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Environmental risk assessment of veterinary medicinal products intended for use in aquaculture in Europe: the need for developing a harmonised approach

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Abstract

The current and future expansion of aquaculture production appears to be only manageable by using veterinary medicinal products (VMPs) to prevent and reduce disease outbreaks. However, only a very low number of VMPs are available for use in aquaculture systems. In addition, the environmental risk potentially emanating from the use of these products has gained increased attention in the last years. In this context, the present review represents an in-depth analysis of the current two-tiered (phase I and phase II) approach for the environmental risk assessment (ERA) of VMPs mandatory in the European Union and the European Economic Area (EU/EEA), and its applicability to medicinal products intended for use in aquaculture. The following conclusions are drawn: (i) the current regulatory guidance documents detailing the phase I and II ERA procedure should be updated and harmonised across Member States and simple approach(es) applicable to the assessment of the environmental exposure of VMPs intended for use in aquaculture facilities should be devised; (ii) current and future regulatory guidance documents detailing the phase II ERA procedure for VMPs intended for use in aquaculture should comprise advanced mathematical models suitable for addressing different exposure scenarios relevant across the whole EU/EEA (including scenarios addressing the exposure of VMPs to agricultural soils from fish sludge); and (iii) it is recommended that any updates of relevant ERA guidelines clearly detail the types of studies needed to determine potential adverse effects of VMPs used in aquaculture on non-target organisms. Furthermore, the application of risk mitigation measures tailored to the reduction of the environmental exposure of VMPs on an individual aquaculture farm level should be considered in any future or updated guideline. Finally, it is anticipated that the present analysis of the main drawbacks surrounding the current ERA regulatory framework will help competent authorities to harmonise and facilitate the approval process for VMPs intended for use in aquaculture.

Keywords: Aquaculture, Veterinary medicinal products, Environmental risk assessment, Regulatory assessment, European Union

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Background

While worldwide capture fishery production of seafood[1] has remained more or less consistent for the last 30 years [1], the production of farmed seafood has been steadily increasing from approximately 12 million tonnes in 1988 to around 82 million tonnes in 2018 [2]. It is projected that global farmed seafood production will surpass capture fisheries (about 90 million tonnes per year) by the year 2021, exceed a production volume of 100 million tonnes by 2025 and account for almost 60% of all fish forecast to be consumed for food globally by 2030 [1, 3, 4]. However, unlike in some countries in which the proportion of farmed commodities amounts to the big majority of their total seafood production, the share of seafood stemming from aquaculture in the European Economic Area (EEA; i.e. the European Union [EU; excluding the United Kingdom (UK)], Iceland, Liechtenstein and Norway) represents only about one fourth of its total production [5]. Nonetheless, the EEA's aquaculture production appears to have been consistent over the last 20 years, although several of its Member States (MSs), most notably Norway, have almost tripled their farmed seafood produce during that period [2]. In fact, Norway alone accounted for 53.3% of the EEA's total aquaculture production and is presently ranked as the world's seventh largest farmed seafood-producing country [5]. In the EU, Spain (23%), France (13.8%), Italy (11.4%) and Greece (9.2%) were the biggest producers of farmed seafood in 2017, with almost all of the production accounting for finfish (salmon, trout, seabass, carp and tuna) and molluscs (mussels, oysters and clams) [6, 7]. Nonetheless, the supply of foodstuffs originating from aquaculture cannot meet the overall per capita demand (24.35 kg in 2017) and thus the largest part of the EU's seafood destined for human consumption stems from imported or wild capture fisheries [8]. Considering the fact that about one third of worldwide fish stocks are overfished [3], with certain stocks within EU waters (e.g. the Northeast Atlantic or the Mediterranean and Black seas) particularly affected [9, 10], it is reasonable to conclude that the volume of captured wild fish should be reduced and replaced by sustainably farmed seafood to meet the projected increased demand in Europe [10–13]. This is in line with short and long-term worldwide projections, which indicate that the gap between an increasing population-driven demand for seafood and the actual supply could only be closed by augmenting aquaculture production, under the assumption that the volume of capture fisheries remains stagnant or even declines [14, 15]. Indeed, the European Commission (EC) and EU MSs have launched various policy initiatives to promote the growth and development of the European aquaculture sector ([12, 16], summarised in [17] and [18]). Although these measures have not necessarily led to a growth of the EU aquaculture sector in terms of production volume, the farmed seafood sector has undeniably increased in terms of value, a circumstance mostly attributed to the production of high-value species such as salmon [9, 19]. In addition, both the EC and the FAO expect the EU aquaculture sector to grow in the next decade, the latter even predicting an increase in production of 13.1% [3, 20].

Farming of seafood generally has benefits associated with its high nutritional value and its contribution to food security as well as economic prosperity, e.g. through the creation of employment opportunities [12, 21]. However, despite the positive aspects associated with aquaculture, farming of seafood may also entail some major disadvantages, especially regarding its impact on the environment and aquatic ecosystems [21]. Indeed, aquaculture has been associated with contributing to the disruption and pollution of the environment and has been closely linked with the alteration/disturbance of natural habitats and biodiversity as well as the decline of wild fish stocks [22–24]. For instance, non-target wild fauna, including species destined for human consumption such as fish and crustaceans, may be negatively affected by (i) the introduction of aquaculture effluent and wastewater containing potentially harmful compounds (e.g. pharmaceutical residues) or pathogens into various environmental compartments adjacent to the farm; (ii) the introduction of species not native to the ecosystem surrounding the farm; or (iii) through the production of fishmeal and fish oil, which is necessary to feed predatory farmed species, but relies on wild fish stocks [11, 21, 23, 25, 26].

The present article focuses on the assessment of the environmental risks emanating from veterinary medicinal products (VMPs) used in aquaculture, a subject that has gained increased attention in recent years, especially due to the sector's high growth and reliance on the use of VMPs to sustain this development [27–32]. Indeed, it has been estimated that, depending on the type of farming system used (see Table 1 for examples), as much as three quarters of a given amount/dose of a VMP may be released into the environment, which might pose a considerable threat to wild flora and fauna nearby aquaculture installations and beyond ([24], reviewed by [25, 28, 33–35]). For instance, active substances routinely used in aquaculture to treat parasitic or bacterial infestations/infections such as emamectin benzoate or various antimicrobials can have severe adverse effects on non-target organisms: while the former is known to

[1] In the frame of the present review, the term "seafood" denotes fish, crustaceans and molluscs.

