

Use of models for the environmental risk assessment of veterinary medicines in European aquaculture: current situation and future perspectives

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Abstract

Veterinary Medicinal Products (VMPs) are used in intensive aquaculture production to treat a wide range of bacterial and parasitic infestations. Their release into the environment poses concerns regarding their potential ecotoxicological risks to aquatic ecosystems, which need to be evaluated making use of appropriate Environmental Risk Assessment (ERA) schemes and models. This study presents an overview of the major aquaculture production systems in Europe, the VMPs most commonly used, and the environmental quality standards and regulatory procedures available for their ERA. Furthermore, it describes the state-of-the-art on the development of environmental models capable of assessing the fate, exposure, ecotoxicological effects and risks of VMPs in aquaculture production systems, and discusses their level of development and implementation within European aquaculture. This study shows that the use of environmental models in regulatory ERA is somewhat limited in many European countries. Major efforts have been dedicated to assess the fate and exposure of antiparasitic compounds in salmonid cage systems, particularly in Scotland, while models and scenarios for assessing dispersal of antimicrobials, in general, and antiparasitic compounds in the Mediterranean as well as in Scandinavian regions are less available. On the other hand, the use of ecological models for assessing the effects and risks of VMPs is almost absent. Recommendations are provided to improve the chemical exposure and effect assessments and the ecological realism of the modelling outcomes, paying special attention to the protection goals set for the regulatory ERA of VMPs in Europe.

Keywords: antimicrobials, antiparasitics, environmental models, environmental risk assessment, aquaculture

1. Introduction

Finfish aquaculture is an important industry in Europe, contributing to local and regional economies and providing a source of employment for over 40000 people (Eurostat 2017). One of the major concerns surrounding finfish culture is the use of veterinary medicinal products (VMPs) and their potential toxicological impact on the surrounding environment (Telfer *et al.* 2006; Macken *et al.* 2015). VMPs used in finfish aquaculture include antibiotics, antifungals and antiparasitic drugs, which have different emission routes, environmental persistence and side-effects to aquatic organisms (Boyd & Massaut 1999; Costello *et al.* 2001; Armstrong *et al.* 2005; Burrridge *et al.* 2010).

Specific regulations exist for the Environmental Risk Assessment (ERA) of VMPs applied in aquaculture in Europe, which require member states to undertake a risk evaluation and authorization process before any new chemical is marketed (VICH 2000, 2004). The regulatory system is supported by environmental quality standards (EQSs) and environmental modelling tools that allow the calculation of chemical exposure and ecotoxicological risks in the vicinity of aquaculture farms (Silvert *et al.* 1996, 2001; Henderson *et al.* 2001; Cromey & Black 2005). The progress and actual implementation of such tools for the ERA of chemicals used in aquaculture, however, has not gone as far as in other areas such as the regulatory ERA of other chemicals like plant protection products (e.g. see Adriaanse *et al.* 1997a; FOCUS 2001; Boesten *et al.* 2007; Dohmen *et al.* 2016; Baveco *et al.* 2014). Furthermore, it is unclear whether present scientific knowledge in this respect is sufficiently developed and rigorous to represent environmentally relevant conditions in different aquaculture production systems and environments within Europe.

The main objective of the present study is to summarize the state-of-the-art on the development and applicability of environmental models for the ERA of VMPs used in European aquaculture, with the intention of highlighting research directions to improve modelling tools and to aid their effective implementation. In order to define the context in which they need to be applied, we start this paper by providing an overview of the finfish production systems within the European region, the current use of VMPs, and the EQSs and regulatory procedures available for their ERA. Subsequently, we describe the available modelling tools regarding: their production system and chemicals they have been developed for; their input data requirements; the methods used for the exposure, effect and risk characterization; and their validation status with environmental data. Finally we discuss their usability within the context of European aquaculture production, and provide recommendations to improve

the chemical exposure and effect assessments, paying a special attention to the protection goals set for the regulatory ERA of VMPs.

2. Finfish production in Europe

Annual finfish production in Europe, represented by the countries within the European Economic Area (EEA), is approximately 2 Mt/year (FAO 2016 a,b). Norway is the largest producer, contributing 66% of the total production. The second largest producer is the United Kingdom (9.0% of the total production) where most production occurs in Scotland, followed by Greece (4.4%), Spain (3.0%) and Italy (2.6%) (FAO 2016 a,b). Atlantic salmon dominates production, but other major species in terms of production volume are rainbow trout, gilthead seabream, common carp, European seabass and turbot (Figure 1).

Figure 1 about here

Different production systems are used for European finfish aquaculture depending on the environment and species. Land-based hatcheries are used for both freshwater and marine species. Freshwater finfish production occurs in ponds, tanks, raceways, cages and recirculating aquaculture systems (RAS). Large extensive and semi-extensive pond systems are commonly used in Eastern Europe for carp production. Ponds are used elsewhere for trout and other species, but tanks and raceways are used for more intensive production and RAS are becoming increasingly more important, notably for rainbow trout production in Nordic countries (Dalsgaard *et al.* 2013). Atlantic salmon are initially grown in freshwater tanks or on occasion small cages in lakes where they undergo physiological changes (smoltification) to adapt to seawater and subsequently they are transferred to marine cages or net-pens for the grow out stage. Some countries, including Scotland and Sweden, also use freshwater cages for rainbow trout and Arctic char production. Mediterranean marine species such as European seabass and Gilthead seabream are usually farmed in cages and net-pens, although some production also takes place in coastal tanks and ponds with pumped seawater and more extensively in some coastal lagoons.

The variety of production systems presents a challenge for the ERA of VMPs as their use and their potential ecotoxicological impacts will vary depending on the culture system and the environment into which the chemical is discharged. Ideally, ERA models should be robust enough to capture the complexity of the production systems, the chemical application and emission routes, the farm

management practices, the exposure and fate of the substance, and its effects to non-target organisms. However, this is not a simple task as culturing practices and environmental conditions can vary widely across regions. For example, the conditions for on-growing salmon in marine cages in the relatively shallow coastal waters of Scotland are very different to the deep fjords of Norway. Consequently, there is a need to define research needs for the scientific development of new models or for the adaptation of existing ones to the production systems and locations that require chemical risk evaluations.

3. VMPs used in aquaculture production in Europe

Aquaculture VMPs can be mainly classified as antimicrobials or antiparasitic compounds (Table 1), although some anaesthetics are also used in some farm management operations such as fish transportation. Antimicrobials are used to inhibit the growth and/or to kill potentially pathogenic bacteria and fungi. Overall, the use of antimicrobials in aquaculture has decreased in recent years, particularly in salmon producing areas (i.e., Norway, Scotland), following the introduction of vaccines and improved husbandry practices (e.g. water recirculation, optimal feeding) (EUROPE 2011; Henriksson *et al.* 2018). Antimicrobials are particularly used in the early development stages of fish (normally in hatcheries) and to prevent bacterial infections in cage, tank or pond systems after fish stress events such as transport operations or abrupt changes in environmental conditions. Concerns regarding the use of antimicrobials in aquaculture are multiple, including the toxicity to non-target organisms, the interaction with microbial communities and their mediated ecological functions, and the contribution to the development of antimicrobial resistance (Samuelsen *et al.* 1992; Sapkota *et al.* 2008; Tello *et al.* 2010; Tomova *et al.* 2015; Sun *et al.* 2016; Rico *et al.* 2017). Although some country or regional level information exists (e.g. for Norway and Scotland), information on the total amounts of prescribed antimicrobials in European aquaculture as a whole and for many member states is currently unavailable. Regarding their authorized uses in the top EEA aquaculture producing countries, florfenicol and oxytetracycline have the most widespread use, while the antifungals/antiprotozoan list is dominated by bronopol used in salmonid production systems (Table 1). Antimicrobials used in hatcheries are usually applied in powdered forms directly to water, while in pond or cage systems they are administered as additives in medicated feed. Medicated feeds are prepared by adding the active substance to the feed ingredient mixture during commercial preparation. Feeds are coated with oils to prevent chemical losses to the environment. Medicated feeds are applied one or two times a day during a period ranging from 5 to 10 d, according to the medical prescription. Antifungals are usually applied in bath treatments. Bath treatments, either in tank, pond or net-pen systems, are conducted

by reducing the water volume and applying the chemical at the recommended concentration. In net-pen systems, the net depth is reduced and an impermeable barrier is installed to prevent chemical dispersal and to maintain chemical concentrations inside the net-pen for several minutes to one h (Metcalf *et al.* 2009; Burrige *et al.* 2010).

