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The ecotoxicology of marine tributyltin (TBT) hotspots: A review

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ABSTRACT

Tributyltin (TBT) was widely used as a highly efficient biocide in antifouling paints for ship and boat hulls. Eventually, TBT containing paints became globally banned when TBT was found to cause widespread contamination and non-target adverse effects in sensitive species, with induced pseudohermaphroditism in female neogastropods (imposex) being the best-known example. In this review, we address the history and the status of knowledge regarding TBT pollution and marine TBT hotspots, with a special emphasis on the Norwegian coastline. The review also presents a brief update on knowledge of TBT toxicity in various marine species and humans, highlighting the current understanding of toxicity mechanisms relevant for causing endocrine disruption in marine species. Despite observations of reduced TBT sediment concentrations in many marine sediments over the recent decades, contaminant hotspots are still prevalent worldwide. Consequently, efforts to monitor TBT levels and assessment of potential effects in sentinel species being potentially susceptible to TBT in these locations are still highly warranted.

1. Introduction

The strong antifouling (AF) effect of trivalent organotin (OT) compounds was discovered in the 1950s by a Dutch research group led by van der Kerk and Luitjen (1954) and this led tributyltin (TBT) to become the main biocidal ingredient for marine AF paint products, primarily in the form of bis(tributyltin)oxide (TBTO) (IPCS, 1990). In the 1960s, early versions of TBT AF paints for ship hulls were of the "free association" type which allowed a free and rapid release of AF agents over a relatively short time. In the "self-polishing copolymer" paints, which were introduced in the 1970s, TBT was chemically bounded to a polymer backbone and this enabled a slow, controlled release of TBT which maintained the AF effect longer, typically several years (Omae, 2003; Schultz, 2007; Santillo et al., 2008; Amara et al., 2018). In 1980, the annual global use of TBT agents in marine AF paints was about 2-3 x 10^3 tonnes (IPCS, 1990). TBT was also used in other AF applications which contributed to the total release of TBT in marine ecosystems. For example, in Norway about 14 × 10^4 kg of OTs were used in 1986 for AF treatment of nets and sea pens at approximately 600 fish farms (Linden, 1987). In addition, TBT was heavily used as a biocide in a range of other applications such as cooling systems, wood pulping, leather processing, wood preservation processes, and textile treatments (IPCS, 1990). The total use of TBT AF applications resulted in significant TBT pollution in coastal areas all over the world (Hoch, 2001; Sousa et al., 2014) and at the most contaminated sites, the TBT hotspots, the contamination has persisted even until today (see paragraph 4).

TBT has by some ecotoxicologists been ranked as the most hazardous anthropogenic chemical ever to be deliberately released in large quantities to the environment. Thousands of studies about the environmental fate and effects of TBT have been reported during more than 50 years of research, and this field still attracts considerable attention, much due to the actions of TBT as an endocrine disrupting compound with the capacity to influence biological fitness (e.g., growth, development and reproduction) in sensitive species groups. In this regard, focus will be on identifying molecular mechanisms and the Modes of Actions (MoA) which TBT have on sensitive species, and how these mechanisms may be relevant in the toxicity progression also for other marine species.

In this review, we provide a short historical and ecotoxicological summary of the antifoulant biocide TBT, with emphasis on its role as an endocrine disrupting compound. We examine the coastal sites in Norway with the highest known levels of TBT pollution in marine sediments, and we compare these to similar locations found in other countries. We

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then assess the knowledge status on TBT ecotoxicity in marine systems and in various bioindicator organisms, but with an emphasis to the imposex effect in marine neogastropod snails, as this is the best-known ecotoxicological effect of TBT pollution and the main reason why the use of TBT AF paints became banned globally. In the final part, we examine the possible role that marine TBT hotspots may have for continued, mechanism-oriented ecotoxicological research on TBT, especially with relation to the endocrine disruption effect phenomena in different species, including humans.

2. Fate, effects and ban of TBT antifouling products

The environmental behaviors of TBT AF compounds in marine systems are complex. Being ionizable, their speciation is strongly affected by the pH of seawater, but under the mild basic conditions of normal seawater TBT is expected to occur mainly as uncharged hydroxyl complexes (TBT-OH) and behave relatively similar as hydrophobic organic contaminants (Brändli et al., 2009). In seawater, TBT-OH has an acid-dissociation constant (pK_a) of 6.3 to the TBT+ cation (Arnold et al., 1997) and cations of TBT, and other OTs, will be attracted and adsorbed to suspended particles with net negatively charged surfaces, such as organic matter and clay (Arnold et al., 1997; Weidenhaupt et al., 1997; Meador, 2000; Hoch, 2001). These fate processes make TBT accumulate and persist in marine sediments, especially if the sediment is fine-grained, high in organic content (high Total Organic Carbon, TOC) and with low/depleted levels of oxygen (i.e., hypoxic and anoxic sediment conditions). In well-oxygenated surficial sediments, TBT typically has a half-life of 1–5 years, but in fine-grained, O2-depleted - anoxic sediments the half-life can extend to several decades (Dowson et al., 1993, 1996; De Mora et al., 1995; Berge et al., 2006; Langston et al., 2015). Studies show that the sediment/porewater partition coefficient (Kd) for TBT correlate positively to the TOC content of the sediments (Langston and Pope, 1995). The TBT content is therefore often normalized to sediment TOC levels, typically 5% TOC (Abraham et al., 2017). As TBT bound to sediments leak slowly back into the seawater, TBT hotspot sediments represent a long-term secondary source for re-contamination of the water column in these areas, unless active sediment remediation measures, such as dredging and capping, are performed. TBT has been shown to bioaccumulate in all aquatic taxa, with molluscs showing highest bioconcentration and bioaccumulation factors that may result in tissue burdens ranging up to 7 μg g^{-1} (wet weight) (Laughlin, 1996).

The first signs of TBT causing adverse impacts in non-target marine animals came in the early 1970s when scientists started to notice developmental disorders in oysters (*Ostrea edulis* and *Crassostrea gigas*) and in prosobranch neogastropod snails such as dogwhelk (*Nucella lapillus*), mud snails (*Nassarius obsoletus*), and oyster drill (*Ocenebra erinaceus*). The disorders were particularly prevalent at coastal locations near busy boating and shipping activities (Blaber, 1970; Smith, 1971, 1981; Waldock and Thain, 1983; Alzieu et al., 1986; Gibbs, 1993; Matthiessen and Gibbs, 1998; Alzieu, 2000; Sousa et al., 2014). In oysters, a shell thickening and decreased growth phenomenon was noted by oyster farmers in Arcachon Bay (France) as the first place. It gave considerable losses for the local shellfish industry as affected oyster batches were literally unsellable on the market (Waldock and Thain, 1983; Higuera-Ruiz and Elorza, 2011; Horiguchi, 2009). Later studies found that the oyster shell thickening effect occurs when TBT concentrations in seawater exceed 2 ng.L^{-1} (Langston, 2020). In the TBT affected neogastropods, abnormal females exhibited non-functional male-like sexual tissues/organs such as a vas deferens and even a penis-like organ grown superimposed over the female sexual tissues/organs (Fig. 1). This abnormal condition was named “imposex”

