Integrating Environmental Risks and Mitigation into Benefit-Risk Assessment of Veterinary Medicinal Products

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Abstract

The regulation for the authorization of veterinary medicinal products (VMPs) to the European market requires an environmental risk assessment (ERA). The ERA results are then included in a benefit-risk assessment. However, knowledge and experience in the benefit-risk assessment implementation is developing and current guidelines are vague on how environmental risks and risk mitigation measures (RMMs) are integrated into the benefit-risk assessment process. This study was therefore conducted to develop new approaches and knowledge for the integration of environmental risk assessment into the benefit-risk assessment process. Novel methodologies for the integration of ERA data into the benefit-risk assessment were initially developed. The main challenge of implementing a benefit-risk assessment is that benefits are measurements of animal health whereas the risks are environmental measurements therefore comparison is difficult. To address this challenge, categorization approaches for benefits and risks were developed in three different methodologies (i.e., a summative categorization, a visual scoring matrix and a comparative categorization). Work was then done, using available information from the literature to explore the environmental risks of the antibiotic tylosin. Modelling of exposure and toxicity to aquatic and terrestrial ecosystems concluded that a number of treatment scenarios have unacceptable risks and are therefore appropriate for benefit-risk consideration. The data generated for tylosin along with additional risk data for two VMPs of high environmental concern (i.e., ivermectin and diclofenac) were applied to the benefit-risk assessment methodologies previously developed. Valuable insights into differences in applicability, adaptability, sensitivity and transparency of the proposed categorization methodologies were found. Finally, a novel interview approach was employed to gain VMP user insights into users' attitudes and perceptions of RMMs as well as on farm practicality. Overall, the sequential investigations presented in this thesis have built a foundation for the continued development of benefit-risk assessment process for VMPs has been lacking to date.

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Authors Declaration

The content of this thesis is original work that I have conducted as a PhD student under the supervision of Professor Alistair Boxall, Dr. Peter Howley, Dr. Chris Sinclair and Dr. Glyn Jones (June 2014 – November 2018).

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I hereby declare that this thesis is a presentation of original work undertaken by myself, except where otherwise acknowledged. This work has not previously been presented for an award at this, or any other University. All sources are acknowledged as References.

1 Introduction

Integration of the environmental risks into the benefit-risk assessment process for veterinary medicinal products (VMPs) is a novel area of research. There has been limited previous work conducted which considers integration of environmental risks into a benefit-risk assessment for VMPs. Similarly, limited work has considered the benefits and environmental risk trade-offs of pharmaceuticals more broadly. Therefore this chapter begins with a general introduction to the environmental risks of veterinary medicines (Section 1.1). Subsequently, Section 1.2 introduces the application of environmental risk assessment and benefit-risk assessment for VMPs in the European authorization process. Previous work that has considered making the environmental risks comparable to benefits is then reviewed (Section 1.3). Finally, the thesis aims and objectives are defined to support the development of this unique area of research.

1.1 Veterinary medicines and environmental risks

Application of VMPs in livestock product supports an important agriculture sector. A primary source of food and protein is supplied to the global population from livestock agriculture (Aiking, 2014). Further, the global trend for livestock production is growing in both supply and demand (Tilman *et al.*, 2002; FAO, 2011). Intensive livestock production, with large numbers of animals, has developed to support the increasing human food demand (Tilman *et al.*, 2002). However, production with higher densities of animals creates conditions for disease development and transmission (Tilman *et al.*, 2002). VMPs are available to support the treatment and management of these diseases.

VMPs are pharmaceutical substances applied to prevent diseases, treat diseases or alter the physiological functions of animals (Directive 2001/82/EC, as amended by Directive 2004/28/EC (European Parliament, 2004a)). Maintenance of the health of livestock animals involves the use of large quantities of VMPs. For example, Kools *et al.*, (2008) estimated that the 2004 usage of VMPs in 25 European countries was 6051 tonnes in meat producing animals. A diversity of VMPs are available to support treatments of different diagnoses. For example, two major use categories of VMPs are the antibiotics and anthelmintics that treat bacterial and parasitic conditions, respectively (Kools *et al.*, 2008; Boxall *et al.*, 2003a).

Post-application, VMPs can reach the natural environment through a variety of pathways. Depending on the livestock system (i.e., aquaculture, intensively-reared, or pasture), different routes of entry (e.g., through manure or wash off) can result in environmental exposure (VICH, 2004). Exposure pathways are both direct (e.g., topical application wash

off) and indirect (e.g., excretion and subsequent spreading of dung and urine) (Boxall *et al.*, 2003b). Figure 1.1 summarizes the direct and indirect pathways of VMPs into the environment that are currently considered in the regulatory environmental risk assessment process for VMPs.

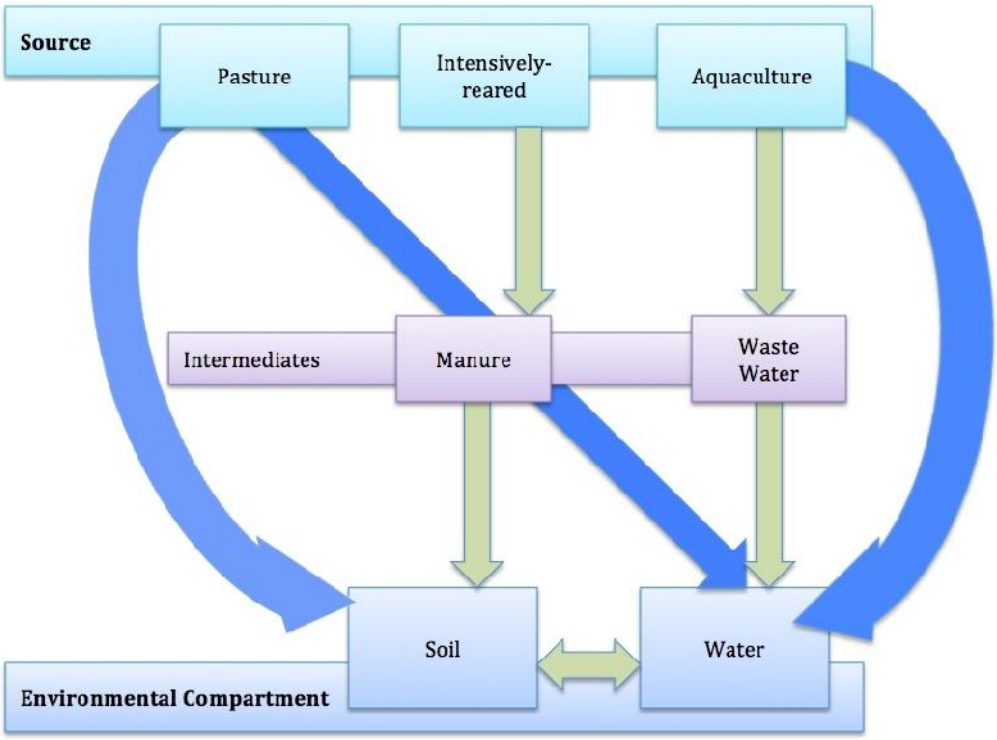

Figure 1.1 Direct (blue arrows) and indirect (green arrows) exposure pathways considered in the European environmental risk assessment of VMPs (EMA, 2008).

Environmental monitoring has detected a range of active ingredients used in VMPs in different environmental compartments across the globe, including representatives of the antibiotic and anthelmintics families (Boxall *et al.*, 2004; Sarmah *et al.*, 2006; Obimakinde *et al.*, 2017).

The observed exposure of the natural environment to VMPs has led to a number of investigations to understand the effects of these substances on non-target species. Toxic effects have been shown for a range of VMPs in both aquatic and terrestrial organisms (Boxall *et al.*, 2004; Lumaret *et al.*, 2012; Pan and Chu, 2016; Obimakinde *et al.*, 2017) and biomagnification of VMPs is also a possibility (Obimakinde *et al.*, 2017). Scientific evidence for environmental risks has led to the development of regulation (Küster and Adler, 2014). Specifically, consideration of the environmental risks of VMPs in the European authorization process was established in 1990 (Directive 90/676/EEC (European Parliament 1990)).

1.2 Regulation of VMP environmental risks and inclusion in benefit-risk assessment

European policies regulate VMPs to ensure product availability for disease management and maintenance of animal and human health and welfare, while minimizing risks to human, animal and environmental health. While these substances have benefits to animals and humans (e.g., through the prevention of zoonotic diseases) and to the economy, they also create a potential for environmental exposure and consequent risk. In Europe there are four VMP authorization pathways, i.e.: centralized, decentralized, national, and mutually recognized procedures (European Parliament, 2004a). For centrally authorized products, the European Medicines Agency's (EMA) Committee for Medicinal Products for Veterinary Use (CVMP) will review applications and advise to authorize or reject authorization (Commission Regulation (EC) No 726/2004 (European Parliament, 2004b)). Centrally authorized products have access to the current 28 member states and 3 European Economic Area countries. All 31 countries have their own competent authorities (EMA, 2017). Decisions for decentralized, national, and mutually recognized processes will involve the competent authorities of the member state for which applicants are seeking market access (European Parliament, 2004a).

All VMP market authorization processes require that environmental risk be included in the benefit-risk assessment (European Parliament, 2004a). Environmental risk assessments (ERAs) generate data on environmental exposure, effects and risks following procedures described in a range of guidance documents (VICH 2000, 2004; EMA 2008). In the benefit-risk assessment, ERA data and other risk data must be compared to efficacy data and the ethical considerations of animal welfare. The benefit-risk assessment must be favourable for VMP authorization. A VMP market application can have three outcomes: (i) authorization; (ii) authorization with risk mitigation; or, (iii) refusal of authorization (European Parliament, 2004a). It is critical that the benefit-risk assessments support decisions so that VMP products are available to adequately treat animals while also not adversely affecting environmental quality.

Conducting a benefit-risk assessment of VMPs involves a high level of complexity. Benefits and risks (i.e., for the target animal, user, environment, and consumer of animal-derived foodstuff) need to be considered (Figure 1.2). Additionally, risks specific to the VMP class may also need to be included (e.g., the risk of antimicrobial resistance selection). The initial independent evaluation of benefits to the main risks decreases the complexity. For example the user safety assessment could result in a risk and consequent risk mitigation measures (Woodward, 2008) similar to the ERA (VICH 2000, 2004, EMA 2008). The independent evaluation of each category will support amalgamation of data into

an overall benefit-risk evaluation. Therefore, it is effective to focus on environmental risk and development of methods, which integrate ERA data in a benefit-risk methodology to support authorization decision-making.

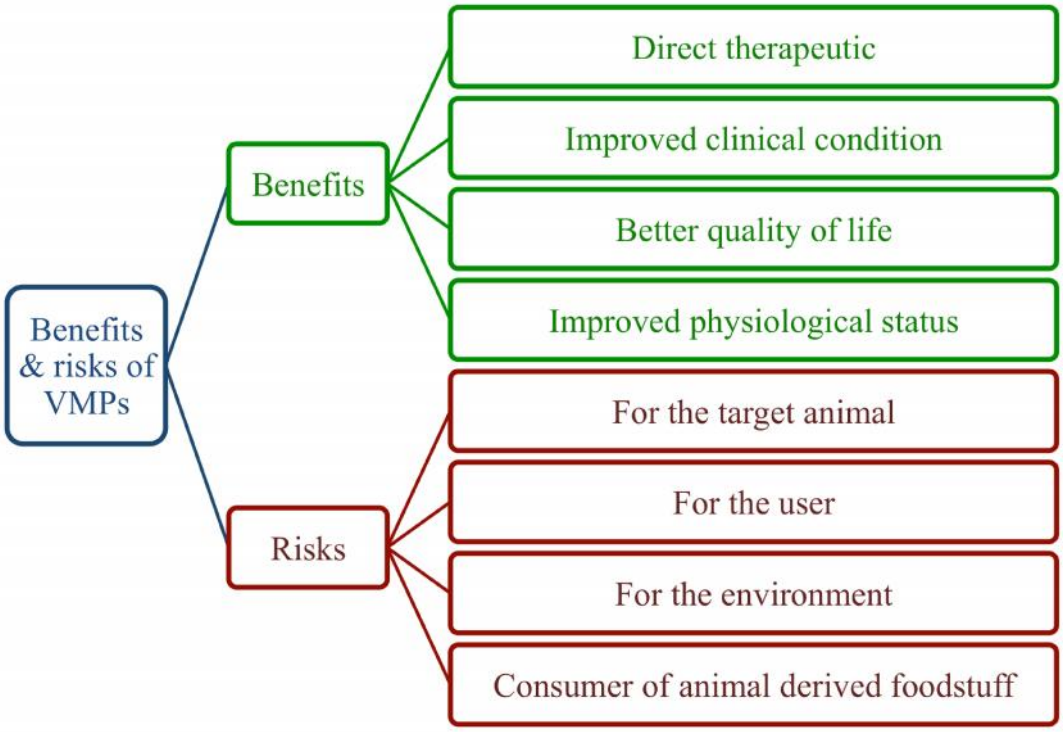

Figure 1.2 Schematic of a subset of benefits and the main risks from the VMP benefit-risk recommendation (EMA, 2009).

Integrating environmental risk in the benefit-risk assessment does not currently follow a standardized and transparent methodology. For example, guidance from the CVMP does not present a structured approach for comparing environmental risks and VMP benefits (EMA, 2009). Expert opinion is highlighted as a key tool. However, while expert opinion is valuable, it can be inconsistent between experts and less transparent than a standardized methodology.