Antiparasitics used in the European aquaculture can be classified into two main groups based on their route of administration: those used in bath treatments and those used by in-feed applications. Pyrethroids (deltamethrin, cypermethrin), hydrogen peroxide and organophosphates (azamethiphos) are administered in short bath treatments (similarly to antifungals) to kill ectoparasites, predominantly sea-lice (*Lepeophtheirus salmonis*) affecting salmonids (Table 1). Avermectins (emamectin benzoate) and benzoylurea insecticides (teflubenzuron, diflubenzuron) are sold with commercial feeds (similarly to antibiotics) and administered for several days to kill several parasitic pests, including sea-lice (Table 1). Environmental concerns related to antiparasitics include the possible effects to non-target invertebrate species in and around the fish farms, including principally microcrustaceans and decapods (Tucca *et al.* 2014; Olsvik *et al.* 2015; Macken *et al.* 2015; Lillicrap *et al.* 2015). Furthermore, some of the antiparasitics used in aquaculture are known to bind to particulate organic material and may be of concern to filter feeders such as mussels (Norambuena-Subiabre *et al.* 2016) or sediment dwelling organisms (McBriarty *et al.* 2018).

Table 1 about here.

In many countries, the unavailability of authorized VMPs to treat particular diseases allows the treatment at the farmer's responsibility following the veterinary cascade (Verner-Jeffreys & Taylor 2015). The cascade entails a risk based decision tree that allows use of clinical judgement to select and apply a chemical that is authorized for other use or species, balancing the benefits against the risks of not strictly following the clinical recommendations on the product characteristics summary. Such risks include those related to animal care, operator health, consumer's health as well as environmental health. Farmers may be open to litigation if they ignore the warnings of the product characteristics summary and/or if there are clear negative consequences of the chemical's use. However, environmental impacts are difficult to demonstrate unless proper chemical and biological monitoring programs are executed. An example of a common treatment done under the veterinary cascade is the use of florfenicol, originally licensed for Atlantic salmon (Table 1), to treat the rainbow trout fry syndrome caused by the bacterium *Flavobacterium psychrophilum* (Verner-Jeffreys and Taylor 2015). The need for a veterinarian cascade is the result of the limited number of authorized VMP treatments to control major disease problems, which is considered to be one of the key bottlenecks of the sector

in Europe (Verner-Jeffreys and Taylor 2015) as well as in other parts of the world (e.g. North-America; Henriksson *et al.* 2018).

4. ERA procedures, protection goals and environmental standards

In Europe, the regulatory ERA of VMPs used in animal production - including those applied in aquaculture - is conducted under the framework set by the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH 2000, 2004). The objective of VICH is to harmonize the data requirements for the registration of veterinary medicines in Europe, the United States, Japan, Canada, Australia and New Zealand, ensuring that unacceptable environmental risks do not take place due to their use in animal rearing facilities. The main protection goal stated in the VICH guidance document is *'the protection of ecosystems'* in a broad sense, while it specifies that the *'impacts of greatest potential concern are usually those at community and ecosystem function levels, with the aim being to protect most species'*. The VICH guidance is based on a tiered approach. Under VICH Phase I guidance (VICH 2000), the ERA of a veterinary medicine for aquatic environments - except for antiparasitics - stops if the concentration in the environment (i.e., the so called environmental introduction concentration) is expected to be $<1 \mu\text{g/L}$. If this concentration is exceeded, the ERA proceeds to Phase II, which involves a more complex and environmentally relevant analysis.

The VICH phase II guidance for ERA (VICH 2004) is based on a Risk Quotient (RQ) approach that determines whether the predicted environmental concentration (PEC) of a given active ingredient exceeds the predicted no-effect concentration (PNEC) for any of a series of standard test species. A specific branch is dedicated to the risk assessment of veterinary medicines used in aquaculture, in which basic recommendations are provided to perform initial PEC (Tier A) calculations for some aquaculture production systems and refined PECs (Tier B) accounting for chemical sorption routes and dispersal in the aquatic environment (VICH 2004). These recommendations are basic in nature, and lack particular guidance on what algorithms or modelling tools are available or should be used for their calculation in Tier A and B. Toxicity data requirements for the calculation of PNECs are also provided, which includes testing the chemical of concern using a primary producer, a crustacean and a fish species, based on the standard test protocols provided by the Organisation of Economic Co-operation and Development (OECD) or the International Organization for Standardization (ISO).

Recently, there has been increasing awareness about the potential side-effects of antimicrobials on non-target bacteria and other microorganisms (archaea, fungi) and on the ecosystem functions they

mediate (e.g. organic matter decomposition, nitrification, and biological control of pathogens; Rico *et al.* 2014; Roose-Amsaleg & Laverman 2016; Grenni *et al.* 2018). Recommendations have been provided for the inclusion of microbial community-based testing in the aquatic risk assessment of antimicrobials to complement single-species toxicity testing and to offer more targeted protection of key ecosystem functions and services (Brandt *et al.* 2016). Furthermore, the risks that antimicrobial residues can pose on the selection of bacterial resistance genes of clinical concern, although not explicitly addressed in the VICH guidelines, have been widely recognized in the regulatory as well as in the scientific arena (Sapkota *et al.* 2008; Heuer *et al.* 2009; ECDC/EFSA/EMA 2015; Bengtsson-Palme & Larsson 2015; Tomova *et al.* 2015). As a way to facilitate the inclusion of this endpoint in ERAs, resistance thresholds estimated using minimum inhibitory concentrations for clinically relevant bacteria have been proposed (Bengtsson-Palme & Larsson 2016; Rico *et al.* 2017). On the other hand, several studies have indicated a high sensitivity of marine zooplankton copepods affected by multiple pyrethroid pulses (Medina *et al.* 2004 a,b). Similarly, benzoylurea insecticides (e.g. diflubenzuron and teflubenzuron) have raised concerns regarding their potential adverse effects to non-target crustaceans, including commercially important species such as crabs, shrimps and lobsters, due to development effects and impaired moulting (Samuelsen *et al.* 2014; Langford *et al.* 2014; Macken *et al.* 2015; Olsvik *et al.* 2015; Gebauer *et al.* 2017; Bechmann *et al.* 2018). In response to that, Lillicrap *et al.* (2015) provided general recommendations for the inclusion of non-target crustacean tests in the ERA of benzoylurea insecticides. Altogether, these scientific developments suggest the need for an improved regulatory framework for the ERA of aquaculture medicines, which may incorporate new exposure assessment and testing requirements depending on the chemical properties and the toxicological mode of action of the evaluated substance (Lillicrap *et al.* 2015; Lillicrap 2018).