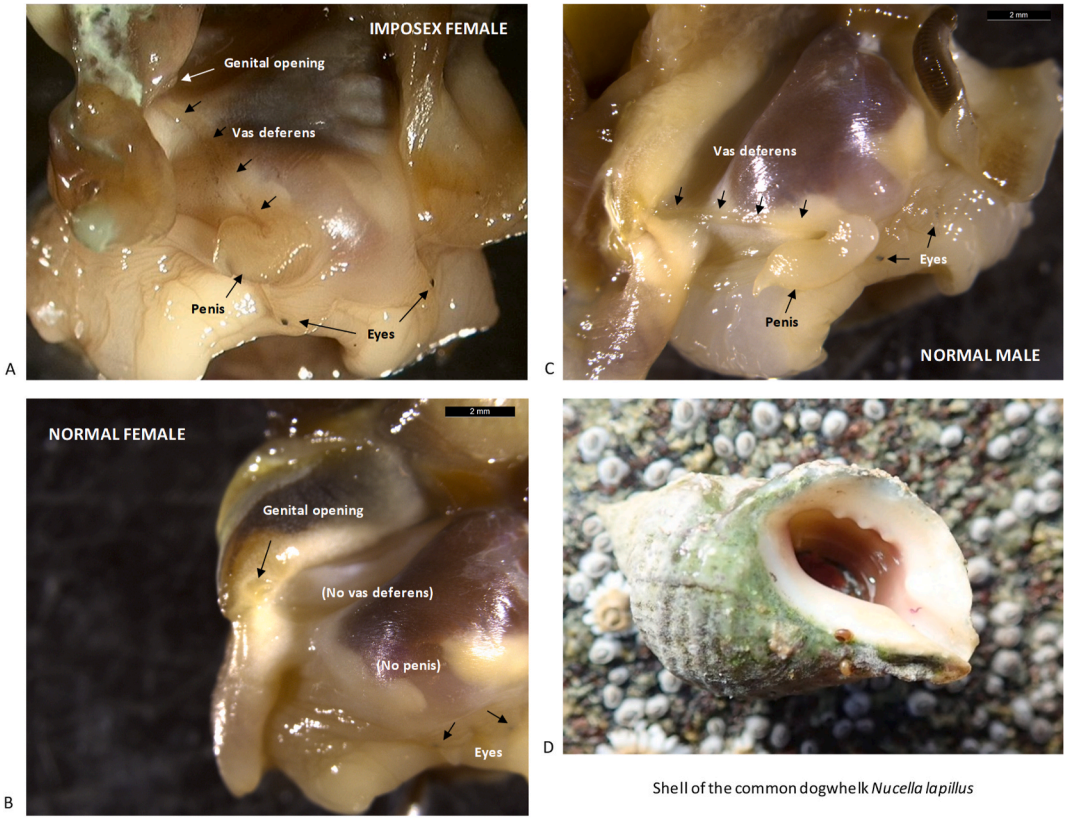


Fig. 1. Imposex in female of common dogwhelk *Nucella lapillus* (A) compared to the normal sexual characteristics of females (B) and males (C) of the same species. Panel A shows imposex at stage 4 according to Oehlmann et al. (1991), with a continuous vas deferens and a penis superimposed on the female sexual characters. Panel D shows a typical dogwhelk shell. Included scale bars are 2 mm. Photos: NIVA.

(Smith, 1971). Detailed studies revealed that the developing females acquired infertility in the advanced stages of imposex (Oehlmann et al., 1991), eventually causing the affected populations to decline and even become extinct (Blaber, 1970; Smith, 1981). Controlled exposure-effect studies in the laboratory found *N. lapillus* to be extremely sensitive with young females developing imposex traits when exposed to TBT concentrations as low as 1 ng.L^{-1} in seawater (i.e., 0.001 parts per billion) and with affected females becoming infertile at TBT concentrations above 3–5 ng.L^{-1} (Bryan et al., 1986; Gibbs et al., 1987, 1988; Evans et al., 1996; Matthiessen and Gibbs, 1998; Birchenough et al., 2002b). Field surveys in the 1980s and 90s demonstrated the imposex phenomenon to be surprisingly widespread, occurring even at locations relatively far from the busiest shipping or boating areas, and being found in several hundred neogastropod species worldwide (Vos et al., 2000; Shi et al., 2005; Titley-O'Neal et al., 2011b; Grilo and Rosa, 2017). The sum of studies on marine molluscs and TBT have demonstrated TBT contaminants may cause a range of different toxicities, including increased larval mortality (IPCS, 1990), inhibited egg development (Bryan and Gibbs, 1991), induced vitellogenin gene expression (Park et al., 2012), reduced survival of hatchlings (Leung et al., 2007), altered population sex ratios (Sousa et al., 2005a), induced DNA damage (Gabbianelli et al., 2006; Hagger et al., 2006; Martinovic et al., 2016), increased expression of heat-shock proteins (Clayton et al., 2000), and female "intersex" condition in certain mesogastropoda species such as the common periwinkle *Littorina littorea* (Bauer et al., 1995; Matthiessen and Gibbs, 1998; Oehlmann et al., 1998; Rank, 2009).

The discovery of TBT AF systems causing widespread contamination and adverse effects in nontarget molluscs caused much concern and led to initiatives to initiate restrictions of OT based AF paints in the late 1980s. The earliest ban was implemented in France in 1982 regarding all leisure boats and small commercial vessels shorter than 25 m (Alzieu et al., 1986; Abel, 1990; Santillo et al., 2008). In the subsequent years, OSPAR countries committed themselves to phase out OT based marine AF paints (OSPARCOM, 2009) and in 1999, the Marine Environmental Protection Committee of the International Maritime Organization finally supported the full phase-out strategy worldwide during the five-year implementation period between 2003 and 2008 (Champ, 2000). Documentation from many field surveys and monitoring programs suggest the ban against TBT AF paints has largely been effective, although even after 2008 some suppliers continued to produce and sell these products in several countries (Turner and Glegg, 2014), even at the present time (Paz-Villarraga et al., 2022; Uc-Peraza et al., 2022a).

3. Trends of marine TBT effect monitoring

Organotins in sediments and TBT specific effects became mandatory determinants of the OSPAR Co-ordinated Environmental Monitoring Programme (CEMP) from 2003 onwards (OSPAR Agreement, 2010-1) and guidance for these activities is provided in Technical annex 3 of the JAMP Guidelines for contaminant-specific biological effects monitoring (OSPAR, 2008). OSPAR CEMP (2009) developed a six-class quality scheme (class A-F) for assessing TBT-specific biological effects in five marine gastropods (*Nucella*, *Nassarius*, *Buccinum*, *Neptunea*, *Littorina* spp), including effect parameters (imposex/intersex) and TBT contamination data for seawater and sediments to enable an integrated (exposure-effect) assessment in these bioindicators.