In the case that an ERA results in an acceptable risk and adequate benefits, the benefit-risk will be favourable (EMA, 2009). The ERA can result in an acceptable risk when results are below defined thresholds. Comparison of ERA data and thresholds is applied in two steps (i.e., Phase I: exposure assessment; and, Phase II: risk assessment). Phase I is conducted by applying a decision tree to evaluate specific aspects of exposure (VICH, 2000). For example, VMPs for non-food producing animals, which are considered to have lower use and be specific for individual treatment, have less environmental concern, and can therefore conclude at Phase I. The exposure calculations involve the estimation of a predicted exposure concentration for soil (PECsoil) or an environmental introduction concentration for water (EICaquatic). Products which do not exceed Phase I criteria (i.e.,

PEC(soil) ≥ 100 µg/kg; EIC(aquatic) ≥ 1 µg/L) are concluded to have acceptable environmental risk (VICH, 2000). Assuming sufficient benefits and acceptable risks from other criteria in Phase I (e.g., consumer safety), the product will then be authorized; otherwise, more rigorous data collection and testing in Phase II will be required (Figure 1.3).

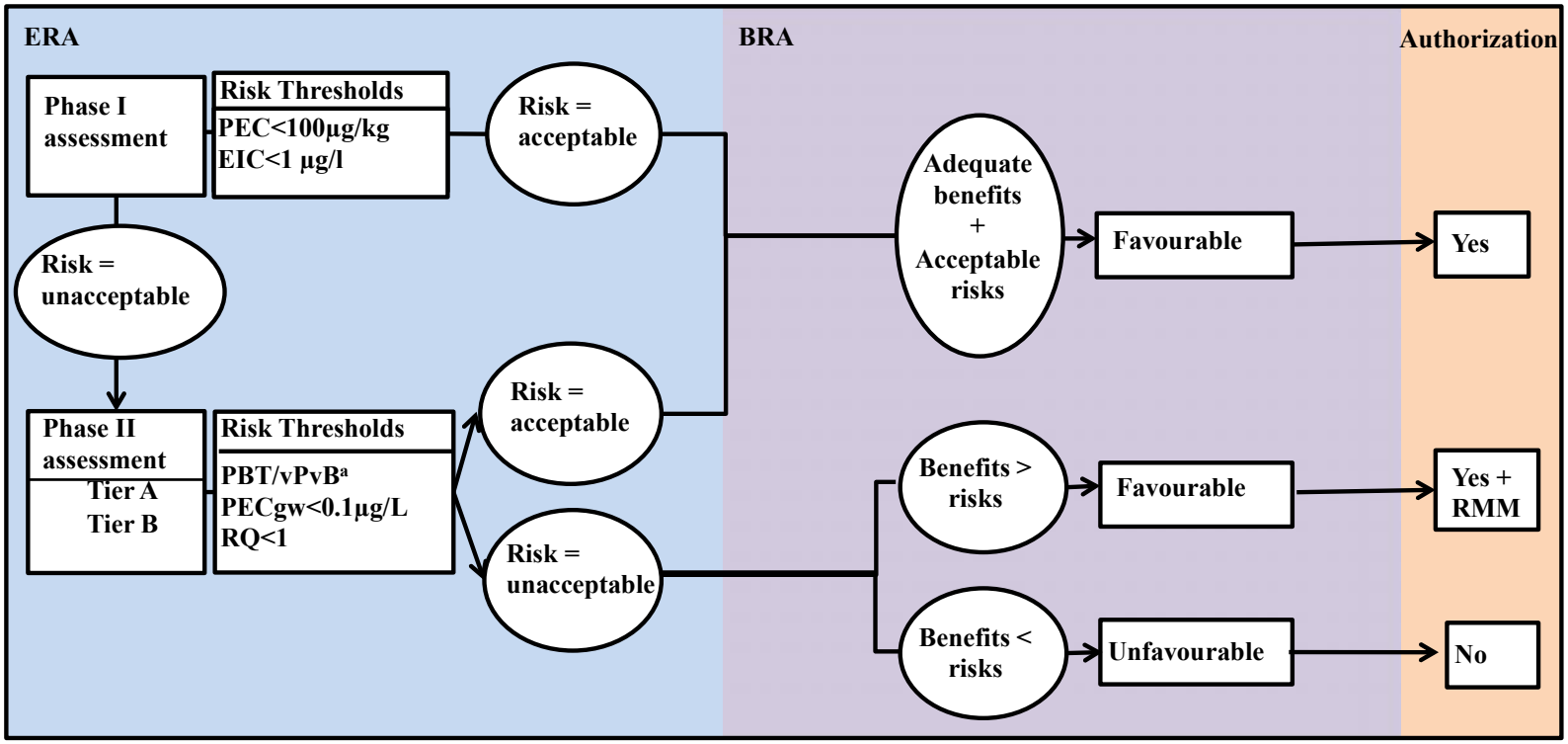

Figure 1.3 Overview of how environmental risk assessment data from Phase I and II feed into the benefit-risk assessment (BRA) and inform the final authorization decision. Flow illustrates how the three benefit-risk methods (see text) will fit into the authorization process. [a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vPvB) criteria defined in EMA (2012a). PEC: Predicted exposure concentration, EIC: Environmental introduction concentration, PECgw: groundwater PEC, RQ: risk quotient (exposure/effect), RMM: risk mitigation measures.

Phase II generates hazard, exposure and risk data in a tiered approach. Tier A is more basic and conservative while Tier B is more intensive and realistic. At either Tier A or Tier B the results may be below required risk and hazard thresholds, defined in the guidelines by the International cooperation on harmonisation of technical requirements for registration of veterinary medicinal products (VICH, 2004), and the same pathway as Phase I can lead to authorization (Figure 1.3). If the risk is unacceptable after Phase II Tier B, the benefit-risk evaluation will critically support authorization (Figure 1.3). The specific data used to support the decision include hazard data, which classify a VMP as a PBT compound (persistent, bioaccumulative, and toxic) or a vPvB (very persistent, very bioaccumulative) based on criteria defined by EMA (2012a). Additionally, exposure data for groundwater (PECgw) is initially generated in simple conservative models. Refinement with models, developed by the Forum for Pesticide Fate Models and their Use (FOCUS), which were developed to support pesticide regulations, is recommended (Montforts, 2006; EMA, 2008). Finally, the risk quotient (RQ) compares exposure and effects data. The effect is measured by environmental compartment (i.e., aquatic, terrestrial, sediment, and dung), by testing indicator species (e.g., *Daphnia* and earthworms) to measure which exposure concentrations cause adverse effects (e.g., mortality, changes in growth or reproduction). From these data a predicted no effects concentration (PNEC) is calculated. The risk quotient is calculated by dividing the PEC by the PNEC (i.e. RQ=PEC/PNEC). The risk is considered acceptable to a compartment if the RQ is less than 1.

In the case of an unacceptable risk, mitigation measures are an option to refine the risk quotient (VICH, 2000, 20004; EMA, 2009). Risk mitigation measures (RMMs) can be applied as specific instructions in product literature aimed to decrease or remove the environmental exposure of VMPs and therefore change the risk level (EMA, 2008). Risk mitigation measures are applied on a case-by-case basis through discussion with regulators (VICH, 2004). The guidance documents do not give specific instructions on the assignment of RMMs (VICH, 2000; 2004; EMA, 2008). Additionally, RMMs are applied during a market authorization application but are addressed to VMP users (Montforts *et al.*, 2004). There is no legal basis that binds users to the application of RMMs and no guarantee that RMMs will be implemented in practice (Montforts *et al.*, 2004).

Establishing favourable/unfavourable benefit-risk evaluations requires integration of benefits and ERA data. The consideration of benefits focuses on the direct therapeutic benefit for authorization (EMA, 2009). In most cases the product is compared to the lowest efficacy level of available products to establish sufficient efficacy (EMA, 2009). The exception is the case of ectoparasiticides, which require 80-100% efficacy levels (EMA,

1994). Integration in a benefit-risk method must focus on making benefit and risk data comparable. Therefore a review was conducted to identify previous work in which the environmental risks from VMPs or other pharmaceuticals have been investigated with the aim of comparison with benefits.

1.3 Studies comparing pharmaceutical benefits and environmental risks

The main challenge of integrating environmental risk into a benefit-risk assessment is that benefits are received by the treated animal whereas risks are received by the surrounding ecological system. This section presents the results of a literature review of previous work attempting to make benefits and environmental risks of pharmaceuticals comparable. The first section presents the results specific to VMPs, which are very limited. The second section then expands to consider studies of the broad pharmaceutical category.

1.3.1 Valuation of environmental impacts of VMPs

Monetary valuation is a possible approach to move towards the comparison of environmental risks and benefits, specifically economic benefits. For VMPs, there are a large number of studies reporting the potential adverse impacts of VMPs on the environment, but only two case studies have been identified where an attempt has been made to link predicted or observed VMP impacts in the natural environment to economic costs. In the first case, diclofenac, a non-steroidal anti-inflammatory drug (NSAID), applied to cattle in India caused a 99% decrease in Indian vulture populations (Green *et al.,* 2004, 2007). This decline of the vulture populations increased the food available to dog populations; therefore, dog populations grew as did the incidence of rabid dog bites. Estimated medical expenses from rabid dog bites of US$34 billion were thought to have been incurred over the 14 years of the vulture population decline (Markandya *et al.,* 2008). The second example is ivermectin, a parasiticide, whose use is thought to pose an unacceptable risks to aquatic and terrestrial biota (Liebig *et al.,* 2010). Of specific terrestrial concern for this compound is the dung beetle. Ivermectin is excreted in dung at concentrations that are toxic to dung beetles (Floate *et al.,* 2005). Depletion of dung beetle populations has potential for knock-on effects on predator species and also affects dung degradation (McCraken *et al.,* 1993; Floate *et al.,* 2005). Food availability is increased when dung degrades and grass is no longer fouled. Dung degradation supports nitrogen volatilization and the availability of nitrogen for plants. The ecosystem services provided by dung beetles from dung degradation was estimated by Losey and Vaughan (2006) at US$38 million per year in the United States. Toxic effects to dung beetles therefore have potential to result in the loss of valuable ecosystem services.

1.3.2 Pharmaceuticals

The scientific literature rarely considers both the benefits and environmental risks of pharmaceuticals, as would be applicable to the authorization process. Acuña *et al.,* (2015) considered the benefits of using a human medicine along with environmental detection data in a post-authorization analysis. They compared the human consumption of diclofenac to environmental detection data. Global maps illustrated national consumption data and maps of environmental occurrence data. Data gaps clearly identified a need for monitoring programs, especially in areas of high usage. However, risks and benefits were not explicitly considered.

Tyler *et al.,* (2009) investigated the effects of equine estrogens used in hormone replacement therapy in fish. Evidence for feminization was found and it was concluded that further studies should re-evaluate the risk-benefit balance to include environmental impacts. However, to date this does not appear to have been done.

Other studies have considered the environmental benefits and costs from implementing technological solutions for wastewater treatment to remove pharmaceuticals (Lienert *et al.,* 2011; Schuwirth *et al.,* 2012; Logar *et al.,* 2014; Molinos-Senante *et al.,* 2013; Wenzel *et al.,* 2008). Methods applied in some of these investigations resulted in monetary characterization of the benefits of treatment plant upgrades. Logar *et al.,*(2014) applied a choice experiment in Switzerland to conclude that public demand was greater than the cost of treatment plant upgrades to remove micropollutants, including pharmaceuticals. Molinos-Senante *et al.,* (2013) applied a technique called shadow pricing to represent the environmental benefits of wastewater treatment in monetary measurements for three pharmaceuticals. The investigation of Wenzel *et al.,* (2008) applied lifecycle assessment to compare three different treatment options for the removal of micropollutants. Finally, the application of multi-criteria decision analysis has been conducted to evaluate alternatives for removal of pharmaceuticals from the wastewater of hospitals (Lienert *et al.,* 2011; Schuwirth *et al.,* 2012). These studies exemplify possible methods beyond benefit-risk assessment previously implemented to support decisions concerning environmental exposure to pharmaceuticals. However, the different methodologies do not fit with the current requirement to apply benefit-risk in VMP authorization (European Parliament 2004a).

1.4 Aims and objectives of research

Evidence of environmental risks from VMP usage supports the inclusion of environmental risks in the regulatory benefit-risk assessment. However methods to support the integration

of environmental risk and mitigation into the benefit-risk are lacking. Therefore investigation is required in this area to create a foundation for the further development of all aspects of the benefit-risk assessment process. The aim of this thesis is to provide the foundational investigations to support the effective integration of environmental risk and risk management into benefit-risk assessment. The specific objectives of this thesis were to:

1) Develop decision-support methods to integrate VMP environmental risks into the benefit-risk assessment required for the European authorization process (Chapter 2).
2) Perform an in-depth assessment of the cumulative environmental risk for the antibiotic tylosin in order to provide a dataset for evaluation of the decision support methods (Chapter 3).
3) Use information on the environmental risks of tylosin and two other VMPs (ivermectin and diclofenac) to evaluate the environmental risk categorizations developed in Objective 1 in order to support practical application of benefit-risk methodologies (Chapter 4).
4) Investigate VMP user opinions and attitudes of the environmental consideration and risk mitigation of VMPs to support application of RMMs in the integration of environmental risk into benefit-risk assessment (Chapter 5).

In Chapter 6 the novel results are discussed to support recommendations to further develop integration of environmental risks and mitigation into benefit-risk assessment. Finally, conclusions are provided in Chapter 7.