Table 1 Main aquaculture systems used across EU/EEA according to the EC [40]

Environmental compartment	Farming method	Species farmed (examples)	Main features
Freshwater	Extensive (ponds)	Freshwater whitefish (*Coregonidae*), zander, pike, carp, catfish and crayfish	Natural or artificial ponds adapted to foster the development of the cultivated species
	Intensive (tanks, raceways, earth ponds, recirculating aquaculture systems)	Rainbow trout, catfish and eel	Open-air concrete tanks, raceways (a cluster of consecutively connected tanks) or earth ponds of various sizes and depths adapted to the different developmental stages of the cultivated fish In a raceway, river water is collected upstream and fed back to the river downstream after it has passed through all tanks Recirculating aquaculture systems are closed systems in which effluents from the vessel containing the farmed species are subjected to quality-improving treatments (e.g. filtration and oxygenation) before being fed back to that same container
Marine	Extensive (lagoons and coastal ponds)	Sea bass, sea bream (*Sparus aurata*), eels and different species of mullets, crayfish and shellfish	Lagoons adapted to foster the development of the cultivated species
	Intensive (sea cages)	Finfish (e.g. salmon), sea bass, sea bream and trout (to a lesser extent)	Fish are held captive in large pocket-shaped nets anchored to the seabed

interfere with the moulting cycle of marine crustaceans found in the benthic compartment close to aquaculture farms (reviewed by [36]), the latter may affect the normal functioning of naturally occurring microbial communities and promote the spread of antimicrobial resistance (reviewed by [37]). It is important to note that the type of aquaculture system used can have a substantial impact on the environmental emissions of VMPs. Table 1 provides a basic overview of the predominant aquaculture approaches used throughout the EU/EEA, each with its own pathway(s) and potential risk(s) of environmental release of veterinary pharmaceuticals. For example, while more or less confined freshwater systems (e.g. tanks and recirculating aquaculture systems) allow for an efficient control and containment of VMP emissions if managed correctly and according to applicable legislation (e.g. national implementations of the Water Framework Directive 2000/60/EC [38]), the release of VMPs might be more difficultly contained from open systems deployed in marine waters (e.g. sea cages) or leaking closed systems (reviewed by [35] and [39]). That being said, a potentially detrimental effect of an aquaculture-derived VMP on wildlife does not merely depend on its presence in the environment, but on many different factors (e.g. the compound's chemical properties or the water temperature, salinity and pH), which ultimately determine its environmental concentration, distribution, fate and finally toxic behaviour (reviewed by [27, 35, 39]).

The current legislative framework (i.e. Directive 2001/82/EC [41] and, from 28 January 2022, Regulation [EU] 2019/6 [VMP-Reg; 42] as well as associated regulatory guidance documents) addressing the authorisation of veterinary pharmaceuticals in the EU/EEA does not provide clear instructions on how to perform an environmental risk assessment (ERA) for VMPs destined for use in certain (i.e. non-confined) aquaculture facilities (see section "ERA of VMPs in aquaculture: overview and weaknesses" for more details). Consequently, the approach on how an ERA is performed for VMPs intended for use in aquaculture, if necessary, may vary considerably from case to case, which in turn may result in very different risk assessment and risk management approaches being taken across the EU/EEA and its MSs. However, in the interest of the Union's environmental and animal health, it would be beneficial to devise a detailed and harmonised approach to assess the environmental impact of VMPs used in aquaculture. It is hence the aim of the present work to reflect on current "ERA for VMPs" practices that would need to be modified in order to address the above-mentioned issues, and to summarise current knowledge on ERA approaches applicable to confined and non-confined aquaculture systems.

The need for VMPs in aquaculture

The current and future expansion of aquaculture production is only feasible by using VMPs, in order "[…] to prevent and treat disease outbreaks […], to ensure healthy stocks and maximize production" [43]. Finfish, especially salmon, trout, seabass, seabream and carp are the most important species farmed in Europe [44, 45]. Apart from

the use of pharmaceuticals, management and prevention of diseases in finfish also occur through a range of other measures, which include the design of aquaculture facilities, general husbandry practices (e.g. the use of disinfectants/biocides), vaccination programmes, health-boosting and alternative therapies (e.g. the use of immunostimulants and nutraceuticals such as probiotics and prebiotics) as well as preventive practices such as the use of sea lice cleaner fish [46, 47]. The economic losses incurred due to diseases are very important and can have serious financial consequences for farmers. This is not only because individual animals of great commercial value are wasted, but the disruption of consistent production schedules of companies, engaged in intensive aquaculture, can also result in a massive loss of market share [47].

The number of VMPs available for use in aquaculture is extremely low, resulting in major treatment gaps for several diseases common in aquatic species (e.g. bacterial and viral infections or parasitic infestations). This in turn significantly reduces animal welfare and may also pose a risk for food safety and public health [44]. As of 1 July 2020, only 286 VMPs (314 when considering the UK) are authorised mostly on a national level in the EU/EEA for use in fish reared in captivity, including ornamental fish [48], Table 2). About half of these products are vaccines, while the other half comprises mostly antibiotics (29%) and, to a far lesser extent, products such as sedatives/anaesthetics, hormones or parasiticides [49]. Another factor that complicates the matter is that many of the above-mentioned products contain the same active ingredients, which not only limits the therapeutic options available for fish, but also increases the likelihood of development of resistance against many of these active substances [50, 51]. The low amount of VMPs available for aquaculture might be the consequence of several reasons that render this specific market unattractive for the pharmaceutical industry to invest in, for instance the high cost of product development and/or the burden of performing studies needed for the marketing authorisation (MA) compared to the limited market and thus limited return on investment [45, 52, 53]. With the aim of increasing the availability of authorized VMPs for aquaculture in the EU/EEA, the FishMedPlus Coalition was created in 2015. It is composed of many organisations and institutions active in the aquaculture sector and is led by the Federation of Veterinarians of Europe (FVE) [54]. As a first step, critical diseases or indications for which little or no treatment options are available were identified. Parasitic infections and especially sea/salmon lice were regarded as the main cause of concern with respect to productivity loss [44]. In a second step, the Coalition examined the main barriers responsible for hindering new VMPs entering the market, mainly concluding that the aquaculture industry is, due to its small size, a rather unattractive market for the animal health industry to invest in [45].

The low availability of VMPs may result in the use of exceptional prescription according to Article 11 of Directive 2001/82/EC [41] (the so called "cascade" prescription) turning into a regular practice. Briefly, prescription under the "cascade" allows the veterinarian to prescribe VMPs authorised for a different target species (e.g. pigs) when there is no alternative available for fish. This exceptional prescription is clearly advantageous with regards to animal health and welfare, but is not exempt from risks, since the initial therapeutic protocol, withdrawal period and environmental impact have not been evaluated for that off-label use. To address this issue, the VMP-Reg [42] includes specific provisions applying to the cascade prescription of VMPs to aquatic species. Article 114(3) of this regulation indicates that a list of substances that may be used in food-producing aquatic species should be developed by the EC within five years from it becoming applicable on 28 January 2022. Furthermore, according to Article 114(3)(a) of the VMP-Reg [42], the risks for the environment should be evaluated in the frame of the creation of such a list. Generally, it would be desirable if an ERA conforming to current guidelines would be performed for a substance prior to its inclusion on this list of substances permissible for use in aquaculture.