Many marine TBT effect monitoring programs conducted later than the early 1990s have documented the existence of TBT pollution and neogastropod imposex effects in coastline seas in all continents, i.e., in Europe (Ten Hallers-Tjabbes et al., 1994; Følsvik et al., 1999; Svavarsson, 2000; Svavarsson et al., 2001; Chiavarini et al., 2003; Vasconcelos et al., 2010; Laranjeiro et al., 2018), Africa (Marshall and Rajkumar, 2003), Asia (Horiguchi et al., 1994, 1997; Tan, 1997; Bech, 2002), Oceania (Smith, 1996), North America (Gooding et al., 2003), and South America (Gooding et al., 1999). The imposex effect monitoring programs have most often targeted *N. lapillus* as the monitoring organism due to its cosmopolitan distribution and its extreme sensitivity and vulnerability to TBT. As *N. lapillus* has internal fertilization, lay eggs in capsules fixed to the bottom, hatch as juvenile miniature versions of the adult (i.e., no free-swimming planktonic larvae), they are particularly vulnerable to reductions of fecundity as local populations have limited potential for recovery based on immigration. Other whelk species closely related to *N. lapillus*, such as netted dogwhelk in the genus *Nassarius,* which also have been extensively used for TBT/imposex studies, e.g. Stroben et al. (1992), Barroso et al. (2002); Cuevas et al. (2014); Rial et al. (2018); Cacciatore et al. (2018), Ruiz et al. (2018), are less vulnerable to local population extinctions as they have planktonic larvae.

The peak global usage of TBT in marine AF products occurred most likely sometime during the 1980s, but significant variation among countries is likely due to variable timing and strictness of TBT regulations. After effectuation of TBT bans, marine effect monitoring programs with dogwhelk as bioindicators have largely shown declining imposex trends as well as positive recoveries of local gastropod populations, e.g., (Smith, 1996; Birchenough et al., 2002a; Schøyen et al., 2019). However, in many coastal TBT hotspots, high pollution levels have been shown to persist, including in Europe (Sousa et al., 2005b, 2009; Smith et al., 2006; Gibbs, 2009; Giltrap et al., 2009; Galante-Oliveira et al., 2011; Furdek et al., 2012; Nicolaus and Barry, 2015; Langston et al., 2015; Anastasiou et al., 2016; Ruiz et al., 2018; Cacciatore et al., 2018; Laranjeiro et al., 2018; Filipkowska and Kowalewska, 2019), North America (Coray and Bard, 2007; Tallmon and Hoferkamp, 2009; Titley-O'Neal et al., 2011a), South America (Toste et al., 2011; Rossato et al., 2016; Batista et al., 2016; Mattos et al., 2017; da Costa et al., 2017; Castro et al., 2018), Asia (Choi et al., 2013; Ho and Leung, 2016; Lam et al., 2017; Kim et al., 2017); and Africa (El Ayari et al., 2018). Both historical and recent uses of organotin based AF have been identified as sources for continued high contamination in these hotspot areas. Hull maintenance of leisure boats that earlier have been treated with TBT paint may also represent an important source, e.g., as shown by Ytreberg et al. (2016). TBT contamination has also been linked to other sources. For example, Diez et al. (2002) found TBT at levels of 244 ng.g^{-1} in a sewage discharge and pointed to this as an important secondary source of TBT to the marine environment. The study by Cornelissen et al. (2008) found significant levels of TBT (median 140 μg.kg^{-1} d.w.) in urban runoff particles far away from any yard or maritime activity and they suggested long-lasting house paint and use of TBT as timber preservative to be the possible sources.

4. Marine TBT hotspot locations in Norway versus elsewhere

In Norway, TBT became in the early 1990s one of the mandatory determinants for sediment pollution monitoring surveys (Norwegian Environment Agency, 2018). A considerable amount of sediment TBT data has subsequently been registered in the national Vannmiljø ["Aquatic environment"] database.[2] Olsen et al. (2021) used this database to conduct a ranking of marine sediment locations along the Norwegian coastline for their levels of different priority pollutants. For TBT, the study identified 95 locations (Fig. 2) for which the highest detected TBT levels in surficial sediments were greater than a maximum tolerable risk (MTR) limit of 35 μg.kg^{-1} d.w., i.e., a special limit defined for management of TBT polluted sediments (Norwegian Environment Agency, 2018). TBT data from the top nine locations are listed in Table 1. Among these sites, the highest TBT mean concentration values per site exceeded 30 000 μg.kg^{-1} d.w. whereas the highest TBT concentrations detected exceeded 100 000 μg.kg^{-1} d.w. (Table 1). For comparison, TBT concentration data from highly polluted sediments in other countries are shown in Table 2, although making simple comparisons of such hotspots can be challenging due to differences in

[2] The Norwegian Vannmiljø ["Aquatic environment"] database.

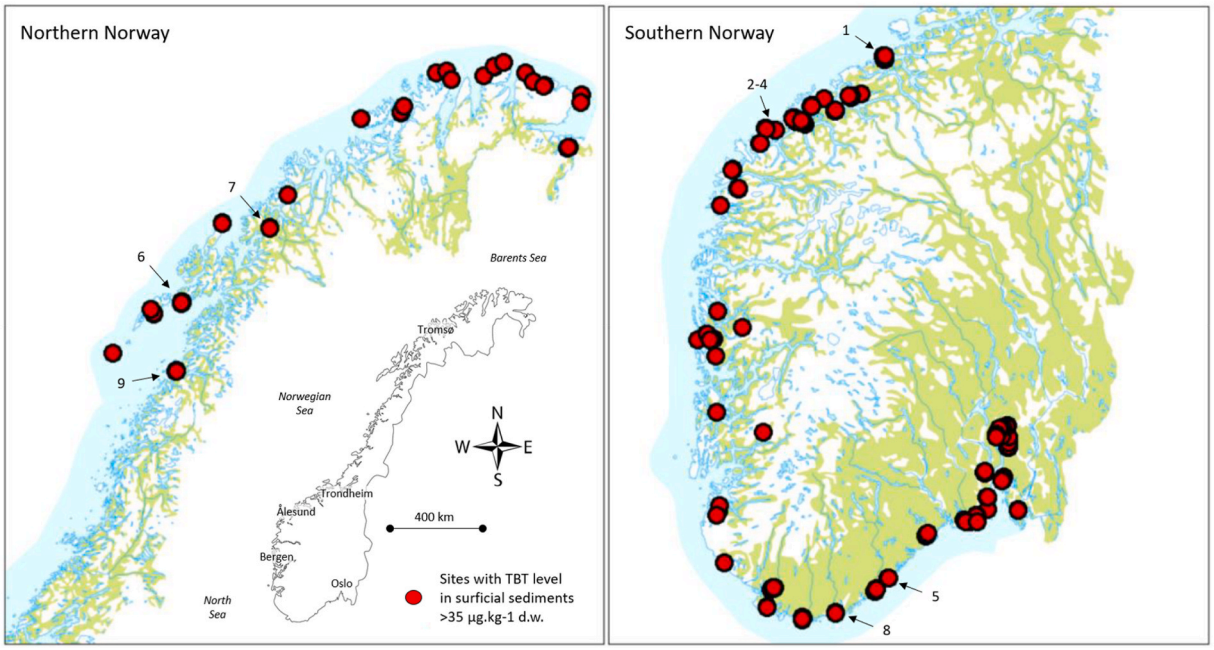


Fig. 2. Map showing the geographical distribution of TBT hotspots along the Norwegian coastline, highlighting 95 costal sites (red dots) where TBT contents in surficial sediments have been quantified (after 2006) at concentrations above the maximum tolerable risk (MTR) limit of 35 µg.kg^{-1} d.w., according to data registered in the *Vannmiljø* database. Arrows and numbers 1–9 indicate the top nine sediment sites listed in Table 1. Data and map reproduced from Olsen et al. (2021) with modifications.

Table 1
The top nine TBT hotspots in Norway based on data registered in the *Vannmiljø* database after 2007. TBT concentrations are shown as min, mean, max measurements data in marine surficial sediments. The data were obtained from the database mid-2021. N = number of samples analyzed per sediment location.