National regulations for the ERA of aquaculture medicines should in principle be based on the requirements set by the VICH (2000, 2004) guidelines; however, the level of development and implementation varies largely at the different member states. In the majority of the countries chemical ERAs are performed by using generic aquaculture production scenarios, which entail typical chemical use rates, realistic worst-case environmental conditions to assess chemical exposure, and PNECs (derived with laboratory toxicity data) for ecosystem's protection. On the other hand, the Scottish Environment Protection Agency (SEPA) has established specific EQSs for sea-lice treatments (SEPA 2014; Table 2). These standards have a spatial-temporal component, meaning that maximum allowable concentrations are set for different time spans after the treatment and for different seabed distances from the farms (allowable zone of effect). In Scotland, specific dilution and dispersal models have been developed as well as guidance on how to use the site-specific information around

the farm (particularly water currents) to calculate the maximum biomass that can be grown and treated without exceedance of these EQSs (SEPA 2008). Such an approach differs notably to the one used in the other European countries, meaning that specific ERAs for the use of a given compound need to be performed at the farm level; while generic, national-wide ERAs are performed for the authorisation of the substance in the other countries. The approach followed in Scotland is more time and resource demanding, but requires that specific chemical exposure assessments are performed under very different conditions, thus ensuring that the influence of the farm and environmental scenario on the risk assessment is well integrated. The implementation of such regulatory approach has put pressure on the scientific development of chemical or even environment-specific modelling tools that can be used by regulators and farmers. Moreover, it has supported the development of several monitoring studies to demonstrate the protectiveness of the proposed EQSs for aquatic communities under specific environmental conditions. This, however, does not imply that model predictions and EQSs developed for the Scottish situation are applicable to other regions in Europe. For example, Langford *et al.* (2014) compared measured concentrations of five sea-lice treatments (diflubenzuron, teflubenzuron, emamectin benzoate, cypermethrin and deltamethrin) in Norway with the standards proposed by SEPA (2008) and demonstrated that diflubenzuron exceeded the EQSs in 40% of the samples, while emamectin benzoate and teflubenzuron exceeded the sediment standards in 50% and 67% of the monitored samples, respectively. The authors of this study advocated the need for a re-evaluation of some substances in Norway, paying special to the adequacy of the available exposure models to simulate chemical dispersal from different farm configurations and environmental conditions in the Norwegian fjords. In addition, they highlighted the need to develop and test suitable EQSs that can be used in different aquaculture production regions of Europe and that ensure the protection of the wildlife surrounding marine aquaculture farms (Langford *et al.* 2014).

5. Models for the ERA of VMPs used in aquaculture

In this section we provide a description of existing modelling tools that have been developed to assess the fate, dispersal, exposure and ecotoxicological risks of VMPs in aquaculture production systems. A literature search was conducted in SCOPUS using the terms: aquaculture, model, modelling, medicine, antibiotic, and antiparasitic. The focus of the selected models was predominantly at the farm/local scale, as the ecological risks of veterinary medicines have been traditionally assessed at a short distance from the point of administration. Additionally, chemical fate and effect models that have not been exclusively developed for VMPs but that may have direct application are briefly described indicating their potential contribution to aquaculture ERA.

5.1 Models for inland aquaculture production systems

Inland aquaculture production in Europe occurs in a variety of systems including hatcheries, semi-extensive and intensive ponds, tanks, raceways and RAS. These produce contaminant emissions into freshwaters or marine coastal waters that are comparable to point source wastewater discharges derived from other human activities (e.g. urban, industrial). The major difference, in most cases, is the high water-flow (e.g. raceways for trout farming) and the need to rapidly pour farm waters into streams, preventing the treatment in WWTPs (Waste Water Treatment Plants). For this reason, models aimed at estimating initial chemical concentrations and diffusion into surrounding water bodies are very important for an exposure assessment. To a lesser extent, finfish are also produced in cages and net-pens located in lakes and freshwater reservoirs, so models for such production systems are also included in this section.

Only a limited number of models have been explicitly developed to assess the environmental fate and risks of veterinary medicines applied in inland production systems (Table 3). Metcalfe *et al.* (2009) provide a series of generic algorithms to calculate initial exposure concentrations for different production systems (e.g. ponds, net-pens, cages, or flow-through systems) and subsequent dilution into surrounding aquatic ecosystems. These algorithms incorporate basic treatment (i.e., dose, duration) and farm management (i.e., fish density, water discharge) parameters but do not take into account sorption or degradation processes. Although very simple in nature, the set of algorithms provided by Metcalfe *et al.* (2009) and the recommendations provided therein can be considered as the best supporting information to calculate environmental introduction concentrations and to perform the first-tier exposure assessment recommended within the VICH guidelines.

Two models have been developed that allow a refined exposure assessment in freshwater ponds: the Veterinary Drug Concentration (VDC) model (Phong *et al.* 2009) and the ERA-AQUA model (Rico *et al.* 2012, 2013). The VDC model was conceived as an adaptation of a pesticide fate model for rice-paddies (Watanabe *et al.* 2006) to fish ponds. It is based on mass-balance-differential equations and accounts for a large number of dissipation processes (e.g. volatilization, photodegradation, biodegradation, sediment sorption and leaching) to dynamically predict concentrations in pond water and in the sediment compartment (Phong *et al.* 2009). A limitation of the model is that fish metabolism is not dynamically predicted (i.e., simply assumes a percentage of applied chemical mass to be instantaneously lost due to metabolism) and that does not provide exposure concentrations in ecosystems receiving farm effluents. The model has only been used to evaluate the fate of the antibiotics oxytetracycline and oxolinic acid in a pond containing fish (not species specific), and has

not been calibrated nor validated with monitoring data. The ERA-AQUA model is the most sophisticated model available to predict in-pond exposure concentrations and PECs in aquatic ecosystems receiving pond effluents. Similar to the VDC model, the ERA-AQUA model predicts chemical concentrations using mass-balance-differential equations in water and sediment including 15 chemical transfer and dissipation processes (Rico *et al.* 2013). In this model, veterinary medicines are assumed to be administered directly to water or mixed with feed and are up-taken, metabolized, diluted (due to fish growth) and excreted by the cultured species, which is considered as a separate homogeneous compartment (accounting for fish biomass increase and mortality). The model dynamically predicts concentrations in water, in sediment, in the cultured fish and in the effluent discharge point, considering the dilution of the veterinary medicine residues in the environment. The model calculates peak and time-weighted average exposure concentration in these compartments. It uses a risk quotient approach based on PNECs to predict risks for the cultured species (in case of overdosing), for non-target primary producers, invertebrates and fish (acute and chronic) in surrounding aquatic ecosystems, and for consumers possibly eating harvested fish products containing chemical residues (Rico *et al.* 2012, 2013). The model has been used to predict the risks of a wide range of veterinary medicines (antibiotics, antifungals disinfectants, antiparasitics) in several fish and shrimp production systems of Asia (Rico & Van den Brink, 2014; Sun *et al.* 2016). Its chemical fate sub-model has been calibrated and evaluated against a monitoring dataset for sulfadiazine in a shrimp pond of China (Sun *et al.* 2016) and a *Pangasius* catfish pond of Vietnam (Rico *et al.* 2017). However, the model has not been calibrated or validated for use in European aquaculture ponds.

The fate of VMPs applied in (flow-through) hatcheries has been evaluated using the models described by Gaikowski *et al.* (2004) and by Rose and Pedersen (2005). Gaikowski *et al.* (2004) developed and tested the performance of two simple dilution models to estimate disinfectant (chloramine-T) concentrations in hatchery effluents. Both models were validated with the dye rhodamine and can be used for prediction of first-tier hourly exposure concentrations in farm effluents. Rose and Pedersen (2005) provide a more sophisticated modelling approach based on the parameterization of The Water-Quality Analysis Simulation Program (WASP v6.1; Ambrose *et al.* 1993) to an aquaculture scenario downstream of a fish hatchery formed by a settling pond, a receiving stream segment, and two downstream stream segments. The WASP model accounts for several sorption, transformation and transport processes, as well as settling, burial and resuspension of solid particles. It was used by Rose and Pedersen (2005) for the calculation of oxytetracycline concentrations in the water layer and the upper and lower sediment layers. The modelling approach was used to provide concentration estimates and to perform a sensitivity analysis that highlights the main factors influencing the

antibiotic fate. However, to our knowledge, the model has not been validated with field monitoring data for aquaculture antibiotics.