Legal requirements for the ERA of VMPs used in aquaculture

In the EU/EEA, environmental safety of VMPs is evaluated in the frame of a pre-authorisation assessment as required by Article 12(3)(j) of Directive 2001/82/EC [41] or, from 28 January 2022 onwards, according to Article 8(1) of the VMP-Reg [42]. Both pieces of legislation require applicants for new MAs to provide an ERA performed as outlined in VICH guideline (GL) 6 ("Environmental impact assessment [EIAS] for veterinary medicinal products—Phase I" [CVMP/VICH/592/98-FINAL]) [55] and VICH GL 38 ("Guideline on environmental impact assessments for veterinary medicinal products—Phase II" [CVMP/VICH/790/03-FINAL]) [56]. Furthermore, in 2009, the EMA/CVMP "Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL 6 and GL 38" (EMA/CVMP/ERA/418282/2005-Rev.1-Corr.) [57] came into force, providing additional specific technical guidance on ERA in areas where the VICH guidelines mentioned above do not provide sufficient information. Generally, in the EU, regulatory and scientific guidance on ERA and other relevant VMP-associated topics is drafted and adopted by the Committee for

Table 2 List of active substances authorized for use in aquaculture in Europe (updated 1 July 2020; adapted from [48])

	Active substances	Bulgaria	Croatia	Cyprus	C. Republic	Denmark	Finland	France	Germany	Greece	Hungary	Iceland	Ireland	Italy	Latvia	Lithuania	Norway	Poland	Portugal	Romania	Slovakia	Slovenia	Spain	UK
Antimicrobial	Florfenicol	X	X	X	X	X	X	X		X	X			X	X	X	X		X	X	X	X	X	X
	Flumequine	X						X		X	X			X	X					X			X	
	Oxolinic acid					X		X		X							X							
	Oxytetracycline	X	X	X	X		X	X		X			X	X	X	X		X	X	X	X	X	X	X
	Enrofloxacin	X																		X				
	Sulfadiazine/trimethoprim							X	X	X				X							X			
	Chlortetracycline													X										
	Amoxicillin trihidrate													X										X
Antifungal/Antiparasitic	Bronopol							X									X						X	X
	Teflubenzuron												X				X							X
	Emamectin benzoate						X					X	X				X		X				X	X
	Deltamethrin												X				X							X
	Hydrogen peroxide											X	X				X							X
	Azamethiphos																X							X
	Cypermethrin																X							
	Diflubenzuron																X							
	Formaldehyde									X									X				X	
Others*	Chorionic gonadotrophin (hCG)	X																						
	Buserelin												X	X										X
	Benzocaine					X				X							X		X				X	X
	Isoeugenol																X							
	Tricaine									X		X	X	X			X							X

*Includes hormones, sedatives and anaesthetic agents

Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency (EMA), with the support of the experts from the CVMP Environmental Risk Assessment Working Party (ERAWP). Prior to its adoption by the Committee, any draft guidance is published for consultation to allow stakeholders to provide input.

ERA of VMPs in aquaculture: overview and weaknesses

In the EU/EEA, the ERA as stipulated above is generally performed using a tiered approach based on two phases (phase I and II), which is also applicable to VMPs intended for aquatic organisms.

Phase I

The first phase (phase I) comprises a simple decision tree aimed at establishing whether the VMP enters the environment and, if so, to what extent [55]. According to VICH GL 6 [55], if the VMP is either "[…] metabolized extensively […]", and/or "[…] used to treat small numbers of animals […]" or non-food-producing species, and/or is "[…] a natural substance […]" (not affecting the concentration or distribution already present in the environment), and/or is already exempt from ERA by law, then no further assessment is required. Furthermore, an ERA may also not be required for a VMP used in aquatic species in confined facilities if the environmental introduction concentration (EIC) released into the environment is below 1 µg/l (i.e. the initial predicted environmental concentration in surface water [$PEC_{sw\text{-}initial}$] < 1 µg/l) or mitigating measures reduce the released amount of the VMP to below that concentration. Finally, as stipulated in VICH GL 6, if the VMP does not fulfil the above-mentioned criteria or if it is an ecto- and/or endoparasiticide, phase II of the ERA must be performed in line with VICH GL 38 [56] in order to determine the environmental risk of the VMP.

Phase II

While the trigger for a phase II assessment is well-defined in VICH GL 6 [55] for confined aquaculture facilities (i.e. an EIC ≥ 1 µg/l), there is no clear guidance available on how to calculate the trigger value for non-confined aquaculture facilities, i.e. the guideline does not mention specific formulas or models. The EMA/CVMP GL in support of VICH GLs 6 and 38 [57] briefly touches on the topic by mentioning that the EIC should be equal to the recommended dose described in the summary of product characteristic (SPC) of the VMP in µg/l. Consequently, if the applied dose exceeds this trigger value of 1 µg/l, the product would enter a phase II assessment and the predicted environmental concentration in surface water (PEC_{sw}) should be calculated. However, again, only brief indications are given in VICH GL 38 [56] on how to perform such calculations, which are, in addition, subject to several uncertainties, as no detailed approach on how to calculate the exposure is provided. The EMA/CVMP GL in support of VICH GLs 6 and 38 [57] refers to the manual and models developed by the Scottish Environment Protection Agency (SEPA) for the application of medicines by bath treatment or in feed to calculate the exposure in phase II [58, 59]. If further assessment of the risk is necessary, the GL recommends that applicants contact the national regulatory authorities in the relevant country that the MA is being targeted for advice. However, this lack of clear guidance on how to use the SEPA or other models, and which pertains to all MSs, may result in a disharmonisation in the way the phase II exposure assessment is calculated within the EU/EEA.

Exposure calculation of VMPs for aquatic species

Having the right tools to perform an exposure assessment is crucial in the frame of an ERA, as this defines if a VMP would require an effect assessment (i.e. phase II studies). Should that be the case, the exposure assessment will determine the size of the risk identified in the risk characterization process. When considering appropriate models for predicting environmental release of VMPs used in aquaculture, an added layer of complexity is that the models have to factor in that, in the EU/EEA, different types of aquaculture production systems are used, which are located in very different environmental compartments (e.g. freshwater, seawater, brackish waters; Table 1), and which are subjected to a large range of different environmental conditions (e.g. water temperature differences between aquaculture farms located in the Atlantic Ocean and the Mediterranean Sea). For instance, fish are poikilotherm species not able to regulate their internal body temperature, resulting in different metabolism rates depending on water temperature. Therefore, the absorption, distribution, metabolism and excretion (ADME) of a VMP may vary across different types of aquaculture systems in different EU MSs [60].

