, in 20 taxa representative of marine biodiversity (selected from the WoRMS database). The detailed search strings used in *PubMed* searches are supplied in Appendix S1 in the online Supporting Information.
Table S3. Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) full reports for all 18 endocrine-relevant protein targets queried in the SeqAPASS tool.
Table S4. SeqAPASS results *versus* the WoRMS database.
Appendix S1. Detailed initial strings used for the PubMed searches, used to create Fig. 2 concerning knowledge on the best-documented molecular targets and adverse biological effects of endocrine-active compounds, in 20 taxa representative of marine biodiversity (selected from the WoRMS database).

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