Table 3 about here.

The regulatory ERA of the antifungal bronopol applied to prevent (or reduce) *Saprolegnia* spp. infections in salmon and rainbow trout freshwater cages in Scotland is performed with the 'Pyceze model' developed by Elanco Animal health (formerly Novartis) and the University of Stirling. The model is an adaptation of the Bath-Auto model (SEPA 2008) that is the present regulatory model for bath treatments in Scotland. The Pyceze model uses wind speed and direction or measured current flows to calculate the dissipation of bronopol after administration over a period of 3h post-treatment. It provides the predicted concentration (3h) and the size of the mixing zone against time for comparison with the available EQSs, and has been validated with data collected from field trials in Scotland.

In Scotland, SEPA have approved three models (ELSID, VISUAL PLUMES and CORMIX) for evaluating outflows and discharges of hatchery effluents (SEPA, 2013). These are used as initial dilution and mixing models to evaluate nutrient and VMP dispersal in coastal and transitional water bodies. As described in SEPA (2013), the choice of model largely depends on the discharge scenario and should be discussed in advance with SEPA staff.

Besides the ones described above, a large number of models capable of evaluating the dispersal of contaminants in aquatic ecosystems exist in the literature, which have not been yet implemented for the ERA of aquaculture VMPs. Organic chemical fate models for lotic ecosystems have been reviewed by Koelmans *et al.* (2001) and Sharma and Kansal (2013). Some of the models included in these reviews have been broadly used for the regulatory ERA of other chemical substances in Europe (and overseas) and have large potential for adaptation to aquaculture ERA. For example, the TOXSWA model simulates exposure of pesticides in agricultural edge-of-field water bodies such as small ditches, pond and streams (Adriaanse 1997b; Adriaanse *et al.*, 2013). The model can be parameterized for almost all organic chemicals and, with small adjustments, may be used to predict the fate and exposure of VMPs in aquaculture ponds, principally those applied directly to water (note that the fish compartment is not included and will require some efforts to be incorporated). The GREAT-ER model was originally developed to evaluate the discharge of down-the-drain chemicals in river networks taking into account removal in WWTPs (Koormann *et al.* 2006). The model has potential to simulate river

networks impacted by several aquaculture farms (with or without WWTP) at the regional scale and to assess the combined exposure of aquaculture chemicals with other chemicals emitted from urban or industrial areas.

5.2 Models for marine aquaculture production systems

Cages are the main marine finfish aquaculture production system in Europe, and are used in coastal fjords, sea inlets and more exposed marine locations. Unlike semi-closed or closed systems, such as ponds and raceways, cages are open systems so chemical and organic wastes are released directly into the environment. Two principal types of ERA models exist for cage systems in the marine environment: (1) models that assess dilution and dispersal of chemicals applied in bath treatments (i.e., antifungals and some antiparasitics), and (2) 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 (Table 4).

In addition to the equations proposed for pond systems, Metcalfe *et al.* (2009) also provide algorithms to estimate initial chemical concentrations from bath or in-feed medication used in aquaculture cages. More sophisticated models have been developed to refine the environmental exposure of bath-treatments used in cage systems, using different environmental data. For instance, Gillibrand and Turrell (1997) provided an algorithm to estimate the chemical bath dose that can be used in Scottish salmon cages, considering water replacement rates and the corresponding EQS. They also provide a basic modelling approach to predict concentrations at a given distance from the administration point and to calculate the extension of the mixing zone (i.e., area in which the EQS is exceeded). Using this model, they compared their predictions with dichlorvos concentrations measured in a fish farm (Turrell 1990; Davies *et al.* 1991) and estimated the maximum annual mass of dichlorvos that could be used in 63 Scottish lochs (= sea inlets) using a database of physical and hydrological characteristics. Although limited by a number of basic assumptions (e.g. diffusion coefficient data), Gillibrand and Turrell (1997) provided one of the first advection-diffusion modelling approaches to estimate the dispersal of veterinary medicines, which served as an example for more sophisticated modelling tools that were developed later.

SEPA (2008) developed the BathAuto modelling tool that integrates a short-term model for salmon sea-lice treatments that are rapidly broken down or that bind to particles in water (e.g. cypermethrin, deltamethrin), and a long-term model, developed by Gillibrand and Turrell (1999), for compounds that require multiple applications (e.g. azamethiphos). The short-term tool calculates water exposure

concentrations 6h after administration, taking chemical dispersion and advection into account, and a limited number of input parameters (Table 4). The long-term tool incorporates chemical diffusion and decay, and calculates exposure concentrations over a period of 72h in a loch, strait or open water scenario. It has been calibrated and evaluated with chemical release experiments conducted with dichlorvos (Davies *et al.* 1991). Both, the short- and the long-term modelling tools, are bi-dimensional and can predict the area in which the calculated concentration exceeds the proposed EQS as well as the predicted peak exposure concentration. The BathAuto model is used to perform farm-specific ERAs in Scotland and estimates the number of cages that can be treated in a given time span and the amount of chemical that can be used to comply with the EQSs.

Table 4 about here.

Falconer and Hartnett (1993) developed the Depth Integrated Velocity And Solute Transport (DIVAST) model. It is a two-dimensional, hydrodynamic and solute transport model for evaluating the environmental impacts of estuarine and coastal Atlantic salmon aquaculture in Ireland. The model has been used to evaluate eutrophication processes and includes several water quality constituents (e.g. several forms of nitrogen, dissolved oxygen, phosphorous, salinity). Furthermore, it has been used to predict the dispersal of the sea-lice bath treatment of dichlorvos applied to Atlantic salmon cages in Beirtreach Bui Bay, Ireland (Falconer & Hartnett 1993).

VMPs applied in-feed are modelled using particle tracking models which assess the dispersal of solid wastes from fish cages. In Scotland, AutoDEPOMOD is presently used in the regulatory ERA of in-feed VMPs (SEPA, 2005). Originally developed as DEPOMOD by Cromey *et al.* (2002) to estimate the ecological impact of suspended solids, the model uses semi-empirical quantitative relationships between the calculated solid accumulation rate ($\text{g/m}^2/\text{year}$) and has been adapted to consider the effectivity of emamectin benzoate and teflubenzuron against sea lice (SEPA 2005). Recently, the model underwent a major revision which involved recalibration and validation of near field modules and inclusion of a far field module for assessment of environmental risk at greater distances from the farm. The updated model is known as NewDEPOMOD (Black *et al.* 2016). This revision comes at a time when concerns have been raised over the far-field effects of in-feed VMPs in Scotland (SARF098, 2016).

Cromey *et al.* (2012) developed an adapted version of DEPOMOD, MERAMOD, to predict the benthic impacts of gilthead sea bream and sea bass farms in eastern Mediterranean aquaculture by including new biosolid fate processes that had not been taken into account in DEPOMOD. The main difference

between DEPOMOD and MERAMOD is that the latter assumes that waste feed and other solid particles both in the water column and on the sea bed can be consumed by wild fish which is a common occurrence in the Mediterranean Sea. Furthermore, the cage-specific feed inputs and settling velocities can be specified, which allows the modelling of farms in which more than one species or fish cohorts are grown at the same time. Similarly to AutoDEPOMOD, MERAMOD could be used to predict the sediment deposition of VMPs, however we are not aware of any modelling exercise or validation study considering this aspect.