In this context, as reviewed and cited by Rico et al. [61], Metcalfe et al. [62] present a series of models suitable for the estimation of the $PEC_{sw\text{-}initial}$ for four general types of farming systems used in aquaculture: ponds, net-pen cages, flow-through systems and recirculating systems. For closed or self-contained aquaculture systems, these $PEC_{sw\text{-}initial}$ values equal to VMP concentrations found in the effluent at the point of release, while, for open systems (e.g. marine net-pens), $PEC_{sw\text{-}initial}$ values represent concentrations of VMPs in areas directly neighbouring the treatment area from which these products may

further disperse into the environment [62]. Regarding recirculating systems, Metcalfe et al. [62] propose to use a worst-case scenario for bath treatments, assuming that all flow to the treatment unit is temporarily diverted to waste during the treatment period in order to avoid damage to the biofilter. Under these conditions, the equations presented for the flow-through scenario can be used to estimate the $PEC_{initial}$. In addition, some guidance is also provided on ways to refine exposure assessments using VMP-specific and/or facility-specific data [62].

Furthermore, the EFSA "Guidance on the assessment of the safety of feed additives for the environment" [63] also provides basic formulas for $PEC_{sw\text{-}initial}$ calculation relevant for feed additives used in aquaculture, which could be adapted to calculate initial $PEC_{sw\text{-}initial}$ for VMPs used in aquaculture. It should be noted that EFSA [63] already considers different European food production systems in the frame of its $PEC_{sw\text{-}initial}$ model calculations, i.e. "[…] sea cages versus land-based aquaculture (ponds, tanks and recirculation systems)". It is thereby considered that benthic organisms are the most at risk for those approaches involving the use of sea cages, while pelagic and benthic organisms represent the main at-risk populations from terrestrial aquaculture installations [63]. Therefore, according to the above-mentioned EFSA guidance [63], $PEC_{sediment\ initial}$ ($PEC_{s\text{-}initial}$), $PEC_{sw\text{-}initial}$ or both types of exposure calculations are required depending on where the feed additive is going to be applied.

To our knowledge, there is no advanced model accepted on an EU-wide level which can be suggested for the refinement of the VMP exposure for marine and freshwater aquaculture. In fact, only a limited number of models potentially useful for the calculation of the PEC_{sw} in phase II ERAs for VMPs have been developed. They have been comprehensively reviewed by Rico et al. [61] and Rico et al. [64] and a summary of the models described in these reviews is given in the sections "Exposure models for potential use on inland aquaculture systems" and "Exposure models for potential use in marine aquaculture systems".

Exposure models for potential use on inland aquaculture systems Inland aquaculture systems are dominated by tanks or raceways to produce salmonids and other species in hatcheries, and by ponds for the semi-extensive production of carp [40]. As pointed out by Rico et al. [61], such aquaculture installations release potential contaminants to surface water ecosystems (freshwaters or marine coastal waters) in a similar fashion to urban or industrial point source wastewater discharges, with the main difference being "[…] the high waterflow […] and the need to rapidly pour farm waters into streams, preventing the treatment in [wastewater treatment plants (WWTPs)]". However, direct discharge of aquaculture wastewater into water streams can sometimes be authorised. Rico et al. [64] therefore concluded that "models aimed at estimating initial chemical concentrations and their dilution into surrounding water bodies are very important for […] [assessing the potential environmental impact of such aquaculture systems]".

Rico et al. [61] identified two models that allow a refined exposure assessment in freshwater ponds: the veterinary drug concentration (VDC) model [65] and the ERA-AQUA model [66, 67]. The VDC model is based on the Paddy Rice Pesticide Model (PCPF–1) [68, 69], which is used for predicting pesticide concentrations in paddy fields. The ERA-AQUA model predicts in-pond exposure concentrations and the PEC_{sw} in aquatic ecosystems receiving pond effluents. Both models are based on "mass-balance-differential equations" and account for several dissipation processes, while more realistic estimations of metabolism in the aquatic species are only available in the ERA-AQUA model (reviewed by [61]). Furthermore, according to Rico et al. [61] and Phong et al. [65], the VDC model presents further limitations such as (i) "[…] not provid[ing] exposure concentrations in ecosystems receiving farm effluents"; (ii) "[…] only [having] been used to evaluate the fate of the antibiotics oxytetracycline and oxolinic acid in a [fish] pond containing […] [unknown species]"; and (iii) "[…] not [having] been calibrated nor validated with monitoring data". In contrast, the ERA-AQUA model has been used to assess the hazards of many types of VMPs (e.g. antibiotics, antifungals and antiparasitic agents) and has been calibrated against several datasets from Asia [34, and 70, 71 as cited and reviewed in 61].

There are also other models that could be considered for the ERA of VMPs used in freshwater aquaculture. For instance, the chloramine-T dilution model utilizes two simple dilution models to estimate the EICs of chloramine-T [72] and the "Water Quality Analysis Simulation Program" (WASP version 6.1) modelled a 4.4 km stream network [73]. As reviewed by [61], the latter model has been used by Rose and Pedersen [74] to calculate oxytetracycline concentrations in the water and sediment layers considering different sorption, transformation and transport processes. Finally, the Pyceze® model, which an adaptation of the "BathAuto" model used in Scotland [59], was developed by Elanco Animal Health and the University of Stirling to calculate the dispersion of bronopol in the light of various environmental conditions such as wind speed and current flows [61, 64].

According to Rico et al. [61], other models, which are not usually used in a pharmaceutical context, could also be modified for use in the ERA of VMPs used in

aquaculture. This includes, for instance, the TOXSWA model, which simulates pesticide exposure at edge-of-field waters [75], or the GREAT-ER model, which analyses the discharge of chemicals in water streams considering their removal in WWTPs [76, reviewed by 61].

Exposure models for potential use in marine aquaculture systems Marine aquaculture can take place in the open sea (in cages and net-pens, on the seafloor or suspended below the water surface) or in terrestrial man-made systems such as saltwater ponds or tanks. Cages are thereby the main production system used in Europe, and are primarily deployed in marine waters, although they are also installed in less exposed areas such as sea inlets or coastal fjords [61]. In contrast to the above-mentioned (semi-)closed inland aquaculture systems, waste from marine aquaculture systems (i.e. cages and net-pens) is directly released into the surrounding environment. Rico et al. [61] have identified two principal types of models applicable to marine aquaculture scenarios: "(i) models that assess dilution and dispersal of chemicals applied in bath treatments (i.e. antifungals and some antiparasitics)[,] and (ii) particle[-] tracking models that assess the dispersal of in-feed medication (i.e. antiparasitics, antimicrobials) due to waste feed or faeces in the water and the sediment compartments".