Site*	Location (and city/place) in Norway	Depth in sediment (cm)	Sediment TBT (µg.kg^{-1} d.w.)			N	Study report
			Min	Mean	Max		
1	Kristiansund – inner harbor	0–10	48.1	30 088	79 800	8	Olsen et al. (2021)
2	By Fiskerstrand yard (Sula, Ålesund)	0–2	1270	29 433	101 000	11	Fagerhaug (2009)
3	Åregjerdevågen (Sula, Ålesund)	2–4	210	25 270	196 600	10	Haveland and Hestholm (2008b)
4	Eidssundet by Vegsund yard (Sula, Ålesund)	2–4	2500	23 962	110 000	8	Haveland et al. (2008a)
5	Vikkilen fjord - inner part	0–5	770	8226	93 000	15	Bakke et al. (2008)
6	Svolvær harbor	0–10	0.04	8160	90 000	89	Olsen et al. (2021)
7	Gisundet by Finnsnes	0–10	0.7	6217	55 900	9	Olsen et al. (2021)
8	Kristiansandsfjord - inner part	0–10	1.0	4365	60 000	19	Olsen et al. (2021)
9	Bodø harbor	0–10	1.0	958	48 600	95	Kaurin et al. (2015)

* Geographical locations of sites 1–9 are indicated at the map in Fig. 2.

methodologies (discussed later). Nevertheless, a comparison of these data suggests Norwegian TBT hotspot sediments to be comparable to the most contaminated TBT hotspots internationally, and not surprisingly, the TBT hotspots are typically located close to shipyards or within harbor/port areas. This spatiality confirms TBT AF paint and ship hulls maintenance operations to be key sources for this contamination. However, it is striking to note that while the TBT hotspots in other countries are found in conjunction with major ports and shipyards, the typical Norwegian hotspots are found in conjunction with relatively small yards and harbor/port locations (e.g., fishing villages), spread literally all along the long coastline (Fig. 2). The surficial sediment strata that have formed after the TBT AF paint ban would be expected to contain lower TBT levels than the older strata found underneath. TBT contamination levels in historical layers of sediment core samples have been studied in the two fjords Oslofjord and Drammensfjord in Norway (Dolven and Alve, 2018; Ekeroth et al., 2020), which both are fjords that have significant shipping activities. The TBT levels showed a gradual increase through the 1960s–70s, towards peak concentrations detected in sediment strata from the 1980s–90s, with Drammensfjord showing TBT levels above 2500 µg.kg^{-1} d.w. at the highest, followed at both places by significantly declining levels in sediments strata from the recent decades, but with the average TBT concentration in the youngest sediment layers in Drammensfjord still being significantly above the MTR limit of 35 µg.kg^{-1} d.w. (Dolven and Alve, 2018; Ekeroth et al., 2020). The peak TBT concentrations, recorded in Drammensfjord, were at a level similar to the highest concentrations detected in Rotterdam harbor during the 1990s, as reported by Stronkhorst (1996) who found TBT concentrations up to about 2100 µg.kg^{-1} d.w. in sediments from the inner and most polluted part of the harbor.

The presence of abraded TBT antifouling paint particles (TBT APPs) is likely to be a key reason why sediments close to shipyards may have extreme levels of TBT and also why TBT monitoring data from the same geographical area may vary so much (Table 1, Table 2). The relevance of TBT APPs for ecotoxicological studies in marine TBT hotspots was highlighted by Elgethun et al. (2000) and this issue has recently gained increasing attention, e.g. (Turner, 2010; Eklund et al., 2014; Choi et al., 2014; Batista-Andrade et al., 2018; Soroldoni et al., 2018; Muller-Karanassos et al., 2019; Abreu et al., 2020; Alshemmari et al., 2020; Soroldoni et al., 2020; Abreu et al., 2021; Muller-Karanassos et al., 2021; Soon et al., 2021; Soroldoni et al., 2021; Moreira et al., 2021; Torres and

Table 2
Examples of TBT concentration in hotspots from countries outside Norway. The shown locations are ranked from high to low levels based on the maximum levels of TBT or sum butyltins.

Site	Depth in sediment (cm)	Sediment TBT concentrations (μg.kg^{-1} d.w.)	Study report
Hong Kong shipyards	0–2	Maximum 129 320[a] Average median 1220[a]	Ko et al. (1995)
Ulsan Bay shipyard, South Korea	0–2	Max 112 484[a]	Shim et al. (2002)
Kelly Boatworks-Shipyard, USA	Surficial sediment[c]	Max (with paint chips) 68 613 Without paint chips 1196	Elgethun et al. (2000)
Shipyard, Portland and Boothbay Harbor, USA	0–2	Maximum: 30 256[a]	Page et al. (1996)
Falmouth Dockyard, Port Pendennis, UK (1997 survey)	Surficial sediment[c]	Maximum: 20 700	Langston and Burt (2007)
Caldera Region, Chile	0–2	Means: 4015–16 932[b]	Mattos et al. (2017)
Korean coastal waters	0–4	348–9576 highest concentrations for each sampling year	Choi et al. (2009)
Port of Gdańsk and Gdynia, Poland	Surficial sediment	14–8100 (sum butyltins), highest mean TBT: 4733	Filipkowska and Kowalewska (2019)
Imbituba Harbor, Brazil	0–10	Highest mean (n = 3): 9183[b]	de Oliveira et al. (2010)
Toulon Bay, Mediterranean coast of France	0–5	Maximum: 6600[a]	Pougnet et al. (2014)

[a] TBT analysis results originally expressed on the basis of tin (Sn) content are converted to TBT content by multiplication by a factor of 2.44, but not normalized to TOC.
[b] TBT values normalized to 5% TOC by multiplying the measured value with 5 and then divided by the actual TOC content of the sediment where TOC was measured.
[c] Not specified.

De-la-Torre, 2021; Turner, 2021; Lopez et al., 2022; Sparks and Awe, 2022; Uc-Peraza et al., 2022b). Several studies express interest for TBT APPs as ecotoxicologically relevant forms of secondary microplastic particles, i.e., being synthetic polymers or resins which carry high relative concentrations of toxic biocidal compounds that have the capacity to cause adverse effects in many sediment related species, e.g. (Muller-Karanassos et al., 2021; Torres and De-la-Torre, 2021; Turner, 2021; Sparks and Awe, 2022), making the occurrence of TBT APPs in coastal, marine environments a major environmental concern. Regrettably, surveys in Norwegian hotspots, have typically not systematically considered the issue of TBT APPs, which is a weakness of the TBT data registered in the Vannmiljø database.