In addition to the models described above, there are other models that have not yet been implemented for the ERA of VMPs, but that have large potential for their application. For example, Kim *et al.* (2004) expanded the Princeton Ocean Model (Blumberg & Mellor 1987) and formed a coupled three-dimensional hydrodynamic and ecotoxicological model (EMT-3D), which considers several processes (e.g. adsorption/desorption from organic matter, uptake and excretion by marine organisms, etc.) and that can be used to assess the bioaccumulation of aquaculture chemicals into different marine organisms. Another example is the integrated hydrodynamical and chemical fate model MAMPEC (Van Hattum *et al.* 2014), which was originally developed for predicting environmental concentrations of antifoulants in harbours, rivers, estuaries and open waters, and which offers possibilities for adaptation to aquaculture cage scenarios.

6. Are available models suitable to perform ERAs for the main aquaculture VMPs and production systems in Europe?

Table 5 shows a summary of the available models regarding their usability to assess exposure, effects and risks of VMPs in the major European aquaculture production species and systems. Given the current development status of most modelling approaches, further efforts should be dedicated to test and adapt the current existing tools for different aquaculture species, VMPs and environmental scenarios. For example, models for assessing the exposure of VMPs applied to fish ponds have been originally developed for aquaculture production systems and species raised in (sub-)tropical Asian environments, and therefore never applied for European ERA scenarios. Tools like the ERA-AQUA model (Rico *et al.* 2012, 2013) offer enough flexibility to perform ERAs for chemicals and freshwater species raised in Europe such as carps grown in earthen ponds or rainbow trout tanks with slow flow, and should therefore be tested for such purposes. On the other hand, only two models have been explicitly used to assess dilution and dispersal of in-feed medication and bath treatments applied to

hatchery tanks or raceways, and further evaluation of these tools for different chemicals and scenarios may still be warranted.

Models available for the marine environment have had a clear focus on assessing environmental exposure of bath treatments or in-feed medications used for treating sea-lice infestations in Atlantic salmon (Table 5). Some of the bath treatment models may not be currently in use as they were developed for assessing environmental exposure of chemicals that are no longer authorized (e.g. dichlorvos; Gillibrand and Turrell 1997). As already demonstrated by several authors (e.g. Cromey *et al.* 2002), marine particle tracking modelling tools can, with few adjustments, be used to predict the fate of chemical substances administered mixed with pelleted feeds; while marine antifouling models (e.g. MAMPEC) may also be adapted to perform risk assessments of VMPs. To date, the number of studies demonstrating the applicability of these modelling tools for these purposes is scarce, particularly for antimicrobial compounds. Further research should be dedicated to test and adapt models developed to assess the environmental exposure and risks of VMPs used in Scottish salmon cages for the particular fjord ecosystems of Scandinavian countries, and for the major aquaculture species produced under Mediterranean conditions.

Table 5 about here.

7. Are available models properly addressing the protection goals and standards set in European regulations?

Most of the available models do not assess ecotoxicological risks or simply rely on the use of regulatory EQSs for making comparisons with the calculated exposure concentrations (Table 5). As indicated above, the models applied under the Scottish regulation use these EQSs to assess the suitability of farm licenses in new locations, and to predict the maximum amount of chemical applied and corresponding fish biomass that can be cultivated. It must be noted, however, that EQSs and the majority of calculated PNEC used in prospective ERAs are based on assessment factors (i.e., 10-1000) applied to a single species laboratory-based toxicity value (typically an EC50 or a NOEC) to account for long-term effects in the environment neighbouring aquaculture. These assessment factors were selected to ensure that the proposed EQS or PNECs are sufficiently safe to prevent unacceptable chemical effects at the community and ecosystem function levels, the protection goals set by the current EU regulation (VICH 2000, 2004). However, the use of PNEC or EQS-based RQ models still offer large limitations. The first limitation is related to the uncertainty on the protection level provided by the proposed safe environmental concentrations (PNECs or EQSs), since they have been seldom validated under a wide range of environmental conditions or using model ecosystem studies (i.e.,

micro- and mesocosms) that reflect (semi-)natural conditions. Another major limitations of such ERA approaches include the incapacity to predict ecological risks when exposure patterns differ (or temporally exceed) those used in the toxicity experiments, or the inability to characterize the magnitude of direct and indirect ecotoxicological effects on populations and communities when the proposed thresholds are exceeded.

The integration of chemical effect models in the ERA of aquaculture VMPs offers opportunities for evaluating the consequences of generic EQS or PNEC exceedances identified in the low tiers of the ERA. Such models provide opportunities to improve the linkage between exposure and individual-level effects, and can be used to predict and describe ecotoxicological risks at the population and community-levels (Galic *et al.* 2010, Schmolke *et al.* 2010). In this respect, toxicokinetic/toxicodynamic (TKTD) models can be used to assess the effects of variable or prolonged exposure patterns over individual endpoints (Ashauer & Escher, 2010), in the surrounding environment of aquaculture farms that apply multiple antiparasitic treatments in one or several fish pens. These models have been developed for quantal effects (e.g., mortality, immobilisation; Jager *et al.*, 2011) as well as for graded effects (e.g., growth, reproduction; Jager *et al.*, 2006). TKTD models for quantal effects are starting to be introduced in aquaculture to assess the risks of repeated pulses of salmon sea-lice treatments to non-target crustaceans such as the northern shrimp (*Pandalus borealis*, PestPuls project Renée Katrin Bechmann, IRIS International Research Institute of Stavanger, personal communication). Population effect models have recently been used in ERA to assess the recolonization of polluted areas and to assess the intrinsic recovery capacity of aquatic populations to chemical stress (Van den Brink *et al.* 2007; Galic *et al.* 2010). In aquaculture, they have been extensively used to predict population dynamics of parasitic sea-lice under different environmental conditions and management practices (Krkošek *et al.* 2009, Rittenhouse *et al.* 2016); however, they have not yet been used to predict VMP risks to non-target aquatic organisms. In this respect, they offer opportunities to assess how local effects to a range of organisms may propagate to the whole population and to places further away the administration area (action at distance). They can also be applied to evaluate which VMP use practices should be implemented to prevent long-term population declines in semi-confined areas with multiple farms and VMP applications such as the Scandinavian fjords. Finally, ecosystem models such as AQUATOX (Park *et al.* 2008) or others (see reviews by Koelmans *et al.* 2001 and Sharma and Kansal 2013) enable evaluation of the interaction between species and can be used to study the propagation of chemical-related effects to higher levels of biological organization (communities, ecosystems). Although these models have been extensively used to assess nutrient alterations, or invasive species effects to freshwater and marine ecosystems (Dowd 2005; Naylor *et al.* 2005), they

have never been used to predict aquaculture VMP effects on structural or functional parameters of ecosystems.

It should be noted that the integration of population and ecosystem models in the ERA of aquaculture VMPs is based on the acceptability that some chemical-related effects may occur under certain spatial and temporal frames (Figure 2). Therefore, this requires an *a priori* decision on the magnitude of effect that can be tolerated inside and outside a defined area (i.e., allowable zone of effect) within a given temporal scale, which should be supported by the definition of more specific protection goals than the ones already provided by VICH (VICH 2000, 2004). Moreover, similarly to the exposure models, the implementation of such ecological models for the ERA of aquaculture VMPs will require well defined (site-specific) ecological scenarios, built on the basis of vulnerable taxa representative for the main VMP classes and impacted freshwater or marine environment. Such ecological scenarios should be constituted with a set of parameter values that encompass biological trait information for the selected vulnerable taxa. Such trait data is used to assess and describe the susceptibility of the selected taxa to be exposed to the applied VMPs (e.g. life cycle characteristics), their capacity to recover from chemical stress (e.g. dispersal and reproductive characteristics) and their interaction with other species (Rico *et al.* 2016; Franco *et al.* 2017).