Several chemical exposure models have been developed to assess the environmental impact of bath treatments. For instance, the BathAuto model was developed by SEPA [59] and contains two modelling tools to calculate the short and long-term exposure concentration of chemicals. It has been used to determine the concentration of azamethiphos (long-term model) as well as cypermethrin and deltamethrin (short-term model) to ensure compliance with environmental quality standards [64]. As reviewed by Rico et al. [61], the DIVAST model "[…] is a two-dimensional, hydrodynamic and solute transport model […]" that was developed to "[…] evaluat[e] the environmental impacts of estuarine and coastal Atlantic salmon aquaculture in Ireland", which has been extensively calibrated and verified against laboratory and field data with details of model refinements and verification tests [77].

The AutoDEPOMOD model [78] and its updated version, the NewDEPOMOD model [79], were designed "[…] to assess the dispersal and deposition of waste solids from salmonid cage farms and their biological effects on benthic communities", although they are not well suited to assess such effects "[…] in areas with wind-wave resuspension" [64]. In addition, an adapted version of the DEPOMOD model, the MERAMOD model, was developed by Cromey et al. [80] to assess the impact of aquaculture in the Eastern Mediterranean [64]. However, the authors of the EU-funded "Tools for Assessment and Planning of Aquaculture Sustainability" (TAPAS) report [64] state that they "[…] are not aware of any chemical modelling exercise being performed with the MERAMOD model or any validation exercise being undertaken with [the] DEPOMOD [model] or its adapted/follow-up versions for [VMPs]".

Finally, the "Marine Antifoulant Model to Predict Environmental Concentrations" (MAMPEC 3.1.0.3) is a model developed to predict environmental concentrations for the exposure assessment of antifoulants in the marine environment and is also being used to assess the exposure to antifoulants from aquaculture nets, freshwater systems and discharges of chemicals from ballast water [81].

Environmental fate and effect studies required to address the environmental risks of VMPs to aquatic species

Phase II requires assessing the physicochemical properties and undertaking environmental fate and effect (ecotoxicity) studies. These tests must be performed following internationally accepted test guidelines, i.e. according to test guidelines established by the Organisation for Economic Co-operation and Development (OECD) or the International Organization for Standardization (ISO), in addition to being performed according to the principles of good laboratory practice (GLP).

Environmental fate studies required to address the environmental risks of VMPs to aquatic species VICH GL 38 [56] recommends studies to be submitted to address the fate of a substance in the aquatic environment. Adsorption/desorption studies according to OECD test guideline (TG) 106 should report both the organic carbon-water partitioning coefficient (K_{oc}) and the distribution constant (K_d) values for a range of soils. Furthermore, a degradation study according to OECD TG 308 should also be submitted to calculate the half-life (DT_{50}) of the substance in the water and sediment, with such studies being preferably performed under saltwater conditions for substances intended for use in marine aquaculture systems [56, 63].

Finally, the applicant has the option to submit photolysis and hydrolysis studies. The reasoning for the former is that, for products "[…] added directly to […] water, it is considered that photolysis may […] [play] a role in the degradation of the active ingredient […]", in which case the light-induced degradation of the substance in question should be assessed according to OECD TG 316 [57]. Likewise, EFSA [63] suggests that studies on the effects of hydrolytic processes on active substances may be submitted in case hydrolysis is the predominant route of substance degradation, in which case such effects would have to be assessed in accordance with OECD TG 111. In

cases where the *n*-octanol-water partition coefficient ($logK_{ow}$) of an active substance is ≥ 4, "[…] evidence from […] ADME and biodegradation studies […] as well as molecular mass should be considered to […] establish whether there is the potential for bioaccumulation to occur" [57]. In case bioaccumulation is suspected, the EMA/CVMP GL in support of VICH GLs 6 and 38 [57] recommends the performance of a bioconcentration study in fish according to OECD TG 305. Fairly recently, in vitro tests have been developed to investigate the bioaccumulation potential of a substance in fish (i.e. OECD TG 319A and OECD TG 319B). Furthermore, the 2020 OECD work plan for the "Test Guidelines Programme" (TGP) [82] includes the development of a new TG on the "*Hyalella azteca* bioconcentration test" (HYBIT). Regarding the assessment of the risk for secondary poisoning, the abovementioned guideline [57] advocates for "[…] the use of a [predicted bioconcentration factor (BCF) based on quantitative structure activity relationship models (QSAR models)]" and for applicants to seek regulatory guidance if in doubt.

Environmental effect studies required to address the environmental risks of VMPs to aquatic species Regarding the effect studies required, VICH GL 38 [56] stipulates a tiered approach as outlined below. In the first tier (tier IIA), acute ecotoxicity testing is conducted on organisms at three different trophic levels. These include either freshwater or marine species of algae, crustaceans and fish, for which the concentration that causes a 50% effect (EC_{50}), or, in the case of fish, the concentration lethal to 50% of the fish (LC_{50}) is derived. The lowest lethal/effect concentration ($L[E]C_{50}$) from any trophic group is then used to derive the predicted no effect concentration (PNEC) via the application of a predefined assessment factor to account for inter- and intraspecies variability (i.e. a factor of 100 is applied to the EC_{50} determined in algae or a factor of 1000 is applied to the EC_{50}/LC_{50} determined in crustaceans and fish). The ERA is then based on the determination of a risk quotient (RQ), which represents the ratio between the predicted environmental concentration (PEC) and the PNEC. If the resulting RQ is ≥ 1, a risk to the environment cannot be excluded and the next stage is to refine the PEC by considering the information described in the sections "Phase II" and "Exposure calculation of VMPs for aquatic species". Only if the refined PEC/PNEC still results in a RQ ≥ 1, tier IIB testing is required. In this case, the no observed effect concentration (NOEC) or the concentration that caused 10% of effect (EC_{10}) need to be determined from chronic studies in the corresponding taxonomic group that had the highest RQ in the tier IIA assessment. The recommended marine tests are thereby the algal growth inhibition test according to ISO 10253, albeit using the NOEC and not the EC_{50} value, a marine crustacean chronic toxicity or reproduction assay, a marine fish chronic toxicity assay and a marine sediment invertebrate toxicity test. However, these latter tests are poorly defined in VICH GL 38 [56], in which it is only stated that regulatory guidance needs to be sought on the appropriate test to be performed. If the tier IIA RQ for aquatic invertebrates is ≥ 1, VICH GL 38 [56] recommends determining the $PEC_{sediment}/PNEC_{sediment}$ ratio, whereby the latter value is computed using the equilibrium partitioning, which in turn is calculated by applying the sediment-water partitioning coefficient to the invertebrate PNEC. VICH GL 38 [56] further stipulates that, "[f]or substances with a log K_{ow} ≥ 5, the [resulting] RQ […] [should be] increased by an extra factor of 10 to take account of possible uptake via ingestion of sediment", while, in case the RQ is still above the permissible level of 1, the performance of a (long-term) study using benthic organisms exposed to sediment containing the active substance in question is suggested. However, in a similar fashion to the chronic toxicity tests proposed for marine organisms, VICH GL 38 [56] instructs the applicant to seek regulatory guidance before performing a marine invertebrate sediment test.