2 Three methods for integration of environmental risk into the benefit-risk assessment of veterinary medicinal products

Integrating environmental risk and benefits data for VMPs in decision-making will support VMP use when the benefits are greater than the risks. At present, environmental risks data for VMPs are not comparable to therapeutic benefits. There is no standardized approach or method to compare both environmental risks and therapeutic benefits. Here, building off the background information on the current regulatory process described in Section 1.2, three methods are described that could be applied to incorporate environmental risk into the benefit-risk assessment of VMPs, specifically methods that can be applied using data mainly generated for market authorization assessments. Finally, a broad discussion is presented of implementing benefit-risk methodologies in the current legislative framework and possible future directions.

2.1 Benefit-risk method development

A major challenge to incorporating environmental risk into the benefit-risk assessment is the differences in scales for benefits and risks (i.e., the treated animal vs. the environment). Structured methods are therefore needed to better communicate benefits and risks, support decision-makers, and overcome differences in measurements and recipients of the benefits and risks. For example, a VMP may have a high level of efficacy for a disease in sheep but also have a high RQ for *daphnia*; the challenge is how to compare the two endpoints. Consideration of the benefit and risk profile of this example product in a standardized method would support the challenging comparison. Further, available RMMs have no guarantee of consistent implementation (Montforts *et al.*, 2004; EMA 2012b; Liebig *et al.*, 2014). Therefore benefit-risk methods implemented prior to assignment of risk mitigation measures will better represent accepted risk.

Here we present three benefit-risk methods that have been developed to fit within and enhance the current decision-making process. This was done by first considering the VMP environmental evaluation procedure and data requirements and assessing how these could be used to inform a comparison of benefits against risks. The challenge of incomparable endpoints was then addressed through development of a basic categorization mechanism. Finally, the data requirements were combined in three categorization methods. These steps are described sequentially.

Division of benefits and risks into categories was developed to support direct comparisons. Categories, which are, organized into levels of increasing risk and benefit can be directly compared; the higher level indicates a higher benefit or risk. For example, in a 5 level

benefit-risk categorization, a level 3 risk will have two combinations of benefits>risks, and benefits<risks as well as one combination where benefits=risks (Figure 2.1).

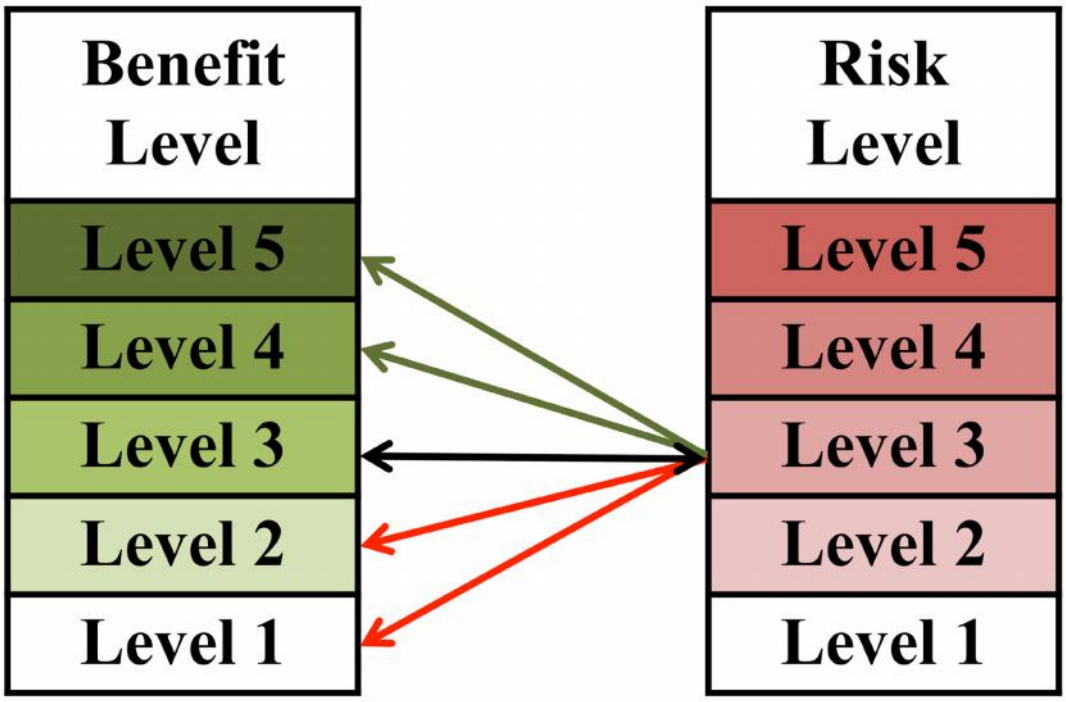

Figure 2.1 Subset of possible combinations for a level 3 risk in a categorization method with 5 levels of risks and benefits to support authorization decisions for VMPs. Black line connects scenario with the same risks and benefits (i.e., authorization dependent on decision rule). Red lines connect example scenarios with higher risks than benefits (i.e., no authorization); green lines connect example scenarios with higher benefits than risks (i.e., authorization).

VMP products are currently assessed individually based on their benefits and risks, and not compared to other products available on the European market other than for determining efficacy (EMA, 2009). Three methods for benefit-risk assessment are developed by applying categorization. Two of these methods support the evaluation of a product independently without comparing to other products available for the same indication (i.e., summative classification and a visual scoring matrix); the other supports comparative evaluation of a number of different products with the same indication (i.e., comparative classification).

Example criteria are applied to the benefits and risks to demonstrate the categorization methods. Four criteria for benefits and five environmental risk criteria were selected through discussions of the project consortium to represent important benefit and risk aspects. The benefit criteria selected for demonstration focus on application of VMPs for prevention and treatment of disease. The definition of VMPs in Directive 2001/82/EC also includes products for restoring, correcting or modifying physiological functions or to support medical diagnosis (European Parliament 2004a). Criteria for the benefits can be

adapted to consider products those benefits are not specific to disease (e.g., oestrus synchronization to increase reproduction). The four example benefits criteria are: (i) efficacy; (ii) resistance; (iii) severity; and, (iv) disease distribution. To emphasize the focus on the concepts thresholds are not suggested, but rather quantification options are briefly discussed.

The first benefit criterion is efficacy, which considers how effective the VMP is in its specific treatment. The measurement of efficacy will be dependent on the type of drug and would measure the success rate of the treatment. Second, a resistance criterion could measure the VMPs contribution to prevention of resistance, specifically for antimicrobials and antiparasiticides. Quantification of the contribution of the VMP to the fight against resistance could measure specific tests against resistant strains or consider if the mode of action is different than available products and therefore likely to be effective against strains resistant to other VMPs. Third, a high disease severity, considers the consequences of non-treatment. For this criterion, the highest benefit would be treatments for life-threatening diseases, ranking could be applied to quantify this criteria. Finally, widely distributed considers how many animals will benefit from the VMP.

Environmental risk categorization applied five criteria: (i) PBT/vPvB; (ii) PECgw; (iii) RQ; (iv) spatial risk; and, (v) temporal risk. The first three (PBT/vPvB, PECgw, and RQ) result from the environmental risk assessment and will be included in a market authorization application. These criteria have established thresholds (i.e. PBT/vPvB in EMA (2012a); RQ<1; PECgw<0.1µg/L). Additionally a spatial and temporal category are introduced, which would capture how widespread the severity of the risks are in time and space and be evaluated for exceedances separately from the ERA risk criteria. Setting the spatial and temporal criteria is further discussed in Section 2.3.

The example benefit and risk criteria are applied selectively in the different categorization methodologies. Selection of criteria was adapted based on the intended application of the methodology. The three approaches are: a summative categorization, the visual scoring matrix and the comparative categorization (Sections 2.2.1, 2.2.2, and 2.2.3, respectively). The selection of which approach to use will depend on the scenario being assessed and preferences of practitioners involved in the benefit-risk process. Our aim in presenting these methods is to demonstrate different approaches to categorization of benefits and risks, not to provide absolute comparisons. The selection of criteria and thresholds will be important for implementation and this is discussed later.

2.1.1 Summative classification method

Summative categorization supports the application of a decision rule (e.g., the benefit level must be equal to or greater than the risk level for authorization). It defines levels of benefits and risks through combinations of threshold exceedances. The method is demonstrated in Table 2.1 with 5 levels of benefits (left) and risks (right). The highest level (5) is set by exceedance of all criteria. The lowest level (1) is set by all criteria being met. Different combinations of exceedance and non-exceedance define intermediate levels. This first approach is very simple and involves a direct comparison of risk and benefit levels for different endpoints. The second approach is more complex and provides more information on where the risks and benefits lie and is designed to promote discussion and debate around the authorisation of a VMP.

Table 2.1 A summative classification system for treatment benefits (left) and environmental risks (right) of a VMP; thresholds for potential criteria can vary (see text for further details). Green colours differing in intensity indicate desirable benefits. Red colours differing in intensity indicate degree of exceedances.

BENEFIT					RISK					
	Potential criteria					Potential criteria				
Levels	High efficacy	Contributing to fight against resistance	High disease severity	Widely distributed	Levels	PBT /vPvB[a]	PECgw[b]	RQ[c]	Spatial risk	Temporal risk
Level 5	Exceeds all criteria				Level 5	Exceeds all criteria				
Level 4	Exceeds 3 criteria				Level 4	Exceeds 1 or 2 criteria			2 Exceeded	
Level 3	Exceeds 2 criteria				Level 3	Exceeds 1 or 2 criteria			1 Exceeded	
Level 2	Exceeds 1 criterion				Level 2	Exceeds 1 criterion			None Exceeded	
Level 1	None Exceeded				Level 1	None Exceeded				

[a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vPvB) criteria defined in EMA (2012a); [b]Predicted exposure concentration for groundwater; [c]Risk quotient (predicted exposure concentration / predicted no effects concentration).

2.1.2 Visual scoring matrix

The visual scoring matrix categorizes the entire benefit and risk data sets into levels of increasing severity (i.e. negligible (N) to very high (VH)) (Table 2.2). Table 2.2 demonstrates how benefit and risk criteria could be separated into different levels, by assigning specific intervals to each level. Example scores range from 0 to 4 increasing in a geometric series (i.e. $score_n = 0.5(2^{(n-1)})$, where n = 1, 2, 3, 4) from negligible risk (N) to very high risk (VH). Example benefit criteria focus on disease treatments and include details of the livestock and infection. The demonstration applies percentages to three risk criteria. The percentage of animals successfully treated with normal and resistant strains could be tested (Table 2.2, efficacy and efficacy against resistant strains, respectively). The severity could measure the number of cases, which result in a severe outcome (e.g., mortality). The demonstration intervals were assigned so that the higher end has a larger interval (i.e., VH = 70%-100%), the intermediate levels a moderate interval (i.e., H, M, L = 20% interval) and the lowest the smallest interval (N = 0 – 10%). The categorization must capture and communicate benefits effectively and for adjusting and defining criteria and intervals, expert and veterinarian opinion will be required.

Risk criteria are from the ERA and have also been divided into intervals specifically for concept demonstration. Values below the acceptable levels of RQ and PEC values are assigned to the negligible category. For RQ intermediate levels capture changes in the order of magnitude of the RQ. The very high level will capture all values greater than the assigned threshold (e.g., RQ> 10^3, Table 2.2). The RQ is subdivided to clearly indicate where risks will be received (i.e. environmental compartment and test organism). If the PEC is below thresholds specified by the VICH then this will be assigned to the negligible category. Different intervals for values of the PECgw in µg/L are designated for intermediate categories. The highest category captures exceedances of its specified category. The PBT criteria are separated into categories based on the number of criteria exceeded (Table 2.2). In this case the negligible category is defined as the acceptable level (i.e., not PBT). The unacceptable levels are the high and very high levels.

Scores could be compared if the total matrix score was the same for benefits and risks. However, the primary advantage of the matrix is the visual component, which supports transparent communication to decision makers and flexibility (i.e., a strict decision rule isn't the basis of the approach). The colour coding of the ERA data clearly and quickly communicates the distribution of benefits and risk across the criteria (Table 2.2); the calculation of the score is clear from the matrix, which is essential to the scoring system. The scoring system can be used in decision-making but should not be the primary

determinant. Coplan *et al.,* (2011) proposed a visual approach to communicate the health benefits and risks of medicines to patients; transparent communication of the data resulted in greatly improved communication and decision-making (Levitan *et al.,* 2011).

Overall, the increased details communicate specifics of where the benefits and risk will be distributed. The use of the matrix can support discussion and application of decision-maker judgment over specific decision-rules.

Table 2.2. Possible benefit matrix (right) and risk matrix (left) for visual comparison and scoring of VMPs (explained further in text). Thresholds are used as a demonstration of the concept rather than a recommendation. Colours indicate benefit intensity from high (i.e., green) to moderate (i.e., yellow) to low (i.e., red).

Level			VH[a]	H[b]	M[c]	L[d]	N[e]
Score			4	2	1	0.5	0
	Target Animal	Infection					
Efficacy	Livestock species 1	Species 1	≥70 %	50%-69%	30%-49%	10%-29%	<10 %
		Species 2					
	Livestock species 2	Species 3					
Efficacy against resistant strains	Livestock species 1	Resistant species 1	≥70 %	50%-69%	30%-49%	10%-29%	<10 %
		Resistant species 2					
	Livestock species 2	Resistant species 3					
Severity	Livestock species 1	Species 1	≥70 %	50%-69%	30%-49%	10%-29%	<10 %
		Species 2					
	Livestock species 2	Species 3					

Level			VH	H	M	L	N
Score			4	2	1	0.5	0
PBT			vP + vB	P +B + T	2 of 3	1 of 3	Not PBT
RQ	Compartment	Organisms					
	Surface water	Algae	RQ≥ 10^3	10^2≤ RQ <10^3	10≤ RQ <10^2	1≤ RQ <10	RQ < 1
		Daphnia					
		Fish					
	Sediment	Sediment organisms					
	Soil	Plants					
		Earthworms					
	Dung	Dung beetles and flies					
PECgw			PEC ≥5	1≤ PEC <5	0.5≤ PEC <1	0.1≤ PEC <0.5	PEC < 0.1

[a]Very high; [b]High; [c]Moderate; [d]Low; [e]Negligible.