Figure 2 about here.

8. Concluding remarks and recommendations

Although significant progress has been made in the development of alternative biological and mechanical disease prevention and treatment measures, chemotherapy, and the environmental concerns that it generates, is expected to remain an important issue for European aquaculture. This will be particularly important as some farmers have expressed the need of more chemicals to treat some infectious diseases (Verner-Jeffreys and Taylor 2015), particularly in the context of acquired resistance among the target pests (e.g. sea-lice, some pathogenic bacteria), and due to the introduction of new aquaculture species that require new product authorizations. Therefore, the assessment and minimization of the environmental side-effects of available or newly developed VMP treatments will be a key research priority to preserve the environmental sustainability of the European aquaculture industry.

The majority of models that have been developed to perform ERAs of VMPs have focused on antiparasitic exposure assessments in the surroundings of marine salmon production systems. Still some efforts are needed to adapt, test and validate exposure models to in-feed (antibiotic) treatments used in salmon cages and to key Mediterranean species (e.g. Gilthead seabream, European seabass).

The validation of such models will depend on the availability of quality chemical monitoring datasets, which can also be used to refine the processes included in the exposure assessment. Important processes to take into account in the refinement of PEC calculations include chemical partitioning between water, suspended materials and sediments, as the majority of antiparasitic bath-treatments have strong affinities for organic matter and in-feed medications are prone to end up in seabeds after excretion by treated fish and deposition of uneaten feeds. The particle tracking models developed for aquaculture wastes generally consider only near-field effects. This could be a limitation, since VMPs can be transported with particulate materials and form contaminant plumes, affecting coastal ecosystems at relatively large distances from the place of application (several kms; Ernst *et al.* 2014). This is particularly important in areas with one-directional currents favouring dispersal towards the coast and in locations with multiple farms, which contribute to cumulative impacts. Although some studies have started to apply hydrodynamic models to investigate dispersion of particles attaching VMP residues from fish cages and far-field effects (e.g. Navas *et al.* 2011; Rochford *et al.*, 2017), further progress is needed to provide regional assessments that help to set boundary conditions for site-specific modelling approaches - see examples from Scotland, Wolf *et al.* (2016), and Norway, Albretsen *et al.* (2011). Further improvements for models used in marine ERAs should also consider the integration of mechanistic effect modelling tools that are capable of linking exposure concentrations to individual endpoints (by toxicokinetic/toxicodynamics) and population-level effects after pulsed exposure conditions (i.e., due to several chemical applications in one or several farms within the same water body).

Far less models exist for inland aquaculture production systems as compared to marine aquaculture. Further adaptation of existing tools to salmon hatcheries, carp ponds and rainbow trout tank systems are required. Refinements of exposure assessments could be achieved by linking the chemical exposure output of existing farm-level modelling tools with river or stream modelling tools that are capable of assessing chemical dispersal in lotic systems at a larger-scale. Such approaches may also take into account the impacts of nutrient (N and P) inputs in combination with other stressors (e.g. flow regimes, water quality fluctuations, Tello *et al.* 2010).

To sum up, the ERA of aquaculture chemicals has been developed to a varied extent by the different EU member states. Scotland has led the way partly due to the nature of the environment and the particularities of its regulatory system, while a less dedicated use of ERA models has taken place in other salmon-producing countries (e.g. Norway, Sweden) and in Mediterranean and Eastern Europe regions. Basic guidance, such as that provided by VICH (VICH 2000, 2004), contributes to harmonizing

the ERA protection goals, procedures and basic data requirements among countries, but it is not without faults and science-based tools and results need still to be debated and potentially incorporated into revised versions (Lillicrap 2018). Taking a step forward, it would be useful if a common and widely validated ERA modelling approach could be developed for at least those countries that rely on generic ERAs. In this regard, the selection of a suitable set of exposure models, which cover the main species and environmental scenarios in Europe, would be beneficial for various reasons. Firstly, it would help in directing economic efforts towards its improvement, testing and validation. Secondly, different stakeholders (i.e., risk assessors, regulators, farm managers) can be better acquainted with its use, and thirdly this will prevent different levels of ERA and enforcement being taken among different member states. A common modelling strategy for ERA will also benefit from a set of ready-to-use realistic (worst-case) environmental scenarios that represent the main physico-chemical conditions, geographic regions and management practices within Europe, similarly to the approach adopted within the regulatory ERA of plant protection products (FOCUS 2001). The development of such a task for aquaculture would require that the major aquaculture zones in Europe are classified according to their environmental characteristics (e.g. current and bathymetry characteristics), and that main aquaculture production practices are identified for at least the key species produced. In this way, the toolbox should also be complemented with a set of specific protection goals that consider the temporal and spatial frame of allowable chemical effects, and ecological modelling tools that allow the prediction of population and community-level effects under such relevant spatial-temporal frames.

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Table 1. List of authorized veterinary medicines used in aquaculture production in the top EEA aquaculture production countries.

	Norway [†]	United Kingdom [‡]	Greece [§]	Spain [¶]	Italy ^{††}
Antibiotics					
Florfenicol	AS, H	AS, (RT)	GS, ES	RT	FF
Oxytetracycline		AS, RT	GS, ES	AS, RT, TB, GS, EE, ES, CC	FF
Chlortetracycline			GS, ES		FF
Amoxicillin		AS	GS, ES		RT
Flumequine			GS, ES	RT	FF
Sulfadiazine-trimethoprim	FF		GS, ES		FF
Oxolinic acid	AS,H, RT, TB		GS, ES		FF
Antifungals					
Bronopol	AS, RT	AS, RT		AS, RT	FF
Antiparasitics					
Azamethiphos	AS	AS			RT
Teflubenzuron	AS	AS			RT
Diflubenzuron	AS				RT
Eamectin benzoate	AS, RT	AS	GS, ES	AS, RT	FF
Deltamethrin	AS	AS, RT			FF
Cypermethrin	AS	AS			RT
Hydrogen Peroxide	AS	AS	GS, ES		FF
Formaldehyde			GS, ES	GS, TB	FF

AS: Atlantic salmon, RT: rainbow trout, GS: gilthead seabream, ES: European seabass, TB: turbot, EE: European eel, CC: common carp, H: halibut, FF: all finfish. Species between brackets indicate examples of use under the cascade.

[†] NIPH, 2009. Pharmaceutical use in Norwegian fish farming in 2001–2008. Electronic Citation. Accessed on: January 2013. Norwegian Medicines Agency (2017) Pharmaceuticals for fish, holding Marketing authorisation in Norway. Electronic Citation Accessed January 2018. The Norwegian Veterinary Institute, (2016) Use of Antibiotics in Norwegian Aquaculture on behalf of Norwegian Seafood Council. February 3, 2016.

[‡] VMD (2016). Veterinary Medicines Directorate (VMD) of the United Kingdom. Product information Database. Available at: <http://www.vmd.defra.gov.uk/ProductInformationDatabase/>. Accessed on: 30 July 2016.

[§] Ministry of rural Development and Food, Hellenic Republic. Accessed on: 2 August 2016 (www.minagric.gr)

[¶] AEMPS (2016). Spanish Agency of Medicines and Sanitary Products. Online information centre AEMPS-CIMA. Available at: <https://cimavet.aemps.es/cimavet/CargaFormulario.do>. Accessed on: 12 July 2016.

^{††} Agnetti A, Latini M, Di Raino E, Ghittino C (2012). Il controllo delle malattie dei pesci nel bacino del Mediterraneo. XV Convegno Nazionale SIPI - Workshop "Acquacoltura Mediterranea: aspetti normativi e sanitari a confronto" Erice, 2012.