5. Environmental regulation and management of marine TBT hotspots

Sediment remediation measures, such as dredging and capping, are common management actions for improving the quality status of marine TBT hotspot sediments. Such operations are very costly, and their implementation must therefore be based on appropriate environmental regulations. In this context, national guidelines which instruct the processes of ecological risk assessment, quality classification and remediation management of polluted sediments are important. These regulations and guidelines at the national level should also comply with transnational agreements and mechanisms such as the EU Water Framework Directive (WFD) and the Marine Strategy Framework Directive (MSFD), which have the superior goals of establishing good environmental status (MSFD) and good ecological status (WFD) throughout European waters. In Norway, the first quality assessment and classification system for marine systems was implemented in 1997, with a five-class scheme based principally on chemical concentrations of selected priority pollutants quantified in specified marine matrices (water, sediment or biota) (Molvær et al., 1997). In 2007, the Norwegian Environment Agency (NEA) replaced this concentration-based scheme with a risk-based (or effect-based) quality classification scheme, which defined quality classes (Table 3) based on the risk/likelihood for ecotoxic impacts of priority contaminates and the use of safety factors to compensate for intrinsic uncertainties that existed regarding their possible long term ecological effects. Due to the high toxicity of TBT to several non-target marine organisms, the effect/risk-based quality classes for this sediment contaminant were set to exceptionally low concentration levels (Table 3). These strict quality classes represented a challenge, firstly as analysis of TBT concentrations to such low levels with required precision and accuracy is almost technically unfeasible, as the LOQ for sediment TBT analyses for most chemical analysis laboratories is 1 μg.kg^{-1} d.w. Secondly, the classes were defined so low that surficial sediments, obtained even from relatively pristine locations along the Norwegian coastline, would most likely not meet the "good quality" demand based on their TBT content. To untie this Gordian knot, NEA therefore decided to implement a preliminary and more liberal quality classification scheme for "management purposes" especially for TBT concentrations in marine sediments (Table 3), and also to define the special MTR limit for management of TBT polluted sediments at 35 μg.kg^{-1} d.w. (Norwegian Environment Agency, 2018). If sediments exceeded this MTR limit, it will trigger demands for a more thorough risk assessment study and secondly potentially lead to demands for active sediment remediation actions. Large scale sediment remediation projects have now been initiated or already performed in some of the worst Norwegian TBT hotspots, while others are being planned. Further descriptions of these efforts fall beyond the scope of this paper. But interestingly, also the EU WFD has seen the rationale for implementing quality standards for TBT pollution in marine surficial sediments that are more realistic. In a report to the EU WFD, Sahlin and Ågerstrand proposed that a sediment based quality standard for TBT of 1.6 μg.kg^{-1} d.w. (normalized to 5% TOC level) would most likely be protective for sediment dwelling species in both freshwater and marine systems (Sahlin and Ågerstrand, 2020).

6. Toxicity mechanisms of TBT induced imposex in neogastropoda

The discovery of imposex in the early 1970s created a need for clarifying the effect mechanisms and the Modes of Actions (MoA) involved. The studies were in the earliest phase preferably addressing possible inhibitory and modulative interactions of TBT to metabolic pathways and detoxifying enzyme systems in different model species, particularly including the cytochrome P-450 dependent monooxygenase system and glutathione *S*-transferases, e.g., (Fish et al., 1976). Eventually, the research narrowed in on endogenous hormones regulation systems, e.g., (Lee, 1991), and later to control mechanisms of gene transcription mediated via intracellular and nuclear receptors, e.g., (Evans, 1988). During the following years of research, three major imposex MoA hypotheses have been described, namely: the increased testosterone MoA, the APGWamide neuropeptide activation MoA, and the retinoid X-receptor (RXR) agonism/activation MoA. An overview of key research reports that have been in support of each respective imposex MoA is shown in Table 4, and a brief outline of these three areas of research is described next.

The first major attempt to elucidate the imposex MoA was the "increased testosterone" or "increased androgen" hypothesis which alleged that TBT acted by inhibiting the enzymatic conversion of androgens to estrogens by the P-450-dependent aromatase system (CYP19A), causing a shift in the androgen-estrogen balance in females, and thereby making them start to develop and grow male sexual

Table 3
Effect/risk-based and management-based quality classification system for TBT concentrations in sediments according to the Norwegians guidelines for risk assessment of contaminated sediments (M-409 & M-1132/2018[a]) and the Norwegian quality standards for water, sediment and biota (M-608/2016-revised 2020[b]).

Sediment quality scheme on TBT concentration	Unit	Class I Background	Class II Good	Class III Moderate	Class IV Bad	Class V Very bad
Effect/risk-based	$\mu g.kg^{-1}$ d.w.		0–0.002	0.002–0.016	0.016–0.032	>0.032
Management based[c]		0–1	1–5	5–20	20–100	>100

[a] Norwegian Environment agency - Guidelines for risk assessment of contaminated sediments.
[b] Norwegian Environment agency - Quality standards for water, sediment and biota.
[c] The maximum tolerable risk (MTR) limit for management of TBT polluted sediments is set to 35 $\mu g.kg^{-1}$ d.w.

Table 4
Research publications that have supported each of the three competing imposex MoA hypotheses in marine neogastropods, all implying a receptor-based gene activation scheme.

Imposex MoA hypothesis	Published reports supporting each respective MoA
Increased testosterone	Bettin et al. (1996); Oehlmann et al. (1996); Ronis and Mason (1996); Matthiessen and Gibbs (1998); Alzieu (2000); Oberdörster and McClellan-Green (2002); Gooding et al. (2003); Santos et al. (2005); LeBlanc et al. (2005); Oehlmann et al. (2007); Stange et al. (2012)
APGWamide neuropeptide activation	Oberdörster and McClellan-Green (2000, 2002, 2003); Oberdörster et al. (2005)
Retinoid X Receptor (RXR) agonism/activation	Nishikawa et al. (2004); Nishikawa (2006); Castro et al. (2007); Iguchi et al. (2007); Nakanishi (2007); Horiguchi et al. (2008); Sternberg et al. (2008); Nakanishi (2008); le Maire et al. (2009); Horiguchi et al. (2010a); Horiguchi et al. (2010b); Sternberg et al. (2010); Lima et al. (2011); Urushitani et al. (2011); Stange et al. (2012); Chapman and Guillette (2013); Pascoal et al. (2013); Dominguez-Ojeda et al. (2014); Urushitani et al. (2018); Lagadic et al. (2018); Giraud-Billoud and Castro-Vazquez (2019); Giulianelli et al. (2020)

characteristics, notably vas deferens and penis analogue tissues (Bettin et al., 1996). A range of the early imposex MoA studies were in support of this theory (see Table 4). This MoA research direction also involved possible involvements of other enzyme targets and systems such as the steroid 5α-reductase 3(α),*β*-hydroxysteroid dehydrogenase pathway and UDP-glucuronosyltransferase (UGT) phase II enzymes (which are key for glucuronidation and the subsequent excretion of testosterone). However, this hypothesis implies strong similarities of steroidogenesis in neogastropoda and vertebrates and that the different steroid compounds involved have similar sexual regulation roles in gastropods and vertebrates. Most recent research in this area tend to contradict both these assumptions (Mizuta and Kubokawa, 2007; Scott, 2012, 2013; Fodor et al., 2020).

The second MoA theory is known as the APGWamide hypothesis. In molluscs, the neuropeptide neurotransmitter APGWamide (Ala-Pro-Gly-Trp-NH2) is produced and released from neurosecretory cells in the pedal ganglia. In gonochoristic (distinct sexes) neogastropods, APGWamide is key for regulating sexual development and reproductive behaviors in males (Smit et al., 1992; LeBlanc et al., 1999; LaFont, 2000). The APGWamide MoA theory alleges that TBT exposed young female gastropods will develop abnormally high concentrations of APGWamide, making them start developing male-like tissues which subsequently will start producing androgens that further promote the male-like sexual growth (including penis development and spermatogenesis). This theory is sometimes called the penis morphogenic factor (PMF) hypothesis. However, since this MoA theory build on the premise of androgen mediated signaling and regulation in females, it suffers many of the same weaknesses as the increased testosterone hypothesis.