2.1.3 Comparative classification

A comparative approach is not currently explicitly consistent with the VMP authorization process. However, such an approach would support substitution of VMPs with higher environmental risk for those with lower risk, given that benefit is reasonably maintained. Substitution principles are currently applied to chemical regulation (Swedish Chemicals Agency, 2007).

Comparative categorization focuses on the differences between a product applying for authorization and previously authorized VMPs with the same clinical use. Table 2.3 demonstrates a 5 level categorization method designed to evaluate changes between the product and the alternative. In this case criteria that relate to the specific treatment will be consistent between the alternatives and, therefore, would not be assessed in this method.

An example of five levels is provided to determine whether benefits and risks are increasing or decreasing; level 3 is a neutral level with highest risks and benefits at level 5 and lowest at level 1 (Table 2.3). The comparison of combinations is consistent with Figure 2.1. Application of this method requires determination of thresholds that constitute a significant change. The output would be a separate benefit and risk level for the authorization of a new product compared to an authorized VMP. A decision-rule could be applied to the levels assigned relative to the trade-offs between products.

Table 2.3 Comparative benefit classification (left) considering changes in 2 criteria and comparative risk classification (right) considering changes in 3 criteria to evaluate alternative products for the same treatment (colours differing in intensity indicate undesirable changes (i.e., red) and desirable changes (i.e., green). Thresholds for potential criteria can vary (see text for further details).

BENEFIT				RISK				
		Example criteria				Example criteria		
Category	Change in benefit level	High efficacy	Contributing to fight against resistance	Category	Change in risk level	PBT/vPvB[a]	PECgw[b]	RQ[c]
Category 5	Highly increased	Both higher		Category 5	Highly increased	≥2 criteria increased & none decreased		
Category 4	Increased	1 higher		Category 4	Increased	2 criteria increased & 1 decreased or 1 criterion increased & 2 without change		
Category 3	No Change	No difference		Category 3	No Change	No substantial in any criteria or 1 criterion increased & 1 decreased		
Category 2	Reduced	1 lower		Category 2	Reduced	2 criteria decreased & 1 increased or 1 criterion decreased & 2 without change		
Category 1	Highly reduced	Both lower		Category 1	Highly reduced	≥2 criteria decreased & none increased		

[a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vPvB) criteria defined in EMA (2012a); [b]Predicted exposure concentration for groundwater; [c]Risk quotient (predicted exposure concentration / predicted no effects concentration).

2.2 Selection of criteria

The three benefit-risk methodologies presented all require efficacy data and criteria for benefits. The list of benefits from VMP use is extensive (EMA, 2009); only a subset is presented in Figure 1.2.

Ensuring that the benefit-risk assessment adequately represents the benefits can be done through the selection of benefit criteria. For example, an increase in available products is beneficial to contribute to the fight against resistance (Tables 2.1-2.3). Additionally, animal welfare could be considered in the benefits by measuring the severity of diseases that are prevented (Tables 2.1, 2.2). Finally, the number of animals affected could be measured and used for weighting purposes. The focus of this chapter is to present methodologies for the comparisons of VMP benefits and environmental risk. The use of example criteria supports the presentation of developed methodologies. Discussion with regulators and veterinarians could identify benefits criteria.

All three methods utilize currently required data for environmental risk (i.e., PBT/vPvB, PECgw, RQ). Additional criteria for spatial and temporal risk are included in the summative approach (Table 2.1). To some extent, spatial risk is already considered. In the authorization process, minor use products are considered those for which the disease occurs infrequently or in a specific geographical area (EMA, 2016). A limited market authorization considers a product that will be used infrequently (EMA, 2016). However, additional adjustment of environmental risk criteria may also be desirable, as discussed below.

2.3 Setting benefit and risk levels

Balancing the benefits and the risks with any of the three methods will require carefully selected thresholds for categories. The current concepts use only illustrative thresholds; setting thresholds extends to the judgement side of the risk assessment. To emphasize this, the thresholds have not been specified where possible (e.g. benefits criteria in the summative categorization). Setting appropriate risk levels is vital; implementing any of the proposed methods will require a shift from a single level for risk to multiple levels (Figure 2.2). This can be accomplished through combinations of exceedance (e.g., summative classification method; Table 2.1). Alternatively, increasing thresholds could be applied (e.g., visual scoring matrix; Table 2.2). In the case of the comparative method, thresholds for a significant change must be selected carefully to emphasize meaningful changes.

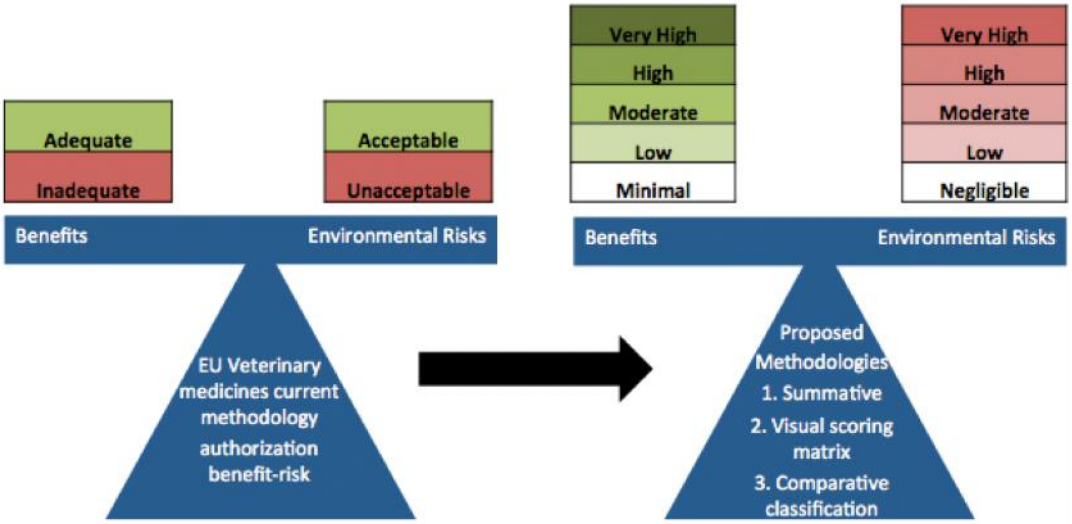

Figure 2.2 Illustration of the change in benefit and risk levels based on current practice (i.e., left side with 2 levels) and proposed benefit-risk methodologies (i.e., right side with 5 levels).

For all three methods, certain cases will need careful consideration. The case where benefit and risk levels are equal will require judgement by decision-makers. Another important case will be risks in the highest level (i.e., level 5: Tables 2.1 and 2.3; or VH: Table 2.2). The highest risk level could be specified as a cut-off point that could not be set aside by any level of benefit. However, if benefits are also at the highest level, more flexibility may be necessary. Flexibility can be applied or restricted by the decision-maker. The use of multiple benefit-risk levels over the current single thresholds better capture the reality of complexity and support an increased understanding and evaluation of both benefits and risk.

Increased understanding of environmental risk to support benefit and risk assessment requires additional environmental risk criteria, for example consideration of both spatial and temporal risk. Investigation of spatial environmental risk could be conducted with data currently generated in the ERA, for instance considering whether the VMP will be used in an area where it poses an unacceptable risk. PEC values are generated with FOCUS models for different areas in the European Union (EU) in the Phase II ERA. FOCUS models are adapted from pesticide exposure modelling to generate 10 surface water PECs and 9 groundwater PECs for different areas in the EU (FOCUS, 2000, 2001). The combination of the surface water PEC and effects data would create 10 RQs. In the case where some scenarios have more than 1 type of water body, the highest RQ would be conservatively considered. How many FOCUS scenarios exceed the trigger would be a spatial measure of the risk; a threshold could be applied. For example, a threshold could be defined as more than 5 scenarios with a RQ≥1. The application of FOCUS has the benefit that data can be generated for specific scenarios; however, these scenarios do not include

those suggested by Schneider *et al.,* (2007) and likely others, relevant for VMPs. Further, the FOCUS results do not consider terrestrial spatial aspects.

Consideration of the temporal aspect of risk should consider the timing and duration of exposure. Treatments that are continuously applied are more likely to accumulate in the environment. Similarly, for treatments that overlap with a sensitive life stage, the risk will be higher. Therefore, it is suggested that products used during the entire year and used during seasons with sensitive life stages require special consideration. Both the temporal and spatial criteria are an opportunity to consider the larger-scale pattern of the fate and exposure data and would require further investigation.

Categorization methodologies currently illustrate environmental risks by focusing on data specifically supported in the VMP guidelines (VICH, 2004). However, the ERA can proceed beyond the Phase II Tier B under regulator advice (VICH, 2004). Additionally, previous criticism has been made of the usefulness of standard ERA data in decision support (Syberg and Hansen, 2016). A specific gap in the ERA testing is a lack of population level investigation. For example, a study by Viaene *et al.,* (2015) demonstrated the importance of interactions within and between populations in chemical exposure testing.

Further opportunity for setting criteria may involve the linking of environmental science and economics. There is continued interest in ecosystem services and valuing nature (e.g., Losey and Vaughan, 2006). Policy has also adapted; for example, within Europe the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) Regulation has integrated environmental evaluation into the required Socio-Economic Assessment (SEA) (Regulation 1907/2006 (European Parliament 2006)). Adaptation of the ERA to consider the economic implications of risk would increase overall understanding of the relevance of potential risk.

2.4 Benefit-risk methods implementation

The implementation of any of the three methods will have potential advantages and disadvantages. It is therefore important to understand points of difference and agreement between the proposed methods and current policy and practice. This section discusses the main features of each proposed method and then expands to the wider context of both policy and scientific development.

For potential implementation there are three important differences between the methodologies (Table 2.4). The first is an independent versus comparative approach. It is advantageous for implementation that the benefit-risk approach be supported by the current

legislative framework. Both the independent methods (i.e., the summative categorization and visual scoring matrix) fit within current legislation. If comparative assessments (e.g., a substitution principle, which encourages development of alternatives for hazardous substances) are implemented in the future, the comparative method would be supported. The second critical difference is whether a formulaic or more judgement-based approach is applied. Both the summative and comparative methods are more supportive of a formulaic approach and use of a decision-rule. Finally, the methods vary in how levels are assigned. The levels are assigned in the summative and comparative methods by comparing criteria to a single threshold or specific level of change, respectively. Alternatively, the visual scoring matrix assigns levels to the criteria. The desirability of any of these main distinctions will depend on the preferences of decision-makers.

Table 2.4 A comparison of the three main differences between the three developed methodologies.

Summative Categorization	**Visual Scoring Matrix**	**Comparative Categorization**
Independent evaluation	Independent evaluation	Comparative evaluation
Formulaic	Judgement-based	Formulaic
Combinations of single criteria create levels	Multiple thresholds create levels within criteria	Magnitude of change in criteria creates levels

VMP ERA requirements define single thresholds for all current criteria (i.e., PBT/vPvB in EMA (2012a); RQ<1; PECgw<0.1µg/L in EMA (2009)). Values below these thresholds are required for all criteria in a favourable benefit-risk assessment (EMA, 2009). The summative categorization method would only fulfil all thresholds for risks ranked in level 1 (i.e., the lowest risks). In the comparative method, exceedance of current thresholds would depend on the risk level of the alternative. Finally, for the visual scoring matrix, RQ and PECgw criteria in the negligible risk category and PBT in the moderate, low or negligible categories would meet the current thresholds. Therefore, each method would potentially allow authorizations made with environmental risks higher than currently considered acceptable, if benefits are higher than risks.

Environmental risks higher than thresholds can be lowered to acceptable levels by applying risk mitigation measures (EMA, 2009). However, as previously noted, available risk mitigation measures are not reliably implemented for VMPs. Therefore, application of risk mitigation measures may lead to underestimation of environmental risk and a lack of transparency. Conducting the benefit-risk prior to assignment of mitigation measures would create more transparency regarding the environmental risk accepted for a product. Increased transparency could also be used to justify risk mitigation measures when they are

implemented, and potentially strengthen risk communication and risk mitigation measure uptake. All of the three proposed methods would increase this transparency and help to avoid authorizations with higher risks than benefits. Increased transparency would have the advantage of supporting consistent decision-making across a diverse group of European decision-makers.

The greatest advantage from implementing any of the three methods will be for cases where an environmental risk is indicated in a Phase II assessment (Figure 1.3). Previous experience with authorizations suggests 10% of VMPs products may fall into this category (Küster and Adler, 2014). The remaining cases where environmental risk is below the acceptable level still require a benefit-risk assessment (EMA, 2009). In all assessments the methods would support standardized communication of the acceptable environmental risk level and sufficient benefits level. The benefit-risk evaluations are also required post-authorization, (e.g., renewal after 5 years on the market) (EMA, 2009). The proposed methods are clear structures into which updated data can be entered for post-authorization benefit-risk assessments. However, environmental monitoring data for pharmaceuticals are limited (Küster and Adler, 2014; Acuña *et al.,* 2015).