Table 2. Environmental Quality Standards (EQSs) for antiparasitic and antifungal drugs used in Scotland (SEPA 2014). MAC: maximum allowable concentration; ww: wet weight; dw: dry weight.

Active ingredient	Environment	Environmental Quality Standards
Azamethiphos (bath treatment)	Marine waters	MAC 3h: 250 ng/L MAC 24h: 150 ng/L MAC 72h: 40 ng/L
Cypermethrin (bath treatment)	Marine waters	Annual average: 0.05 ng/L MAC 3h: 16 ng/L MAC 24h: 0.5 ng/L
Deltamethrin (bath treatment)	Marine waters	Annual average: 0.3 ng/L MAC 3h: 9 ng/L MAC 6h: 6 ng/L MAC 12h: 4 ng/L MAC 24h: 2 ng/L MAC 48h: 1 ng/L
Hydrogen peroxide (bath treatment)	Marine waters	None (considered to pose an insignificant risk)
Emamectin benzoate (in-feed) §	Marine waters	MAC: 0.22 ng/L
	Marine sediments	MAC: 0.763 µg/kg ww outside AZE [†] MAC: 7.63 µg/kg ww inside AZE [‡]
Teflubenzuron (in-feed)	Marine waters	Annual average: 6 ng/L MAC: 30 ng/L
	Freshwater sediments	MAC: 10 mg/kg dw inside AZE [‡]
	Marine sediments	MAC: 2 µg/kg dw outside AZE [†] MAC: 10 mg/kg dw inside AZE [‡]
Bronopol (bath treatment)	Freshwaters	MAC: 70,000 ng/L

[†] Allowable zone of effect (AZE) of 100 m from edge of cages, increased up to 150 m where strong directional currents exist.

[‡] Allowable zone of effect (AZE) of 25 m from edge of cages.

§ A re-evaluation of the proposed standards for emamectin benzoate has been carried out, so it is expected that new EQSs become available shortly in the Scottish regulation. The new EQSs are: Marine waters: MAC: 0.8 ng/L, Annual average: 0.435 ng/L. Marine sediments: MAC outside AZE: 0.012 µg/kg dw, Annual average: 0.12 µg/kg dw (Benson *et al.* 2017).

Table 3. ERA models for inland aquaculture production systems.

Model name and reference	Production system	VMPs and mode of application	Input data requirements	Exposure assessment	Effect assessment	Risk assessment	Validation status
Simple algorithms (Metcalfe <i>et al.</i> 2009) [†]	Ponds, net-pens, cages or flow-through systems (no species-specific)	All VMPs applied mixed with feed or directly to water	Basic farm management data and environmental characteristics Chemical use data	Algorithms used to estimate first-tier peak PECs and average PECs over application period disregarding dissipation processes	None	Not calculated	None
VDC (Phong <i>et al.</i> 2009) [‡]	Ponds (no species-specific)	All VMPs applied mixed with feed	Pond characteristics Feed consumption rate Chemical use data Chemical physico-chemical properties	The model dynamically predicts VMP concentrations in the pond water and pond sediment	None	Not calculated	Unknown
ERA-AQUA Rico <i>et al.</i> (2012, 2013) [‡]	Ponds or tanks. Can be parameterized for a wide range of finfish and crustacean species.	All VMPs applied mixed with feed or directly to water	Pond data and environmental discharge characteristics Species characteristics Production management data Chemical use data Chemical physico-chemical properties Pharmacokinetics data Ecotoxicity data Food safety data	The model dynamically predicts VMP concentrations in the pond water, pond sediment, cultured species and the aquatic ecosystem receiving pond effluents. Provides peak PECs and TWA concentrations.	Acute and chronic effect assessments for: primary producers, invertebrates and fish	Risks are calculated following a risk quotient (PEC/PNEC) approach	The VMP fate submodel has been evaluated for antibiotics: shrimp pond in China (sulfadiazine) and Pangasius catfish pond in Vietnam (enrofloxacin)
Chloramine-T dilution models (Gaikowski <i>et al.</i> 2004) [§]	Flow-through hatchery (no species-specific)	Antimicrobials (disinfectants) applied directly to water	Chemical use data Water flow	Simple algorithms used to estimate chemical dilution over time in farm effluents	None	Not calculated	Unknown
WASP 7 (Ambrose <i>et al.</i> 1993) used by Rose and Pedersen (2005) [§]	Hatcheries (no species-specific)	Antibiotic applied mixed with feed	Hydrological and physicochemical characteristics of stream receiving effluents Chemical physico-chemical properties of the evaluated substance	The model dynamically predicts VMP concentrations in the water column and sediments in different segments of streams receiving farm effluents	None	Not calculated	Calibrated for state variables (dissolved oxygen, nutrients) but not for VMPs
PYCEZE Elanco Animal health and University of Stirling (no reference) [§]	Net-pens and cages (salmonids)	Antifungals or antiprotozoans applied directly to water (bronopol)	Wind speed or water flow Distance to shore Dispersion coefficient Mixing zone depth Chemical dose Degradation rate	The model dynamically predicts chemical concentrations in the water for 3 h	None	Not calculated	Monitoring data for bronopol in Loch Lanagvat, Isle of Harris (UK)

[†] Used for regulatory purposes; [‡] Not yet used for regulatory purposes; [§] Unknown use for regulatory purposes. See text for acronyms.

Table 4. ERA models for marine aquaculture production systems.

Model name and reference	Production system	VMPs and mode of application	Input data requirements	Exposure assessment	Effect assessment	Risk assessment	Validation status
Simple algorithms (Metcalf <i>et al.</i> 2009) [†]	Net-pens and cages (no species-specific)	All chemicals applied directly to water or in-feed applications	Basic farm, management and environmental characteristics Chemical use data (dose, treatment duration, mode of application)	Algorithms used to estimate first-tier peak PECs and average PECs over application period disregarding dissipation processes	None	Not calculated	None
No name (dichlorvos model) Gillibrand and Turrell (1997) [‡]	Net-pens and cages in lochs (no species-specific)	Antiparasitics applied directly to water (dichlorvos)	Chemical dose Chemical decay rate Diffusion coefficients Morphology and hydrology of the loch	Water concentrations dynamics	Uses EQSs	Calculates the percentage area of the loch that exceeds the EQS during the simulation period, and exceedance of short-term (24h) EQSs	Monitoring data for dichlorvos collected in Loch Airlort (UK) in 1990
BATH-AUTO (SEPA 2008) [§]	Net-pens and cages (salmonids)	Antiparasitics treatments applied directly to water (cypermethrin, deltamethrin, azamethiphos)	Short-term (6h): Chemical dose Current speed Cage volume Distance to shore Water depth Long-term (72h): The above, and additional physical scenario parameters Current parameters Cage configuration Dose and number of treatments Chemical decay rate	Short-term (6h): Water concentration after a single treatment over 6h post-application Long-term (72h): The model produces time-series of peak concentrations and calculates the area exceeding the EQS	Uses EQSs	Compares modelled exposure concentrations with EQSs and estimates the amount of chemical that could be applied to meet the EQS. It also calculates the area in which the chemical exposure exceeds the EQS	Long-term model: monitoring data for dichlorvos collected in Loch Airlort (UK) in 1990
DIVAST Falconer and Hartnett (1993) [‡]	Net-pens and cages (salmonids)	Antiparasitics applied directly to water (dichlorvos)	Bathymetry Tide conditions River inflows, wind speed Open-boundary conditions Cage-site location Production rates Discharge regimes Chemical decay and uptake rates Dispersion coefficients Chemical dose	The model dynamically predicts concentrations of chemical in water at a given distance from the farm (two dimensional)	None	None	Dispersion and sedimentation study in Beirtreach Bui Bay (Ireland)