The third imposex MoA theory is the Retinoid X Receptor (RXR) agonist/activation hypothesis, which alleges that TBT causes an inappropriate activation of the RXR signaling pathway, either directly by ligand binding or indirectly by increasing the concentration of endogenous free retinoid (Sternberg et al., 2010). A key evidence for this MoA hypothesis is the induction of imposex in female neogastropods when treated with the natural RXR ligand 9-cis retinoic acid (9-cis RA), in absence of TBT (Castro et al., 2007). The indirect-effect sub theory suggests that TBT can inhibit acyl coenzyme A:acyltransferase (AXAT) and cause increased endogenous retinoid levels (due to a lowered retinoid AXAT esterification activity). Then, the increased free retinoid level will activate RXR and trigger the development/growth of imposex phenotypes (Sternberg et al., 2010). A recent study by Lesoway and Henry (2021) demonstrated retinoid agonists to promote penis development in the sequentially hermaphroditic *Crepidula* gastropod (which first develops into males, then change sex, and finally matures into females), and that blocking RXR or retinoic acid synthesis decreased penis length in this species. Interestingly, the RXR signaling pathway may also be involved in the organotin induced oyster shell thickening phenomenon. Huang et al. (2020) investigated the possible role of RXR in TBT and triphenyltin (TPhT) induced shell thickening in the Pacific oyster and found that both compounds influenced the shell development process by interaction with RXR and by disruption of this signaling pathway.

RXRs are members of the steroid and thyroid hormone nuclear receptor superfamily and act as dimer complexes, as homodimers or heterodimer partners of class II nuclear receptors, and most often together with the Peroxisome Proliferator-Activated Receptor (PPAR). The PPAR-RXR heterodimer complex regulates a range of cellular processes, including cellular development and differentiation, metabolism, and cell death. A diversity of regulatory functions of PPAR-RXR is possible partly because RXR and PPAR occur in different subtypes (RXR-α, -β, -γ and PPAR-α, -δ, -γ), and with the different combinations of PPAR-RXR subtypes pairs having different functions and roles in transcription of many different genes and gene clusters. Insight on these matters may have great relevance also for deciphering how TBT may exert endocrine disruptive actions to various biological control systems and why certain species and life-stages may have different sensitivities to endocrine disruptive influence from TBT. It should also be noted that an interaction of TBT directly with PPAR may possibly be important for imposex development as well as for other TBT ecotoxicities. For example, the treatment of dogwhelks with the known vertebrate PPAR ligand rosiglitazone has been shown to induce imposex development in absence of TBT, suggesting that PPAR could be more directly involved in modulating this endocrine signaling pathway (Pascoal et al., 2013).

Species variability in toxic sensitivity of TBT can possibly be explained by natural differences in how strong TBT bind to (and activate) RXR. Hence, it is interesting to evaluate RXR protein sequence similarities across species, and compare data from sensitive species, such as the common dogwhelk, with species that have unknown sensitivity to TBT. As part of this study, we therefore did some initial screening tests employing an established *in silico* bioinformatic tool SeqAPASS (Sequence Alignment to Predict Across Species Susceptibility) which is developed by the US EPA (LaLone et al., 2016) to compare RXR protein and conserved ligand-binding domain (LBD) sequences across a range of species, aiming particularly to assess percentage similarity to dogwhelk RXRs. With sequence information from the NCBI protein database (https

://www.ncbi.nlm.nih.gov/guide/proteins/), we aligned the *N. lapillus* RXR-α (NCBI accession ABS70715.1) and RXR-β (ABS70716.1) protein sequences as well as their conserved LBDs (NCBI accession cd06943) against similar data from a broad suite of other species. Two illustrative examples of this similarity screening are shown below (Fig. 3a and b), ranking species and species groups from highest to lowest on similarity with LBD of RXR-α and RXR-β protein sequences of *N. lapillus*. A large number of species showed high sequence similarities with LBD in *N. lapillus*, for example above 75% similarity, whereas others showed considerably lower similarity (Fig. 3a and b). Although being preliminary results, we see these findings as quite encouraging as they could mean that SeqAPASS can be used for targeting particularly sensitive and relevant bioindicator species in future effect studies of TBT, especially when effects are expected to be mediated via an RXR agonism/activation MoA, such as RXR-α and/or RXR-β ligand binding or modulations, but which will lead to different effect phenotypes than imposex, as imposex is exclusively found in neogastropoda. A key purpose of using such a SeqAPASS based screening, can be to filter out