The problem of different recipients of benefits (i.e., animal and farmer) and risks (e.g., to the animal, to the wider environment) is challenging. Balancing is an important role of regulation. In the case of VMPs, the benefits are not only profits for farmers but also animal health and welfare as well as human health (e.g., prevention of zoonotic diseases). Further, it is a legal requirement that reasonable actions be applied to alleviate unnecessary pain and suffering of livestock (Article 3 of Directive 98/58/EC (European Parliament 1998)). The other case where welfare is a significant benefit is the case of human medicinal products. For human medicines an ERA is required but environmental risks do not constitute grounds for refusal of the authorization (Directive 2001/83/EC (European Parliament 2001)). VMPs are a unique case in which regulators must explicitly consider both the ethics of benefits and the environmental risks.

2.5 Adaptability of the three methods

Variability between classes of VMPs can be incorporated into benefit and risk levels. The benefits of drugs will differ depending on the treatment (e.g., disease treatment, zootechnical benefit). For example, different classifications may include or exclude resistance criteria (e.g., antibiotics and non-steroidal anti-inflammatory drugs, respectively) (Table 2.1). The methods could also be adapted in the case that ERAs are

adjusted for specific pharmaceutical classes as has been previously recommended (Brandt *et al.,* 2015).

A decision rule could be implemented with agreed benefit and risk classification. Both the summative and comparative methods would support a more structured decision-rule approach. The applied decision rule could follow the example in Figure 2.1, where a benefit equal to the risk or a level higher is required for authorization. Alternatively, higher levels of risk may need two levels of benefits to satisfy decision-makers and address uncertainty. Consideration of uncertainty is vital in interpreting ecotoxicological data (Breitholtz *et al.,* 2006); thus, more conservative approaches may be favoured.

Flexibility in benefit-risk assessment is key to adapt the ERA component. Scientific work develops and improves the scientific methods for ERA (Werner and Hitzfeld, 2012). Additionally, experience evaluating ERAs for VMPs has developed since becoming a regulatory requirement (Koschorreck *et al.,* 2002; Küster and Alder, 2014). Adaptability will be critical for a benefit-risk assessment to integrate emerging scientific knowledge and regulatory experience. For example, pharmaceutical mixtures in the environment will likely be more toxic than single compounds (Backhaus, 2016). Consideration of the environmental effects of multiple VMP compounds is limited to the case of combination products, which have 2 or more active ingredients (EMA, 2006). The ERA of single compound products does not currently consider mixture toxicity (VICH, 2000, 2004; EMA 2008). Further, pharmaceuticals are likely to occur within the environment with other compounds. The individual evaluation and separation of chemicals (e.g., VMPs and pesticides) has been questioned for human mixture risk assessment (Evans *et al.,* 2015). Effective consideration of mixtures may require data from different chemical regulation sectors (Backhaus, 2016). Adaptation of decision-support systems in all regulations is a future challenge and opportunity for any benefit-risk assessment.

2.6 Conclusion

The development and testing of benefit-risk methods for VMPs with focus on assessing benefits and environmental risks is novel work that requires further investigation. This chapter proposes three methods to examine ERA data in a benefit-risk assessment. Two of these methods have been developed to support independent benefit-risk comparison. Classifications could either support a formulaic approach focused on a decision rule (i.e., the summative classification) or a flexible approach based on decision-maker judgement (i.e., the visual scoring matrix). Both approaches would be supported by current legislation.

Future development of regulation to consider substitutes would be supported by the final method, the comparative classification. Data beyond current ERA requirements are suggested in the classification to support more realistic evaluations. All three methods have potential to support a large and diverse group of decision-makers. The flexibility, adaptability, and transparency of each approach are the main strengths of implementing any of the methods. Additionally, adaptability will ensure that the methods can evolve with scientific knowledge and regulatory experience to address emerging challenges.

Further work with regulators and veterinarians could define benefit and risk categories and decision rules for comparisons. Regulator input would also identify the most suitable method for the VMP market authorization procedure.

Finally, further development of the methodologies requires insights from VMP environmental risk data and testing of data within methodologies as well as consideration of RMMs. The subsequent chapters build on these areas, starting with an investigation of the environmental risk of the antibiotic tylosin.

3 Ecological risks of the macrolide antibiotic tylosin

3.1 Introduction

High quantities of antibiotics are applied in livestock production (Kümmerer, 2008; Van Boeckel *et al.,* 2015). Antibiotics are compounds used in chemotherapeutic applications to prevent or terminate growth of microorganisms (e.g., bacteria) (Kümmerer, 2008). The global consumption of antibiotics for livestock rearing was estimated at 63,151 (± 1,560) tons in 2010 (Van Boeckel *et al.,* 2015). By 2030 livestock antibiotic consumption is estimated to reach 105,596 (±3,605) tonnes (Van Boeckel *et al*., 2015). The main drivers of this increased usage in livestock are increased demand (accounting for 66% of the increase) and increased intensification of farming practices (accounting for 34% of the increase) (Van Boeckel *et al*., 2015).

High antibiotic usage can result in substantial concentrations entering the natural environment. Post application, between 30-90% of orally applied antibiotics can be excreted as unchanged parent compounds (Sarmah *et al*., 2006). It is therefore not surprising that a range of antibiotics have been found in manure samples, including chlortetracycline, tetracycline, and tylosin (Hamscher *et al*., 2002; Ho *et al.*, 2014). Entry to the environment due to manure application has been shown to be the dominant pathway (Baguer *et al*., 2000). Therefore, intensively-reared systems are thought to be the most important source of antibiotics entering the environment. Once compounds have entered the environment transport into different compartments (e.g., surface water and sediment) is possible (Sarmah *et al.,* 2006; Sura *et al*., 2014).

The occurrence of antibiotics in the natural environment may result in the exposure of non-target organisms and potential effects. There is evidence of effects to non-target species such as plants and algae and potential ecological risks (Sarmah *et al.,* 2006; Guo *et al.,* 2016b). Effects from antibiotic exposures in the laboratory have been observed in species in different environmental compartments (Sarmah *et al.,* 2006). Additionally, the use of antimicrobial compounds, such as VMPs, is a concern for the selection and dissemination of antimicrobial resistance in the natural environment (Kemper, 2008; Marshall and Levy, 2011).

Given the known occurrence of veterinary antibiotics in the environment and the observed toxicity, an ecological risk assessment is now required on all new products (European Parliament, 2004a). The ecological risk is then established by comparing PECs with effects data through the estimation of RQs (Section 1.2). The evaluation of risk concludes as

acceptable or unacceptable as there will always be some level of risk and estimates are subject to uncertainties (Breitholtz *et al.,* 2006).

The level of ecological risk accepted from antibiotic application depends on the defined protection goal. In the case of veterinary medicines the protection goal is to protect ecosystems (VICH, 2004). Therefore, some individual, population and even community effects may be acceptable as long as the structure and function of the ecosystem is maintained. The production of toxicity data for individuals can be statistically extrapolated to community effects through the application of species sensitivity distributions (SSDs), which are statistical distributions of the effects data for a compound to different organisms (Posthuma *et al.,* 2002). General practice in the application of SSDs is to use the distribution to derive a hazard concentration, which likely affects a certain percentage of species also known as an HCx. A value of 5% is typically used (i.e., the HC5). Due to uncertainties in the extrapolation an assessment factor (AF) between 5 and 1, is applied to generate a PNEC (i.e., PNEC = HC5 / AF) (TGD, 2003). Comparisons of PNEC values with PECs are used to assess ecological risks. RQs for communities can be generated from this data (i.e, RQ = PNEC / PEC). A RQ less than 1 is considered acceptable (i.e., RQ<1) (VICH 2004). In the regulated ERA process introduced in the previous chapter, application of SSDs would be conducted under regulatory guidance (VICH, 2004).

The scientific data and understanding of the ecological risks of many VMP compounds is limited (Boxall *et al.,* 2003a). Ecological risk investigations of veterinary antibiotics are made more efficient by focusing on high priority compounds (Boxall *et al*., 2003a). Studies prioritizing compounds report on different aspects of including usage and hazard criteria such as effects concentrations for 50% of individuals (EC50s) (Boxall *et al.,* 2003a). Therefore, evidence for evaluation of priority compounds will be more available for assessment of ecological risks. Only one study has assessed the publically available data to evaluate ecological risk for a high priority VMP compound (i.e., ivermectin an anthelmintic, a substance that is discussed in the next Chapter) (Liebig *et al*., 2010). An investigation of the aggregated evidence for environmental risk of a priority veterinary antibiotic from public sources has not been conducted. Therefore this chapter describes an environmental risk assessment for the macrolide antibiotic, tylosin.

Tylosin was selected as case study compound due to its high usage and evidence of effects on non-target organisms. Tylosin has been identified as highly used antibiotic and is therefore more likely to reach the environment in significant concentrations (Boxall *et al.,* 2003a). Tylosin usage based on veterinary wholesaler data in U.K. in 2000 was 5144 kg (Sarmah *et al.,* 2006). Based on prioritization work for VMPs in the U.K. environment,

tylosin was one of eight antibiotics applied to livestock production that were ranked in the highest priority group (Boxall *et al.,* 2003a). The ranking was supported by availability of sufficient usage and hazard data to support environmental risk concerns for high priority compounds (Boxall *et al.,* 2003a). Other antibiotics identified as high priority compounds included chlortetracycline and amoxicillin from the chemical groups tetracyclines and β-lactams, respectively (Boxall *et al.,* 2003a). In the case of tylosin exposure modelling for European surface water exposure has been previously investigated (Guo *et al.,* 2016a). Additionally, effects data has also been previously reported (e.g., Baguer *et al.,* 2000; Guo *et al.,* 2016b). Applications of tylosin are applied in intensive livestock production systems and subsequent entry to the environment via manure is possible. The focused aggregation of tylosin data provides a previously lacking overview of the current knowledge of environmental risks for a high priority VMP compound.

Tylosin is an antibiotic compound currently used in 14 VMPs in the U.K. (VMD, 2018). Tylosin was discovered in 1961 (Arsic *et al.,* 2018). Use of tylosin in Europe began in 1970 with its use in feed additive VMPs (Arsic *et al*., 2018). The earliest authorization year for the current U.K. products was 1993 (VMD, 2018).

Tylosin is a combination of similar 16-member macrolides compounds dominated by tylosin A (>80%) mixed with tylosin B, tylosin C and tylosin D (Arsic *et al*., 2018). Additionally, Tylosin A, the parent compound, has the highest concentration after metabolism (Loke *et al*., 2000). Tylosin is active against mainly gram-positive and few gram-negative bacteria/organisms (Arsic *et al.,* 2018). Tylosin's mode of action is disruption of the protein synthesis (i.e., binds to 50S ribosome) in bacterial cells (Arsic *et al*., 2018). The molecular structure of tylosin is shown in Figure 3.1.

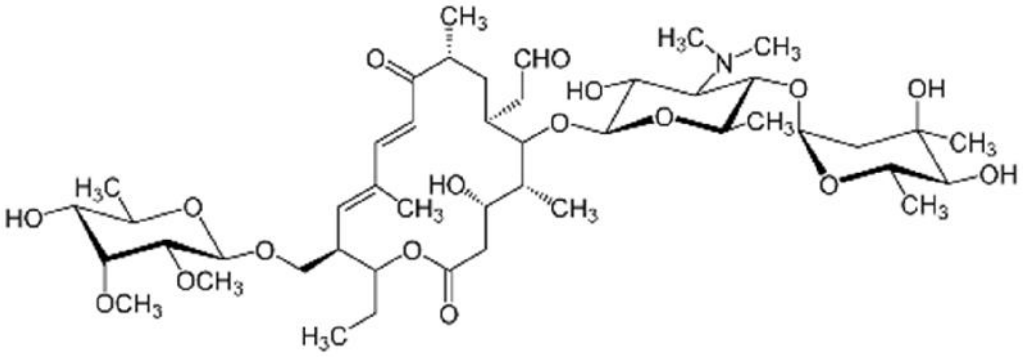

Figure 3.1 The molecular structure of tylosin (image from Chen *et al.,* 2018 SI)

This chapter presents an aggregation of the ecological effects and environmental exposure data available for tylosin for different VMP products and treatment scenarios. An investigation of the evidence for ecological risk in soil and aquatic compartments is

conducted. Toxicity to the ecological community level is investigated with SSD modelling. Exposure data applies modelling approaches that are recommended by the EMA (2008). The novel aggregated evidence for environmental risk highlights scenarios of concern.

3.2 Methods

The cumulative evidence for ecological risks of tylosin were investigated through data collection, analysis and modelling. Data were collected to support models of usage scenarios, exposure and effects. The following sections describe the data collection approach and the modelling applied to evaluate the ecological risks of tylosin.

3.2.1 Usage

Tylosin VMPs are available in the U.K. to treat disease in chickens, pigs, cattle and turkeys (VMD, 2018). A total of 14 products are available that can be administered either by injection or oral application (VMD, 2018). Dosages and frequency of applications were compiled from summary of product characteristics (SPCs) accessed through the Veterinary Medicines Directorate (VMD) database (VMD, 2018). Turkey scenarios were excluded because these applications are not a major source of antibiotic usage (Van Boeckel *et al.*, 2015). Based on the dosage and frequency prescribed for treatments 17 different application scenarios were identified for chickens, pigs and cattle (i.e. 7, 7 and 3 treatment scenarios, respectively). Figure 3.2 summarizes the usage scenarios.