AutoDEPOMOD (Cromeey <i>et al.</i> 2002) §	Net-pens and cages (salmonids)	Antiparasitics applied mixed with feed (teflubenzuron, emamectin benzoate)	Bathymetry Hydrography Farm distribution Feed load and settling velocities of waste material Chemical dose, percentage of excretion excreted and decay	The model dynamically predicts chemical concentrations in sediment beds (three dimensional)	Uses EQSs. Invertebrate community effects (ITI) and total abundance are calculated but only for assessing the effects of solid waste deposition	Comparison of sediment concentrations with EQS	Solid waste dispersal and biological impacts. Scottish coastal farms and sea loch systems (no published validation with VMPs)
MERAMOD (Cromeey <i>et al.</i> 2012) ‡	Net-pens and cages (gilthead sea bream and sea bass)	Chemical treatments applied mixed with feed	Bathymetry Hydrography Farm distribution Feed load, digestibility, and settling velocities of waste material Chemical dose, percentage of chemical excreted and decay	The model dynamically predicts chemical concentrations in sediment beds	Uses EQSs. Invertebrate community indices are calculated but only for assessing the effects of solid waste deposition	Comparison of sediment concentrations with EQS	Solid waste dispersal and biological impacts. Fish farms in the Mediterranean sea (no published validation with VMPs)

† Used for regulatory purposes; ‡ Unknown use for regulatory purposes; § Used for regulatory purposes, Scottish EPA; See text for acronyms.

Table 5. Summary of major aquaculture production systems in Europe and models available for assessing the environmental exposure, effect and risks of VMPs applied via medicated feeds or via bath-treatments. Each letter represents one model. Bold letters represent models that have been explicitly used for this purpose in European scenarios according the existing literature, whereas regular text letters represent models that have potential to be used for such purpose but that have not been yet used according to the existing literature.

Major species (production system), and geographic region	In-feed medication			Bath treatments		
	Exposure	Effect [†]	Risk [‡]	Exposure	Effect [†]	Risk [‡]
Rainbow trout (tanks/raceways), Inland	a, e			a, d		
Carps (ponds), Inland	a, b, c	c	c	a, c	c	c
Salmon (cages or Net-pens), Atlantic	a, j	j	j	a, f, g, h, i	g, h	g, h
Gilthead seabream (cages or Net-pens), Mediterranean	a, k	k	k	a		
European seabass (cages or Net-pens), Mediterranean	a, k	k	k	a		

^a Simple algorithms (Metcalf *et al.* 2009); ^b VDC model (Phong *et al.* 2009); ^c ERA-AQUA model (Rico *et al.* 2012, 2013); ^d Chloramine-T dilution model (Gaikowski *et al.* 2004); ^e WASP 7 model (Ambrose *et al.* 1993); ^f PYCEZE model (no reference); ^g No specific name (dichlorvos model; Gillibrand and Turrell 1997); ^h BATH-AUTO model (SEPA 2008); ⁱ DIVAST model (Falconer and Hartnett 1993); ^j AutoDEPOMOD model (Cromey *et al.* 2002); ^k MERAMOD model (Cromey *et al.* 2012).

[†] Effect assessment based on the use of PNECs or EQSs.

[‡] Risk assessment based on PEC exceedance of PNEC or EQSs

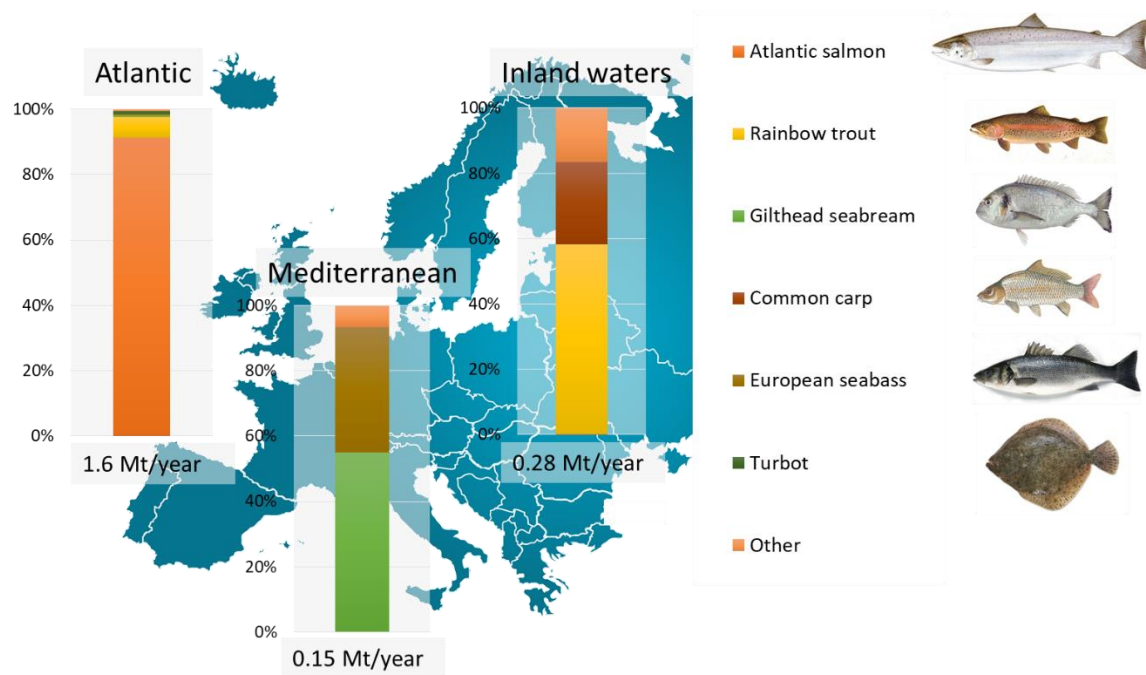


Figure 1. Annual finfish production volume in inland waters and in the Atlantic and Mediterranean regions, and relative contribution per species. The Mediterranean region includes the Black sea. (Production data is for 2014. Data source: FAO 2016b).

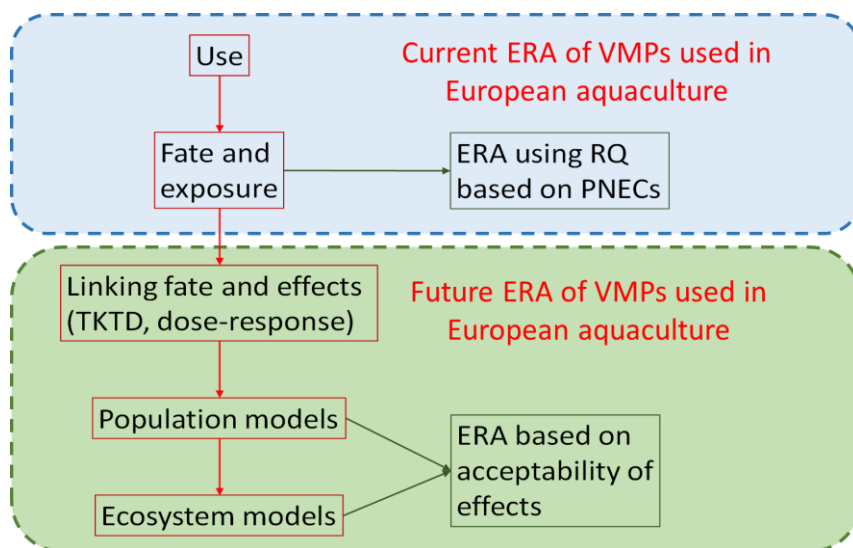


Figure 2. Conceptual scheme showing the current and proposed future modelling approach for the ERA of VMPs in European aquaculture.