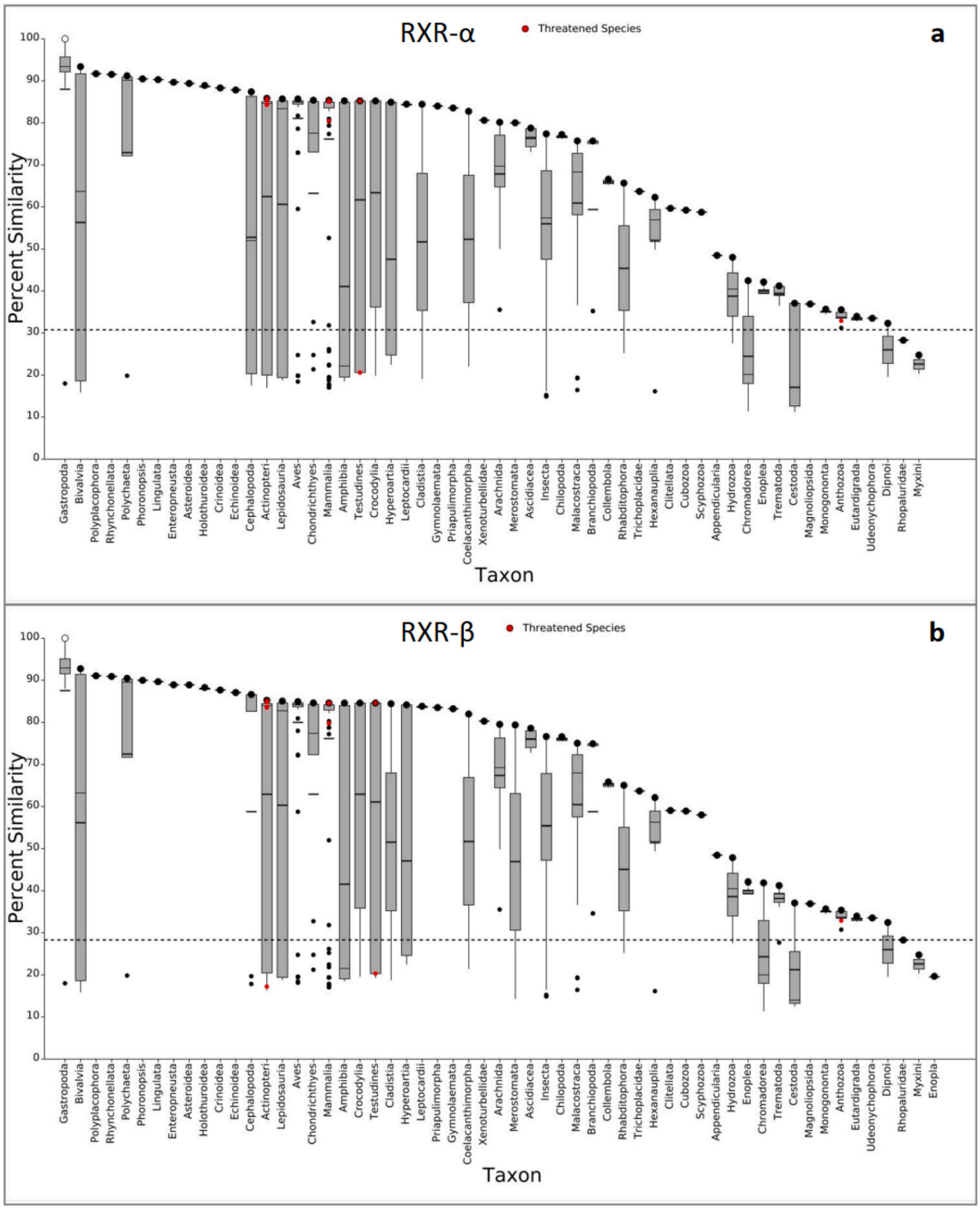


Fig. 3. Protein sequence similarities in the ligand binding domain (LBD) for retinoid X receptor alpha (RXR-α, a) and beta (RXR-β, b) for different species groups compared relatively to *Nucella lapillus*. High degree of similarity could be a screening indicator for the sensitivity to effects of tributyltin (TBT), and similarly acting toxicants, mediated via the RXR signaling pathway. The dashed lines indicate the susceptibility cut-offs (above: susceptible species groups; below: non-susceptible species groups). The red dots indicate species groups that are listed as threatened by the US Fish and Wildlife Service.

particularly sensitive and susceptible taxa, providing improved species targeting and significantly reduced workload for risk assessors. To discuss this issue further, we will in the following paragraph briefly examine the status of knowledge on TBT effects in various non-gastropod taxa.

7. Ecotoxicity of TBT in other species than neogastropods

Marine crustaceans constitute a large group, >50 000 known species, which include many bioindicator species possibly suitable for TBT effect studies (Verslycke et al., 2005; Parmentier et al., 2019). For example, McClellan-Green et al. (2007) pointed to commonly used crustacean bioindicator/bioassay species, including copepods like *Amphiascus tenuiremis*, *Tisbe bulbisetosa*, and *Acartia tonsa*, as well as the grass shrimp *Palaemonetes pugio* as particularly relevant bioindicator species in studies of TBT toxicokinetics and TBT effects on toxicological endpoints such as development, morphology, behavior and survival. The endocrinology of crustaceans often concerns the roles of ecdysone and peptide hormones in processes of molting and vitellogenesis. The main neuroendocrine center of crustaceans is the X organ–sinus gland system, which is located inside decapods' eyestalk and which produce a family of large peptide hormones including the crustacean hyperglycemic hormone (CHH), putative molt-inhibiting hormone (MIH) and vitellogenesis-inhibiting hormone (VIH) (Keller, 1992). The growth process in crustaceans, as in other ecdysozoans, occurs by the repeated molting process regulated by a negative feedback mechanism involving CHH, MIH, and ecdysteroids, and which potentially can be influenced by TBT toxicity (Vogt et al., 2018). For example, the study of Kusk and Petersen (1997) found larval development in *Acartia tonsa* to be extremely sensitive to TBT with inhibition of larval development in a standard 48h biotest occurring already at a TBT concentration of 1 ng. L^{-1}, indicating a similar sensitivity as for imposex in *N. lapillus*. Besides ecdysteroids, the sesquiterpenoids methyl farnesoate (MF) and juvenile hormone are also important during the growth and metamorphosis of crustaceans. In crustaceans, TBT has been shown to impair reproductive performance (IPCS, 1990), decrease neonate survival (Kusk and Petersen, 1997), inhibit larvae developmental ratios (Waldock et al., 1999), decrease juvenile growth rates (Dahllof et al., 2001), and induce changes to the local community structure (Takeuchi et al., 2001; Aono and Takeuchi, 2008). By interacting with RXR and CHH signaling, TBT can influence carbohydrate and lipid homeostasis and may also disrupt methyl farnesoate and ecdysteroid signaling via interactions with other nuclear receptors and thereby alter growth and sexual maturity, respectively, and also influence reproduction via interference with cytochrome P450 system mediated steroid metabolism (Vogt et al., 2018). The brown shrimp *C. crangon* may be considered as a particularly relevant species for assessing endocrine disruption effects in crustaceans in coastal TBT hotspot locations. Studies have shown that TBT concentrations in *C. crangon* in estuarine, coastal and offshore areas are clearly related to sediment concentrations (Verhaegen et al., 2012; Parmentier et al., 2019). Research into possible endocrine disruption impacts of TBT in *C. crangon* have focused on agonistic interference of TBT with natural ecdysteroid hormones at the metabolic pathways that regulates growth and reproduction (Verhaegen et al., 2011).

Ascidians, or sea squirts, are sessile, filter-feeding tunicates that receive increasing attention for their possible role as bioindicators in endocrine disruption effect studies of TBT and other organotins. These animals are close evolutionary relatives to vertebrates as are demonstrated by their free-swimming, tadpole like, lecithotrophic larvae (which has a notochord in the tail and a dorsal hollow nerve cord). The phylogenetic position of tunicates, located between invertebrates and vertebrates, makes them particularly interesting as possible models and bioindicators for endocrine disruption effect studies in the laboratory as well as in marine surveys, e.g. Osugi et al. (2020); Eliso et al. (2020); Sekiguchi et al. (2020). Developmental and endocrine disruption effects of TBT in ascidian test species have been reported in several studies, e.g. (Gianguzza et al., 1996; Patricolo et al., 2001; Dolcemascolo et al., 2005; Cangialosi et al., 2008, 2009, 2010; Mansueto et al., 2011). For example, exposure of *Ciona* to TBT was found to yield changes to sterols and sex steroid levels as well as ovarian morphology (Cangialosi et al., 2010).

Fish have frequently been used as test animals and bioindicators in effect studies with TBT and other organotins, e.g. including commercial species such as Japanese medaka (*Oryzias latipes*), (Horie et al., 2018), red seabream (*Pagrus major*) and black rockfish (*Sebastes melanops*) (Min et al., 2018), and model species such as zebrafish (*Danio rerio*) (Li and Li, 2020a, b; Li and Li, 2021). Exposure of fish to TBT, or other toxic trivalent OTs, leads to bioaccumulation *in vivo* (Miki et al., 2011; Ashraf et al., 2017) and have been linked to a series of toxic impacts, including inhibited growth (IPCS, 1990), induced masculinization (Fent, 1996; Shimasaki et al., 2003), increased sperm abnormalities (McAllister and Kime, 2003), reduced fecundity (Shimasaki et al., 2003), inhibited cytochrome P450 activities (Zhang et al., 2009), impaired ovarian development (Zheng et al., 2005), embryo abnormalities (Zhang et al., 2007), larval malformations (Zhang et al., 2008), increased liver vacuolation (Zuo et al., 2009), induced hematopoietic tissue hyperplasia (Zuo et al., 2012), neurotoxicity (e.g. modulation of the glutamate signaling pathway) (Zhang et al., 2011), increased DNA damage (Zhang et al., 2013), impaired thyroid function (Wu et al., 2020; Li and Li, 2020a, 2021), and induced lipotoxicity (Zhang et al., 2013, 2016; Lyssimachou et al., 2015). Fish species that could be particularly relevant for effect surveys in TBT hotspot field site will be common and shallow-living species that also are relatively territorial/non-migratory and species that because of their feeding or other behaviors are in frequent and direct contact with TBT contaminated surficial sediments, including for example various kinds of Gobiidae species, e.g., (Shimizu and Kimura, 1992; Louiz et al., 2009, 2018).