While current ecotoxicity test requirements as outlined in VICH GL 38 [56] are an obligation in the frame of an MA application, they might not be entirely fit for purpose for identifying specific ecotoxicological effects of some substances. Indeed, some studies [22, 83, 84] have pointed out that the standard data set requirement set out in VICH GL 38 [56] may not be adequate in some cases, for instance "[…] for substances that specifically affect certain organisms or where hazards may not be predicted based on standard environmental hazard assessments alone" [84]. This shows that the choice of standardized tests performed during the authorisation of a VMP might currently not provide an accurate account of the toxicity of a given substance, particularly when it comes to the assessment of long-term effects [22, 83–85]. In the last years, several concerns have also been raised regarding the potential development of antimicrobial resistance in target and non-target bacteria as well as in human consumers [43, 71, 86, 87]. In fact, some recommendations have been published to include a microbial community-based testing to complement the single-toxicity test included in VICH GL 38 [86], and the VMP-Reg [42] indicates that, for new applications containing antimicrobial substances, risk mitigation measures limiting antimicrobial resistance development should be applied.

Due to limited knowledge at the time they were developed, few details regarding toxicity studies to be used when an environmental risk is identified in tier IIA (i.e.

a RQ > 1) were included in both relevant VICH [55, 56] and the EMA/CVMP supporting [57] guidelines. In contrast, other closely related regulatory frameworks have advanced considerably on this topic in the meantime. For instance, the recently published EFSA "Guidance on the assessment of the safety of feed additives for the environment" [63] contains a more comprehensive list of studies that should be submitted by the applicant when a risk for aquatic organisms is still identified in tier IIA after refinement of the PEC. Table 3 summarises these types of studies, which might also be ultimately considered applicable for the ERA of VMPs used in aquaculture.

Assessment of persistent, bioaccumulative and toxic (PBT) as well as very persistent and very bioaccumulative (vPvB) substances According to the EMA/CVMP guideline in support of VICH GLs 6 and 38 [57], substances should be screened for persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) properties, with the aim of establishing whether a substance actually fulfils the criteria for being classified as PBT/vPvB. The "Guideline on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products" (EMA/CVMP/ERA/52740/2012) [88] contains sufficient information on how to identify such (active) substances. As of 28 January 2022, based on its hazards for the environment, a substance classified as PBT/vPvB and intended for use in food-producing species may not be authorized according to Article 37(2)(j) of the VMP-Reg [42], unless deemed "[…] essential to prevent or control a serious risk to animal health".

Terrestrial exposure to VMPs from the use of aquaculture sludge in agricultural soil

Fish sludge contains organic matter and many nutrients [89], which makes it a useful fertilizer for agricultural purposes [90]. An important environmental issue associated with aquaculture is therefore the proper treatment and disposal of sludge generated in ponds and hatcheries. It is estimated that each ton of salmon produced generates 1.4 tons of sludge [91], which consists mainly of uneaten feed and faeces. The chemical composition of salmon sludge varies considerably because the diet fed to the fish changes in the course of their development [92]. It appears that the application of salmon sludge to agricultural soils may generally have beneficial effects: indeed, an increase of total phosphorus concentrations or dry matter accumulation has been reported in some soils after application of such sludge [93, 94], and experimental evidence shows that enrichment with farmed salmon sludge improves the physicochemical and biological properties of soils with low organic matter content [92]. However, it should be noted that residues of VMPs may remain in the sludge and possible effects on terrestrial organisms should be assessed before it is applied to agricultural soils. Consequently, the procedure on how to calculate the exposure pattern should be clearly defined in future regulatory guidance.

Environmental risk assessment for mixtures

Over the past decade, the EC has been made aware of ecological issues associated with chemicals, which resulted in the formulation of a common strategy to face the issue of pharmaceuticals in the environment [95]. Indeed, the use of various VMPs may, through emissions, result in highly concentrated mixtures in the environment potentially posing a risk to wildlife through acute, chronic and sub-lethal toxic effects (e.g. increased mortality or altered reproduction and behaviour) as well as hamper individual organisms or population fitness as a whole [96–99]. This may lead also to a cascade of indirect effects at higher levels of the ecological hierarchy (i.e. the community).

The most challenging issue in assessing the risk emanating from VMP mixtures relates to the high variability in the number of a mixture's constituents and their relative concentrations through time. Thus, in the frame of an exposure scenario, multiple sources and sequential exposures may have to be considered, and the scenario may differ depending on the purpose of the assessment, i.e. the mixture effect assessment for regulatory purposes may considerably differ from a mixture effect assessment suitable for the management of aquatic bodies (both marine and inland waters).

During an MA application, mixture effects need to be assessed when (i) VMPs contain several active substances; or (ii) ecotoxicologically relevant metabolites are present. Regarding the former, some products containing two active substances are currently authorized for use in aquaculture in the EU/EEA [48]. Most of these contain a mixture of sulfadiazine and trimethoprim, two antimicrobials applied in combination due to their synergistic effect against a range of bacteria. In this regard, the "CVMP guideline on pharmaceutical fixed combination products" (EMEA/CVMP/83804/2005 [100], outlines the conditions and data requirements for efficacy, safety and residues documentation for such VMPs. Furthermore, recently published EFSA guidance [101], describing "harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals", could be considered relevant for the ERA of VMPs used in aquaculture. As such, this document states that, in case ecotoxicologically relevant metabolites are present, the risk of the formed

Table 3 Compilation of ecotoxicological effects studies potentially applicable for the ERA of VMPs used in aquaculture as mentioned in VICH GL 38 [56] and the EFSA "Guidance on the assessment of the safety of feed additives for the environment" [63]