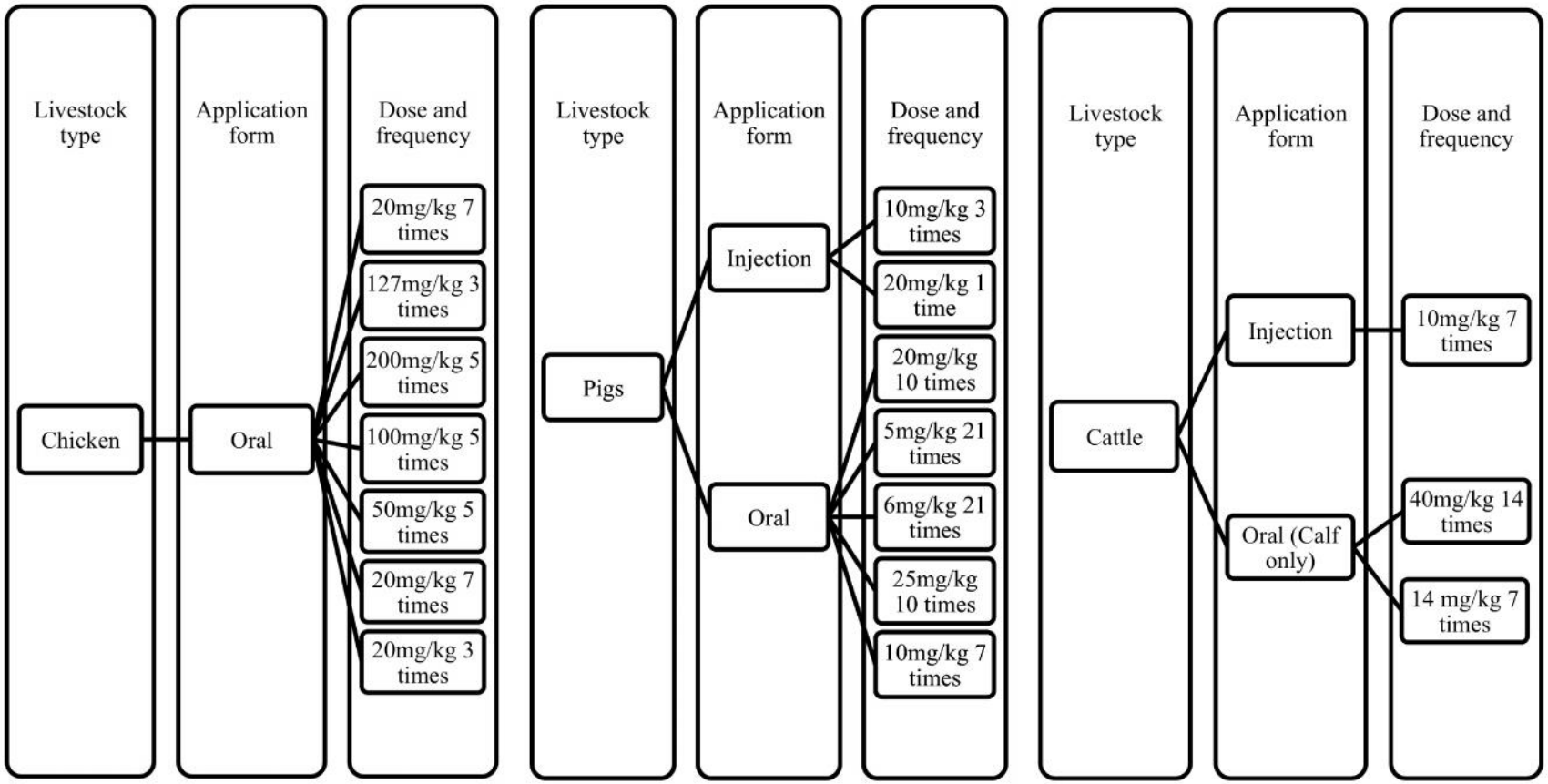

Figure 3.2 Summary schematics of livestock type, VMP applications and dosages.

3.2.2 Exposure scenarios

PECsoil

Usage data was combined with models from ERA guidelines to estimate concentrations of tylosin in soil (PECsoil). The parameters of the PECsoil equation are replicated from the EMA (2008) guidelines in Equation 1. Customization of the PECsoil calculations for specific VMP compounds requires input of the daily dose (D) and number of days of treatment (Ad). Therefore, treatments that were split with 12-hour intervals in between doses were combined for a daily total. In these cases the dosage frequency was halved due to combined doses. Suggestions for repeated treatments after a period of time were not accounted for in the available PECsoil models and therefore not considered (EMA, 2008).

$$PEC_{soil\ initial} = \left(\frac{D \times Ad \times BW \times P \times 170 \times Fh}{1500 \times 10000 \times 0.05 \times Ny \times H} \right) \times 1000 \qquad \text{Equation 1}$$

where:

$PEC_{soil\ initial}$	=	Predicted Environmental Concentration in soil [$\mu g.kg^{-1}$]
D	=	Daily dose of the active ingredient [$mg.kg_{bw}^{-1}.d^{-1}$]
Ad	=	Number of days of treatment [d]
BW	=	Animal body weight [kg_{bw}] (see Table 3.)
P	=	Animal turnover rate per place per year [$place^{-1}.y^{-1}$] (see Table 3.)
170	=	EU nitrogen spreading limit [$kg\ N.ha^{-1}$]
Fh	=	Fraction of herd treated [value between 0 and 1] (see Table 2.)
1500	=	Bulk density of dry soil [$kg.m^{-3}$]
10000	=	Area of 1 hectare [$m^2.ha^{-1}$]
0.05	=	Depth of penetration into soil [m]
Ny	=	Nitrogen produced in one year per place [$kg.N.\ place^{-1}.y^{-1}$] (see Table 3.)
H	=	Housing factor either 1 for animals housed throughout the year or 0.5 for animals housed for only 6 months (see Table 3.)
1000	=	Conversion factor [1000 $\mu g.mg^{-1}$]

Based on the livestock type and developmental stage, default variables are available for the remaining equation parameters (i.e., BW, P, Ny, H in Equation 1). Therefore the tylosin application scenarios were applied to four cattle scenarios (i.e., calf, dairy cow, cattle 0-1 year, and cattle >2 years), three pig scenarios (i.e., weaner pigs to 25kg, fattening pig 25-125kg, and sow with litter) and four chicken scenarios (i.e., broiler, laying hen, replacement layer and broiler breeder). The livestock treatments were applied based on the indication to all the animal type scenarios from EMA (2008) described in Table 3.1. The scenarios included one chicken treatment scenario that suggested application was for the first five days of life. In this case no scenarios were available for birds of this age. To incorporate this scenario the dosage were applied to available chicken models (i.e., broiler, replacement layer, laying hen, broiler breeder). The combination of tylosin treatments with

appropriate livestock scenarios based on indication in product literature resulted in 54 exposure scenarios.

Table 3.1 PECsoil exposure scenario variables for different animal types, replicated from EMA (2008).

Animal type	Number of animals raised per place per year	Bodyweight (kg)	Nitrogen produced in 1 year per place (kgN/y)	Housing factor
Calf	1.8	140	10	1
Dairy Cow	1	425	60	0.5
Cattle (0-1 years)	1	200	18	0.5
Cattle (>2 years)	1	450	35	0.5
Weaner pig (to 25 kg)	6.9	12.5	2.25	1
Fattening pig (25-125kg)	3	65	7.5	1
Sow (with litter)	1	240	26	1
Broiler	9	1	0.23	1
Laying hen	1	1.6	0.35	1
Replacement layer	2.6	0.8	0.24	1
Broiler breeder	1	1.7	0.69	1

The remaining variable is the fraction of the herd treated, which is set based on the VMP type, application method, and treatment characteristics (EMA 2008). Antibiotics in feed and water medication are set to 100% herd treatment. Therefore, for all oral applications it was assumed that 100% of a herd was treated. For injectable applications all pig scenarios were recommended to apply a 50% default for the fraction of herd treated. In the case of cattle injections 50% was recommended for respiratory infections. Tylosin is applied for respiratory infection in cattle in addition to infections of the feet and udders (VMD, 2018). Due to the lack of guidance beyond the 50% value for cattle, all injectable scenarios were set at 50% of herd treated.

PECsoil models were applied which assume complete excretion of dose as the parent compound (EMA, 2008). There is limited knowledge on the variation of antibiotic excretion across different compounds, animals and application methods (Ishiwaka *et al.,* 2018). Only a few studies have specifically examined tylsoin's excretion and do not cover all the exposure scenarios modelled in this investigation (Ishiwaka *et al.,* 2018). Therefore PECsoil scenarios were not adjusted for metabolism and therefore represent worst-case protective estimates of exposure to parent compound (EMA, 2008).

PEC sw

Values for the surface water PEC (i.e., PECsw) were generated for different European regions and different water body types using FOCUS models (FOCUS, 2001). FOCUS estimates of PECsw are representative of different European regions and are adaptable to

VMP scenarios (EMA 2008). Tylosin FOCUS modelling was previously performed by Guo *et al.* (2016a) to estimate the surface water exposure of 8 European scenarios. Parameterization of the FOCUS model for tylosin required input of PECsoil values (kg/ha). PECsw estimates from Guo *et al.* (2016a) considered only broiler chicken applications and did not consider all application scenarios, but instead applied only the maximum, average and minimum application scenarios. Adjustments of the PECsw output from this previous study were applied with conversion ratios based on differences between the inputted PECsoil to adjust the calculations (Table 3.2). The adjusted PECsw values therefore represent the maximum, average and minimum of the full set of scenarios described in section 3.1.2. Further adjustments were not required and the values inputted for tylosin modelling are summarized in Table A1.1 (Appendix 1).

Table 3.2 Maximum, average and minimum PECsoil kg/ha applied in previous modelling (Guo *et al.* 2016a), current modelling and the resulting conversion ratio.

Scenario	Maximum	Average	Minimum
FOCUS[a]	8.448	1.194	0.0656
PECsoil	6.65	0.81	0.025
Conversion ratio	0.79	0.67	0.24

[a]Guo *et al.* 2016a

3.2.3 Toxicity data

Toxicity data were collected from published studies, databases and report documents. Searches of scientific literature were conducted with the Web of Science platform. Search terms combined tylosin with keywords for toxicity, effects, and different test species. Tylosin environmental report information was sourced from the U.S. Food and Drug Administration (FDA, 2015). Further toxicity results were derived from the United States Environmental Protection Agency's ecoxtoxicity database based on search results for tylosin (www.epa.gov/ecotox).

The PNECs were generated from SSD analysis for organisms in the soil and aquatic compartments based on available toxicity data. Based on the advice of the technical guidance document, long-term no-observed-effects concentration (NOEC) results were preferred (TGD, 2003). Previous work has combined NOECs and lowest-observed-effects concentrations (LOECs) in SSD analysis (Burns and Boxall 2018). For the aquatic compartment, sufficient chronic NOEC and LOEC data were available for a range of endpoints (e.g., survival and reproduction). The aquatic SSD was fit to data from 10 aquatic species and 17 endpoint measurements converted to mg/L. For the terrestrial compartment sufficient chronic data was not available and therefore acute NOEC results were applied to the SSD analysis. Data limitations have previously been encountered and SSDs adapted to endpoints besides chronic NOECs (e.g., Guo *et al.*, 2016a; Rico and Van

den Brink, 2014). The soil SSD was fit to data for 8 species and considered 25 effects endpoints for these species measured in mg/kg. SSD distributions were generated with the "SSD generator V1" (EPA, 2018). Conversion of the HC5 to a PNEC value applied an assessment factor of 5 (i.e. PNEC = HC5/5) in accordance with the technical guidance (TDG, 2003).

3.2.4 Chemical fate and risk assessment calculations

RQs were calculated to establish the ecological risk in the soil and aquatic compartments. RQs compared the PEC values from different scenarios to the community level PNEC derived from SSDs (i.e. RQ = PEC/PNEC). Comparison of RQs with the threshold of 1 identified acceptable risk scenarios (i.e., RQ<1) and unacceptable risk scenarios (i.e., RQ≥1). Specific application scenarios with unacceptable risk were identified for the soil compartment. For the aquatic scenarios unacceptable risk levels were identified for the combination of application level (i.e., high, average, low) and the European region.

3.3 Results

The results from exposure and effects modelling for tylosin are presented in the following sections. Subsequently, the RQ evaluation is presented based on the exposure and effects results. The results present a comprehensive understanding of the risk of tylosin in different terrestrial and aquatic scenarios through the application of a cumulative data investigation.

3.3.1 Tylosin soil exposure

The PECsoil of products on the U.K. market are plotted in Figure 3.3. Scenarios are divided based on livestock treated and the mode of VMP application. Oral applications including doses in feed are differentiated from injections by different shading (Figure 3.3).