Marine mammals bioaccumulate organotins via food web accommodated uptake (Berge et al., 2004) potentially leading to several toxic and endocrine-disrupting effects that are known to or expected to be mediated via an RXR agonism/activation MoA (Grün et al., 2006; Evans and Mangelsdorf, 2014). Reported TBT effects in mammals include reproductive anomalies (e.g. reduced spermatogenesis and embryo malformations) (IPCS, 1990), neurobehavioral alterations (Yonezawa et al., 2007), immunological disorders (Antizar-Ladislao, 2008), abnormal adipose tissue differentiation (obesity) (Grün and Blumberg, 2006; Ohtaki et al., 2007), induced cardiovascular toxicity (Chen et al., 2008), inhibited osteoclast differentiation through a retinoic acid receptor-dependent signaling pathway (Yonezawa et al., 2007; Nath, 2008), inhibited mitochondrial ATP synthase activity and disturbed biosynthesis and degradation of steroids (Kotake, 2012), induced behavioral abnormality and toxicity to the developing central nervous system (da Silva et al., 2018).

Human health risks, associated with TBT and other OTs, is a side-issue in the present review, as our focus is predominantly on marine organisms. Exposure, toxicity and risk assessments of TBT/OTs in humans are covered in detail by others, e.g., Antizar-Ladislao (2008) and Heindel and Blumberg (2019). Human risks of TBT are most often associated with consumption of contaminated seafoods. Food safety authorities in Norway and other European countries normally find seafoods to be within food safety limits for TBT, unless the seafoods have been collected from TBT hotspot areas, which generally is not recommended (EU, 2003; EFSA, 2004; EU, 2006; VKM, 2007). In humans (and other vertebrates), endocrine disruption phenomena of TBT may more likely involve increased testosterone as a MoA, in contrast to in molluscs and less advanced taxa (Thibaut and Porte, 2004; Lv et al., 2021). In humans, an issue of particular importance is the potential of TBT/OTs to act as obesogens and to interfere with the endocrine regulation of adipogenesis (Darbre, 2017). Both TBT and TPhT have been demonstrated to act as nanomolar affinity ligands for the PPARγ-RXR heterodimer and to stimulate preadipocytes to differentiate into adipocytes in a PPARγ-dependent manner (Kanayama et al., 2005; Grün et al., 2006; Grün and Blumberg, 2006; Li et al., 2011). Much research is presently

ongoing on possible roles of TBT and OT pollutants in conjunction with human obesity.

8. Summary and remaining knowledge needs

TBT would possibly still have been the key marine antifoulant globally if ecotoxicologists hadn't discovered its many non-target impacts in marine systems. This review provides a brief outline of the large study field that concerns TBT. We examine the knowledge status and discuss the rationale for why it can be worthwhile to address TBT impacts, especially in marine TBT hotspots, of which Norway have many. Away from TBT hotspots, the adverse impacts of TBT have fortunately been in decline, e.g., (Schøyen et al., 2019), but within hotspots the recovery process is apparently far slower and the possible ecological impacts in biota have been investigated only to a limited degree. In our group, we consider such TBT hotspots almost as "natural laboratories" in which the fate and effect aspects of TBT, and co-occurring contaminants, can be thoroughly investigated. Key fate issues that can be studied may for example include aspects like the bioavailability of legacy TBT to different local species and species groups, the efficiency of measures to reduce pollution exposures (sediment remediation operations), natural recovery processes of hotspot sediments under different local conditions, and the role of TBT APPs at sites highly littered with such particles. Studies in hotspots will possibly be particularly suitable for elucidating the MoAs and toxic mechanisms of TBT in various bioindicator species (including both invertebrates and vertebrates). Since the TBT contamination in hotspot sites is preferably embedded within sediments, it is particularly sediment-associated species that are likely to be most relevant as bioindicator study species. Such species may for example include the netted dogwhelk *Nassarius reticulatus*, crustaceans like the brown shrimp *C. crangon* and benthic fish species such as gobies (e.g., like the sand goby *Pomatoschistus minutus*). While endocrine disruption studies in vertebrates are generally benefited by the broad knowledge base that is available on vertebrate endocrine systems, similar knowledge is much more limited for invertebrates, possibly with pest insects as an exception. As discussed by Fodor et al. (2020), effect studies of ED toxicants such as TBT in invertebrates must not be focused on effect pathways that are valid for vertebrates but not for invertebrates.

The most extreme TBT hotspots in Norway are located close to shipyards or in busy fishery harbors (Olsen et al., 2021), where active sediment remediations are likely to be required, if not already performed. A current study in our group has addressed spatiotemporal fate and effect issues in the fjord Vikkilen, i.e., one of the TBT hotspots listed in Table 1 (Schøyen et al., 2022). It is important that such studies are designed and performed so they can provide improved insights into the remaining unknowns of TBT as an endocrine disrupting compound. Such improved insights are important for assessing the operability and realism of sediment quality and risk assessment standards that are authorized by international and/or national bodies. Such standards are the benchmarks that should signal the need for remediation measures and need to be set right in order not to be under-protective nor over-protective. However, the many TBT hotspot sites along the Norwegian coast that show extreme TBT levels, even on a global context, indicates a need for thorough quality verification of TBT data that have been registered in national databases. And the circumglobal presence of TBT contamination and TBT hotspots suggests that this issue has international relevance.

Effect studies in TBT hotspots offer opportunities for detailed studies of endocrine effect mechanisms in various groups of marine bioindicator species, especially regarding nuclear receptor effect pathways. MoAs for TBT induced endocrine disruption effects in invertebrate taxa warrant further investigations, both regarding the critical biological events leading to known phenomena such as imposex in neogastropods, but also for other endocrine effect phenotypes that may causally be linked to TBT pollution in hotspot situations. Whether such endocrine effects can be forecasted at an early stage using New Approach Methodologies (NAMs), such as high-throughput biomarker screening, broad-content ("OMICS") screening and computational predictions, is a topic relevant to the contamination situations in TBT hotspots and may have a broader importance for next generation environmental risk assessment. Similarly, there is still only limited insight on the possible long-term ecological impacts on populations and communities of benthic invertebrates that inhabit TBT hotspots, as well as on combined toxicity phenomena caused by TBT in combination with other inorganic/organic pollutants commonly occurring in hotspot areas. In these studies, different combinations of TBTs and other pollutants, a greater diversity of nuclear receptors and toxicity pathways, and combined toxicities expressed at different levels of biological organization (i.e., molecular, cellular, individuals and population effects) can and should be assessed. Exposure time is believed to influence the nature and intensity of effect interactions as well as the type and quantity of metabolic products which may have relevance for combined toxicity effects. Lastly, from a general perspective, it is essential that TBT fate and effect studies can be performed under exposure scenarios that are potent but still realistic, and such conditions are present in coastal TBT hotspots. Any improved insights from such studies will have relevance in conjunction with future quality verification, refinement and internationally harmonization of risk based environmental quality standards that should serve as regulatory trigger values for sediment remediation requirements in TBT polluted coastal sediments.

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.

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