Study type	Environmental compartment	Endpoint	Reference
TIER IIA			
Algal growth inhibition	Freshwater	EC_{50}	[56]
Daphnia immobilization	Freshwater	EC_{50}	[56]
Fish acute toxicity	Freshwater	LC_{50}	[56]
Algal growth inhibition	Saltwater	EC_{50}	[56]
Crustacean acute toxicity	Saltwater	EC_{50}	[56]
Fish acute toxicity	Saltwater	LC_{50}	[56]
Leptocheirus plumulosus (crustacean)	Saltwater sediment	EC_{50}	[63]
Eohaustorius estuarius (crustacean)	Saltwater sediment	EC_{50}	[63]
Ampelisca abdita (crustacean)	Saltwater sediment	EC_{50}	[63]
Rhepoxynius abronius (crustacean)	Saltwater sediment	EC_{50}	[63]
Corophium volutator (crustacean)	Saltwater sediment	EC_{50}	[63]
Neanthes arenaceodentata (polychaete worm)	Saltwater sediment	EC_{50}	[63]
Chironomus spp. (insect)	Freshwater sediment	EC_{50}	[63]
Hexagonia spp. (insect)	Freshwater sediment	EC_{50}	[63]
Hyalella azteca (crustacean)	Freshwater sediment	EC_{50}	[63]
Diporeia spp. (crustacean)	Freshwater sediment	EC_{50}	[63]
Tubifex tubifex (oligochaete worm)	Freshwater sediment	EC_{50}	[63]
TIER IIB			
Algal growth inhibition	Freshwater	$NOEC/EC_{10}$	[56]
Daphnia reproduction	Freshwater	$NOEC/EC_{10}$	[56]
Fish early life stage test	Freshwater	$NOEC/EC_{10}$	[56]
Sediment-water chironomid toxicity test	Freshwater	$NOEC/EC_{10}$	[56]
Sediment-water *Lumbriculus* toxicity test	Freshwater	$NOEC/EC_{10}$	[63]
Chironomus spp. (insect)	Freshwater sediment	$NOEC/EC_{10}$	[63]
Hyalella azteca (crustacean)	Freshwater and saltwater sediment	$NOEC/EC_{10}$	[63]
Lumbriculus variegatus (oligochaete worm)	Freshwater sediment	$NOEC/EC_{10}$	[63]
Caenorhabditis elegans (nematode worm)	Freshwater sediment and soil	$NOEC/EC_{10}$	[63]
Myriophyllum aquaticum (vascular plant)	Freshwater sediment	$NOEC/EC_{10}$	[63]
Leptocheirus plumulosus (crustacean)	Freshwater sediment	$NOEC/EC_{10}$	[63]
Eohaustorius estuaries (crustacean)	Saltwater sediment	$NOEC/EC_{10}$	[63]
Ampelisca abdita (crustacean)	Saltwater sediment	$NOEC/EC_{10}$	[63]
Rhepoxynius abronius (crustacean)	Saltwater sediment	$NOEC/EC_{10}$	[63]
Neanthes arenaceodentata (polychaete worm)	Saltwater sediment	$NOEC/EC_{10}$	[63]

mixture (parental unchanged form and metabolite[s]) should be assessed. Moreover, the combination ratio of the parent compound and metabolites changes with time depending on metabolic pathways active in the treated organism. Thus, the toxic potency of a mixture can vary over time, and, consequently, also its ecotoxicological impact. In case an unacceptable risk is identified in the first screening steps, the role of the metabolites may be considered in a higher tier refinement.

A mixture may also originate from the administration of multiple VMPs of the same or different class of products at once, a scenario which would, for instance, apply to various antibiotics, antiparasitics or antifoulants. Therefore, risk information from an ERA performed with individual products could be useful to further improve the management of the environmental risk emanating from mixtures in an aquaculture environment. In order to achieve this, both, the concentration addition model, which is commonly utilized to assess the risk of mixtures to ecosystems as a worst-case approach [102], as well as the recently published EFSA "Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to

multiple chemicals" [103], which provides a harmonised framework for risk assessment of combined exposure to multiple chemicals, may provide a useful basis for the performance of ERAs for VMPs.

Environmental risk mitigation measures

The VMP-Reg [42] specifies in Annex II part 3 ("Safety and residues tests") that "[a]n environmental risk assessment shall be performed to assess the potential harmful effects, which the use of the veterinary medicinal product may cause to the environment and to identify the risk of such effects. The assessment shall also identify any precautionary measures which may be necessary to reduce such risk". These precautionary measures should be included in the SPC of a product and should be in line with the "Reflection paper on risk mitigation measures [RMM] related to the environmental risk assessment of veterinary medicinal products" (EMA/CVMP/ERAWP/409328/2010; [104]). However, in this reflection paper, only one RMM related to aquaculture is proposed, which states that "[…] discharge consent by local water authorities is required before use [of a product], because the concentration of the active substance in surface water must not exceed [a given concentration] to avoid adverse effects on the aquatic environment […]". Furthermore, the reflection paper states that this measure must "[…] be in agreement with the legislation of the EU and the member state […]" and would need to be met in countries where local authorities monitor the use and discharge of products from aquaculture.

Nonetheless, due to the wide diversity of aquaculture systems, species and scenarios, it is not feasible to devise a single RMM that would be applicable to every situation for which a risk is identified, unless the VMP is indicated to target species with comparable production systems in similar environments. Thus, for a product intended for use in different types of aquaculture facilities, different RMMs might need to be considered. In addition, although an RMM could be imposed in similar facilities, the environmental conditions surrounding the respective facility would play an important role regarding the effectiveness of the measure, i.e. a mitigation measure effective under "Mediterranean" conditions might not be suitable to protect the environment under conditions prevailing in Northern Europe and vice versa. To further complicate matters, differences between aquaculture systems located in the same area may sometimes prevail as well, which further underlines the difficulty of defining "standard" RMMs valid throughout the EU/EEA. In addition, when applying an RMM, it needs to be considered that this might incur costs to the farmer, as is already the case in other sectors discharging effluents to waters. Consequently, the feasibility and usefulness of RMMs for the aquaculture system in question are important factors to be considered when they are proposed for implementation. For instance, the mandatory installation of filtration systems (e.g. carbon filter cartridges) could render certain aquaculture systems financially unviable.

Main detected gaps of the current ERA of VMPs

To summarize, at least the following points should be addressed/devised to improve and harmonize the ERA of VMPs intended for use in aquaculture:

- Specific formulas or models to calculate the initial PEC to be used in phase I and phase II.
- Specific formulas or models to refine the initial PEC when a risk is identified.
- Specific models for higher tier refinement.
- A detailed list of standard (ecotoxicity) effect studies that should be considered for the ERA of each aquaculture system (i.e. marine or freshwater aquaculture).
- A detailed list of (ecotoxicity) effect studies that should be considered for certain substances where particular data might be required to address certain hazards inherently associated with those classes of substances, for instance parasiticides or antimicrobials.
- A scenario to calculate the exposure of agricultural soils fertilised with fish sludge.
- A discussion on possible RMMs (if any).