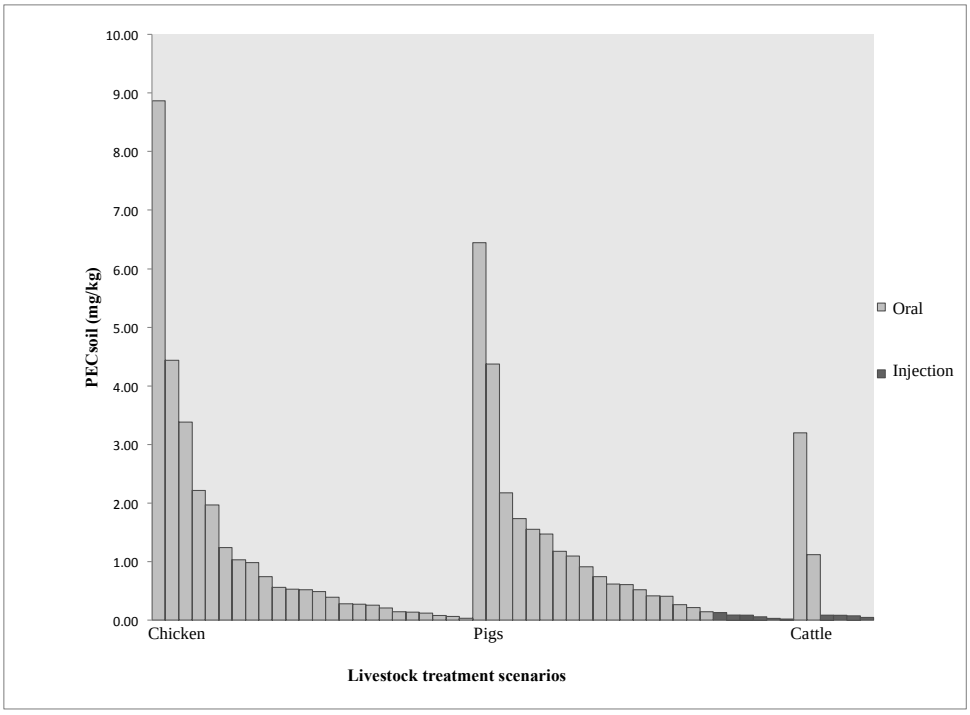

Figure 3.3 PEC soil initial values for tylosin treatment scenarios divided into treatments for chicken, pigs and cattle. Shade indicates whether applications are applied orally or with injection. Full table of livestock dose and number of doses represented by each column is summarized in Table A1.2 (Appendix 1).

A range in PECsoil values were obtained for different treatments across the different livestock types (Figure 3.3). The PECsoil value of 8.87 mg/kg was the highest level of exposure to soil and was estimated for an oral application to chickens. The maximum PECsoil for pigs was below the value for chickens and estimated to be 6.45 mg/kg. The cattle scenarios had the lowest maximum PECsoil estimated to be 3.20 mg/kg. For pig and cattle treatments the lowest PECsoil values were calculated for injection scenarios. The lowest PECsoil was 0.02mg/kg for an application by injection to pigs. The minimum PECsoil for chickens and cattle were similar and calculated to be 0.03 mg/kg and 0.05 mg/kg, respectively.

The evaluation of PECsoil in an ERA for authorization would initially compare the PECsoil to the trigger value of 100 mg/kg to determine whether experimental effects testing is needed (VICH, 2000). In the case that PECsoil is greater than 100 mg/kg the ERA progresses to Phase II and RQs are considered. Based on the results from PECsoil modelling a few cases would not require a Phase II assessment. For chicken, pigs and cattle there are 3, 5 and 4 cases, respectively, where the trigger is not exceeded. However to fully examine the risk of tylosin across different scenarios and all values were considered.

3.3.2 Tylosin surface water exposure

Surface water exposures for tylosin adjusted from Guo *et al.*, (2016a) are plotted in Figure 3.4. Results describe drainage for 6 scenarios of (D1-D6) and specific receiving water types (i.e., ditch, stream, pond). The 4 run-off scenarios (R1-R4) predict pond or stream surface water concentrations. A map of the FOCUS scenarios and associated European areas is replicated from FOCUS (2001) in Figure A1.1 (Appendix 1). A table of the scenario variables is also replicated (Appendix 1, Table A1.3).

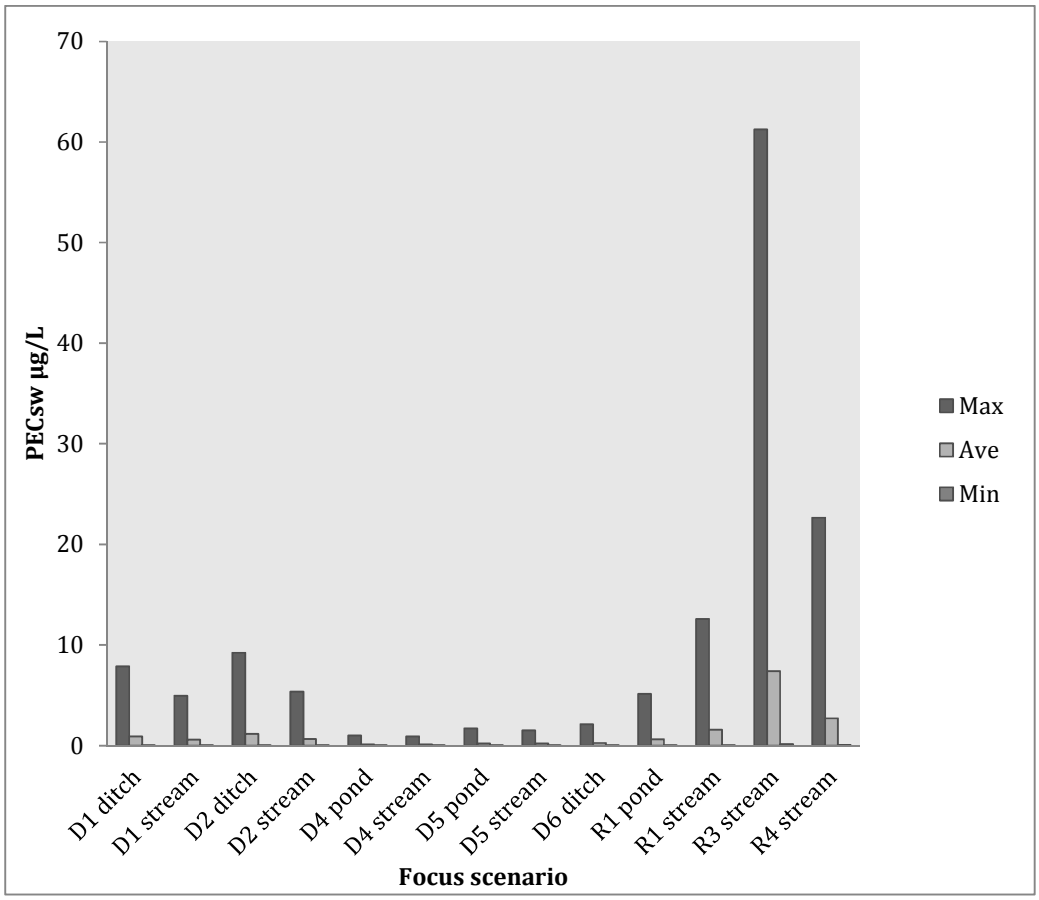

Figure 3.4 PECsw (µg/L) maximum, average and minimum values adjusted from Guo *et al*., 2016a.

The PECsw ranges across the different scenarios (Figure 3.4). The highest exposure scenario was the maximum application at R4 stream (61.3µg/L) and lowest exposure scenario was the minimum application at D4 stream (0.0021 µg/L). The highest PECsw for the different application rates (i.e., maximum, average and minimum) is predicted at the R3 stream scenario. Guo *et al.*, (2016a) found the R3 stream scenario to be the highest exposure scenario for tylosin and two other compounds (i.e., lincomycin and trimethoprim). The second and third highest exposures were also estimated for runoff to stream scenarios (R4 and R1 stream respectively). The three highest scenarios are representative of more southern areas on the European mainland (FOCUS, 2001). The

percentage slope is a variable in the runoff calculations and a parameter that was higher across the three highest runoff scenarios (FOCUS 2001).

3.3.3 Tylosin soil toxicity data

The evaluation of toxicity data and SSD results are presented in this section.

Species sensitivity distribution

Figure 3.5 is an aggregated SSD plot of all NOEC endpoints (i.e., survival, growth and reproduction) for 8 soil species. Two survival endpoints for plants (i.e., emergence and survival after emergence) were available. Reproduction NOECS were only available for soil invertebrate and therefore only 3 values were included for reproduction. The HC5 of the terrestrial SSD is 10.9 mg/kg (confidence interval 1.95 - 61.32 mg/kg). The resulting PNEC protective of 95% of terrestrial species is 2.18 mg/kg.

The SSD analysis indicates that plants are more sensitive than soil invertebrates. The most sensitive tested plant species is red clover. A PNEC value of 10.92 mg/kg was derived for from the HC5 value. Additional testing for the plant survival conducted by Liu *at el.,* (2009) applied tylosin in solution and therefore NOECs were in mg/L and were not included in the SSD, but are summarized with SSD data in Table A1.4 (Appendix 1).

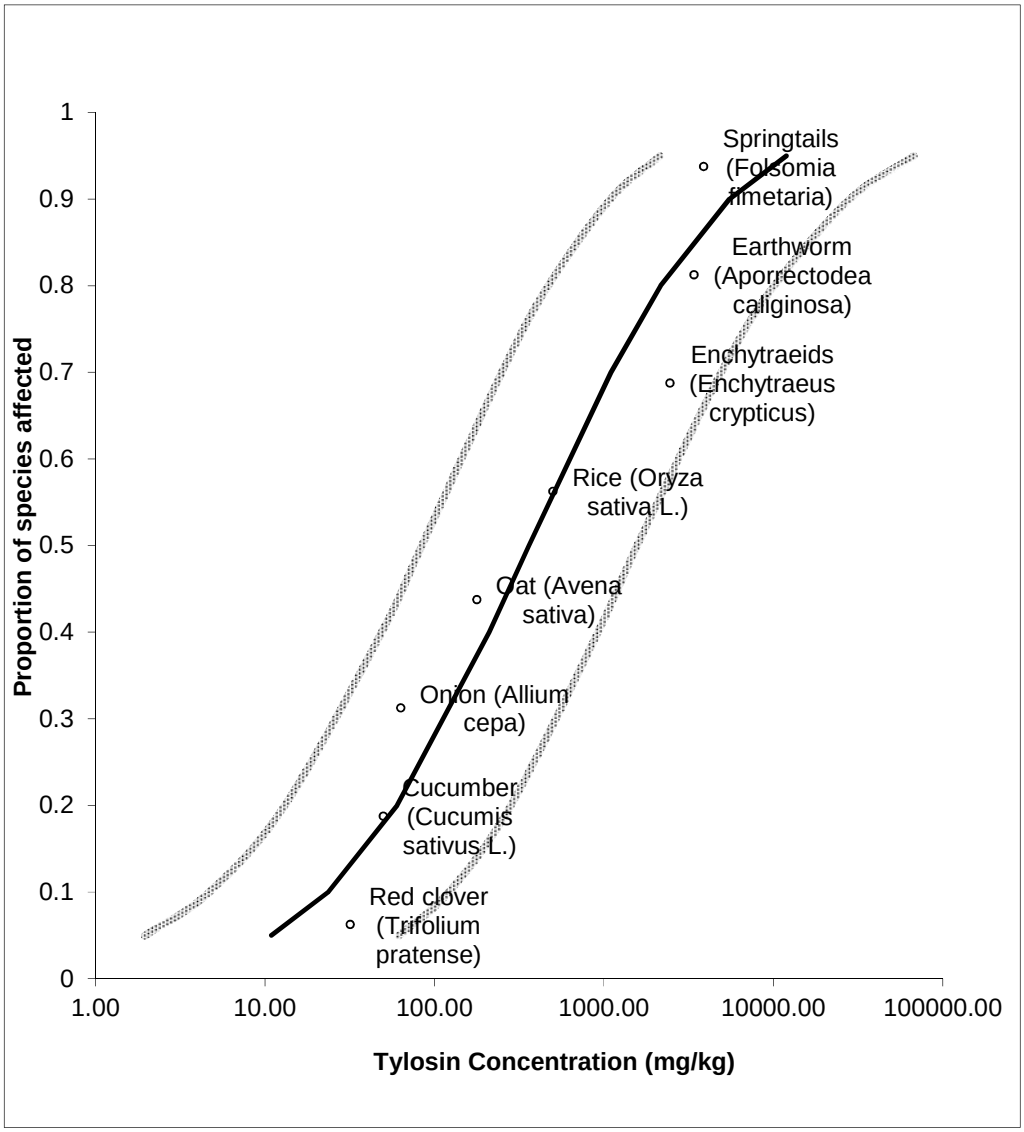

Figure 3.5 SSD of all terrestrial endpoints; detailed data summarized in Table A1.4 (Appendix 1).

3.3.4 Tylosin aquatic toxicity data

Aquatic toxicity data is summarized in the SSD in Figure 3.6. The data used to generate the SSD is summarized in Table A1.4 (Appendix 1). A sufficient number of species with chronic data were available and therefore chronic NOECs are modelled. The SSD does not include acute data, however acute NOECs are included in Table A1.4 (Appendix 1). The HC5 derived from this distribution is 0.008mg/L (confidence interval 0.001-0.068mg/L). The SSD derived PNEC is 0.0016mg/L. This is comparable to the 0.002 mg/L PNEC value reported by Guo *et al.*, (2016b) from the investigation of five algal species. Cyanobacteria are the most sensitive species, which agrees with previous studies (Halling-Sørensen, 2000, Guo *et al*., 2016b).