Conclusions

The EU aquaculture industry needs to augment its production to meet the increasing consumer demand for seafood and to further prevent the depletion of wild stocks. Unfortunately, diseases requiring treatment with VMPs are a major obstacle to the development and profitability of fish farms. Indeed, there are relatively few VMPs specifically authorised in the EU/EEA for use in aquaculture. To cover the presently existing therapeutic gaps, current legislation (Directive 2001/82/CE; [41]) allows the use of VMPs authorised for terrestrial food-producing species in fish in case animal health or animal welfare are compromised and there is no authorised alternative VMP (the so called "prescription cascade"). However, when this cascade is applied in the field, the environmental effects of the "terrestrial" VMPs to be used in aquaculture would generally not have been examined, as the ERA provided during the MA procedure would have only considered the emission route anticipated for the initial terrestrial target species. This practice may change once the VMP-Reg [42] comes into force, since Article 114(3) provides

for the development, within five years, of a specific list of substances currently used in food-producing terrestrial animals or humans that could also be used in food-producing aquatic species. As stated in Article 114(3)(a), the "risks to the environment if the food-producing aquatic species are treated with those substances" should thereby be taken into account when such a list is developed, resulting in, at first glance, an improvement in terms of environmental protection. The development of harmonised and clear ERA guidance addressing all aquaculture approaches practiced across the EU/EEA could be considered very helpful in the frame of the creation of the above-mentioned list should this task indeed involve the performance of ERAs for each active substance. However, it is not yet clear whether this provision will actually entail the performance of ERAs for substances intended to be put on the above-mentioned list, and this article should therefore be cautiously interpreted until more information becomes available in the future. It should additionally be emphasised that the adequate protection of the environment from effects emanating from VMPs used in aquaculture is not solely dependent on legal provisions governing the authorisation of such products, but also on their correct use and application in the field. It is therefore of critical importance that veterinarians and aquaculture facility staff prescribing and using these VMPs, respectively, are properly trained regarding the correct administration of products of interest as well as potential risks for the environment, target animals and the consumer associated with their use.

The present work outlines the guidelines currently available for the ERA of VMPs in the EU, the main knowledge gaps as well as possible solutions to address these gaps. Recommendations are provided to improve the exposure assessment for VMPs used in aquaculture and several standardized studies are suggested to strengthen the effects assessment part. These recommendations should be considered as an improvement of the current system aiming at harmonising and reducing uncertainties for applicants and regulatory authorities. It should also be emphasised that VMPs currently authorized for use in aquaculture can be considered as having the necessary (environmental) safety level when compared to the therapeutic benefit(s) they provide. Furthermore, it is also necessary to consider available information on how active substances can be safely used depending on the type of aquaculture site. In addition, any future regulatory guidance would have to clearly outline how to proceed in case a tier IIA screening is required and, if necessary, how to perform calculations tailored to species of concern (relevant group of organisms) in tier IIB.

Since aquaculture is practiced in very different environmental compartments and settings (e.g. in the marine environment, freshwater environment, ponds, nets, closed, open and recirculating systems), an ERA for each type of site, relevant for the VMP in question, is necessary, and environmental fate data on the VMP should be used accordingly. It is therefore of importance to develop a lower tier model to calculate the exposure that would enable the derivation of a $PEC_{sw\text{-}initial}$ or $PEC_{sediment\text{-}initial}$ depending on the actual environment (i.e. marine or freshwater) and which is based on an approach similar to that used to derive the PEC_{soil} for terrestrial animals. Regarding more advanced exposure models to be used for higher tier refinement, several are mentioned in the above sections (e.g. in section "Exposure calculation of VMPs for aquatic species"). Nonetheless, it should be critically discussed which model(s) is/are best suited and easily applicable to each of the different exposure scenarios.

It is also recognized that the current VICH guidelines might not be protective enough to address some adverse effects on non-target organisms (e.g. antimicrobial resistance development). Again, it should be thoroughly analysed which studies are the most suitable to evaluate ecotoxicological effects on non-target organisms, which would consequently improve the currently performed effect assessment. In that respect, any future guidance on VMPs for use in aquaculture might benefit greatly from advances already made in other EU regulatory frameworks, for instance as detailed in the EFSA "Guidance on the assessment of the safety of feed additives for the environment" [63]. Indeed, from our point of view, any forthcoming guideline on the "ERA for VMPs used in aquaculture" should be reviewed frequently instead of being a closed document, which would allow for the consideration of new scientific knowledge and ensure harmonisation with other European regulatory frameworks, thus resulting in a more comprehensive protection of the aquatic environment.

Finally, a scenario for aquaculture waste sludge (if appropriate to the nature of VMP used) has to be considered in any potential new guidance document, as this sludge might form part of a recycling system on agricultural land.

In conclusion, it is of importance to balance the economic cost of fish production against the actual costs to the environment. Any future new guideline should therefore, on the one hand, provide an ERA framework facilitating the approval of VMPs intended for use in aquaculture, whilst, on the other hand, not compromising the protection of the receiving environmental compartment.

Abbreviations

ADME: Absorption, distribution, metabolism and excretion; CVMP: Committee for Medicinal Products for Veterinary Use; DT_{50}: Half-life; EC: European Commission; EC_{10}: Concentration inducing a 10% response; EC_{50}: Concentration

inducing a 50% response; EEA: European Economic Area; EFSA: European Food Safety Authority; EIA: Environmental impact assessment; EIC: Environmental introduction concentration; EMA: European Medicines Agency; ERA: Environmental risk assessmen; EU: European Union; EUMOFA: European Market Observatory for Fisheries and Aquaculture Products; FAO: Food and Agriculture Organization of the United Nations; FVE: Federation of Veterinarians of Europe; GL: Guideline; GLP: Good laboratory practice; ISO: International Organization for Standardization; K_d: Distribution constant; K_{oc}: Organic carbon-water partitioning coefficient; LC_{50}: Concentration lethal to 50% of the test population; $logK_{ow}$: *n*-Octanol-water partition coefficient; MA: Marketing authorisation; MS: EU/EEA Member States; NOEC: No observed effect concentration; OECD: Organisation for Economic Co-operation and Development; PBT/vPvB: Persistent, bioaccumulative and toxic/very persistent and very bioaccumulative; PCPF-1: Paddy rice pesticide model; $PEC_{sediment}$: Predicted environmental concentration in sediment; PEC_{sw}: Predicted environmental concentration in surface water; $PEC_{sw\text{-}initial}$: Initial predicted environmental concentration in surface water; PNEC: Predicted no effect concentration; $PNEC_{sediment}$: Predicted no effect concentration in sediment organisms; RQ: Risk quotient; SEPA: Scottish Environment Protection Agency; STECF: Scientific, Technical and Economic Committee for Fisheries; TAPAS: Tools for Assessment and Planning of Aquaculture Sustainability; TG: Test guideline; UK: United Kingdom; VDC: Veterinary drug concentration; VICH: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products; VMP-Reg: Regulation (EU) 2019/6; VMP: veterinary medicinal product; WASP: Water Quality Analysis Simulation Program; WWTP: Wastewater treatment plant.

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ICR, MTE and RCG drafted the manuscript, except for the section on "Environmental risk assessment for mixtures", which was drafted by SV. BK, JF, AL and XNK substantively revised the manuscript. All authors read and approved the final manuscript.

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