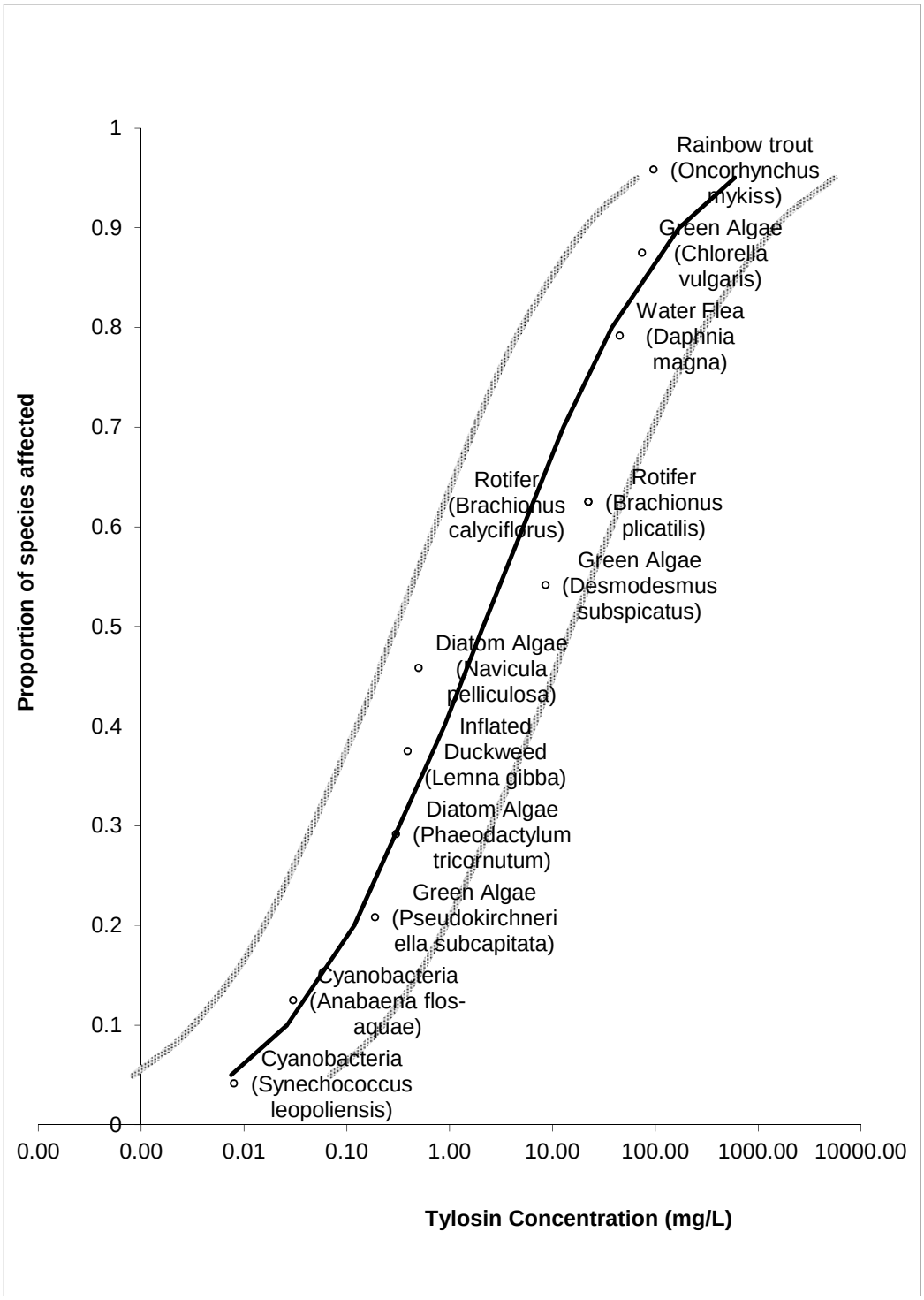

Figure 3.6 SSD of aquatic chronic NOEC results; detailed data summarized in Table A1.5 (Appendix 1).

3.3.5 Risk assessment

RQ values were generated by comparing the PEC and PNEC values (i.e., RQ = PEC/PNEC). The RQ profiles for the aquatic and terrestrial environment are plotted in Figures 3.7 and 3.8. The red line separates acceptable (i.e., RQ<1, scenarios below the red lines) and unacceptable scenarios (i.e., RQ>1, scenarios above the red lines) (Figure 3.7, 3.8).

Soil RQs

For the soil compartment approximately 30% of the scenarios indicate an unacceptable risk (Figure 3.7). RQs for injectable scenarios were all at acceptable risk levels. Unacceptable risks were indicated for 21%, 33% and 33% of the scenarios for oral applications to chickens, pigs and cattle, respectively (Figure 3.7).

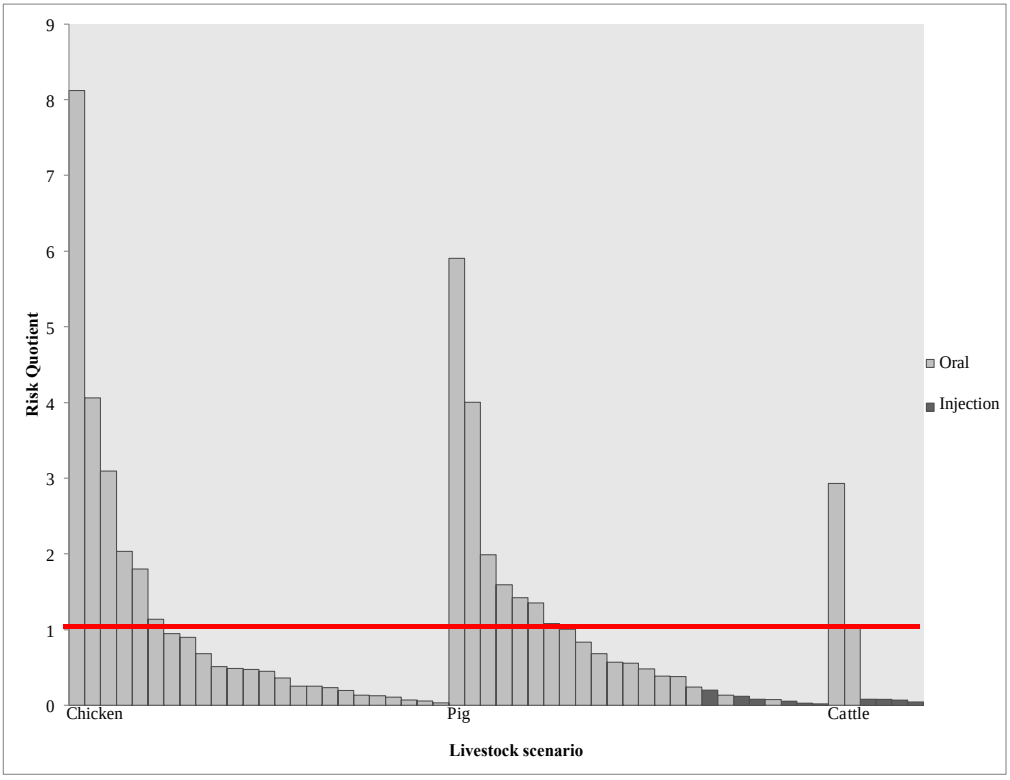

Figure 3.7 RQs for soil livestock scenarios applied in calculation of PECsoil. Full table of livestock dose and number of doses represented by each column is summarized in Table A1.2 (Appendix 1). Unacceptable scenarios exceed the red line and have a RQ>1.

Aquatic RQs

For the aquatic compartment variation in FOCUS scenarios RQs are summarized in Figure 3.8. An acceptable risk was indicated for all FOCUS scenarios with the minimal entry level to the environment. Additionally, all D4 stream and pond scenarios as well as the D5 stream scenario indicated an acceptable risk even at the maximum exposure. The average applications had unacceptable risk levels in 15% of the scenarios. The maximum application rate had only three acceptable scenarios (i.e., D4 stream and pond, D5 stream).

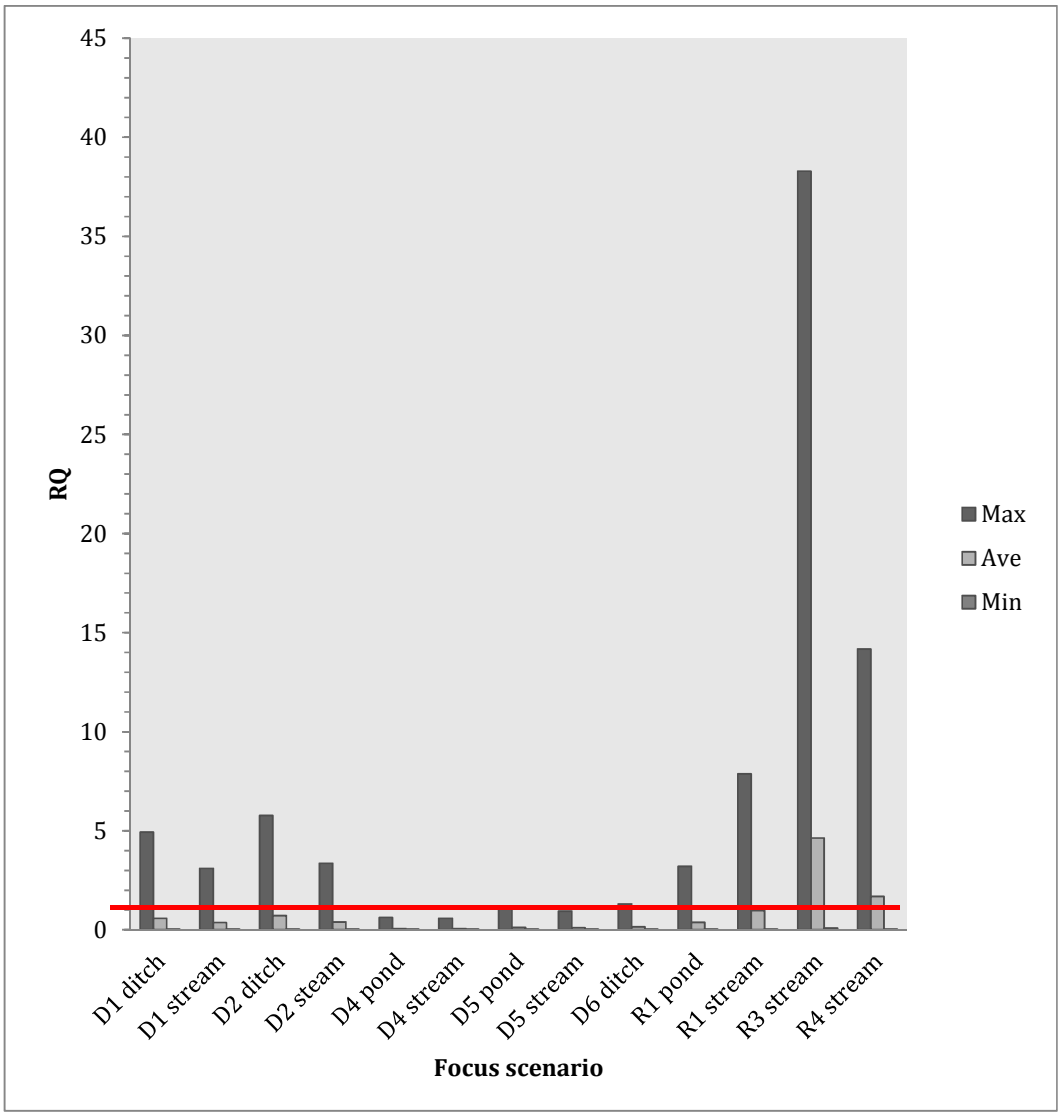

Figure 3.8 RQs for FOCUS surface water scenarios. Unacceptable scenarios exceed the red line and have a RQ>1.

3.4 Discussion

The ecological risk of tylosin has been identified as scenario dependent by this investigation. The combination of SSD analysis and exposure modelling support the identification of risk, however also have limitations. The limitations of exposure and effects data are discussed in the following sections.

3.4.1 Exposure

The exposure estimates range widely for the soil (20.92 µg/kg – 8 869.6 µg/kg). Measured environmental concentrations of soil for comparison with estimates are very limited. Ho *et al.,* (2014) measured concentrations of tylosin in soil amended with broiler chicken manure in Malaysia and found concentrations of 6 to 679 µg/kg dwt. Other available measurements only report the concentration of tylosin in manure. Detection of tylosin in broiler chicken manure in Malaysia was measured between 100 – 13 740 µg/kg (Ho *et al.,* 2014). Whereas

detection in cattle manure in Canada was reported as 10 – 76 µg/kg (Sura *et al.,* 2014). The lack of scenario information in the limited reported detections makes a comparison with model results difficult. However the detections have a wide range and support that tylosin is entering the terrestrial compartment at varying concentrations in different scenarios.

Similarly, variation in the aquatic exposure estimates was indicated (0.0021 mg/L - 61.26 mg/L). For surface water the maximum reported detection is 0.05×10^{-5} µg/L in the US (Boxall *et al.,* 2011). In this case the reported detection is in the range of surface water estimates; however, it is significantly lower than the maximum prediction. In this case it is also difficult to compare general monitoring data with scenario specific models. Further research investigating the detection after specific applications would support the understanding of exposure model realism.

The exposure estimates in this study are worst-case predictions and therefore protective. Further work to understand metabolism will support the more realistic estimation of PEC values.

3.4.2 Effects

The application of SSD modelling supports extrapolation of effects data to the community level. However only data measuring NOEC values were included. Non-standard tests not included in this investigation are summarized below.

Novel studies of aquatic microbes investigated tylosin effects. Significant sublethal effects impacting community structure and composition were indicated for phytoplankton (diatoms and cryptophytes) at levels of 5µg/L (Kline and Pinckey, 2016). The low threshold for these species is below our PECaquatic values indicating a risk level. Kline and Pinckey, (2016) also found that smaller plankton were more sensitive, which could have implications for further investigations of phytoplankton risk. Community composition variation was also observed in bacteria in the Yangtze estuary and found to correlate with including tylosin (Xu *et al.*, 2018).

Springtails are higher on the SSD distribution indicating that they are not the most sensitive. Rather, results indicate that the most sensitive springtail endpoint was reproduction (Table A1.4, Appendix 1). Giordano *et al.*, (2010) conducted further investigation of the effects of tylosin on springtail reproduction. When tylosin was applied to food a significant difference in eggs laid, eggs hatched and body size was measured. However, Giordano *et al.,* (2010) only applied a single very high dosage of 186 000 mg/kg, which is 5 orders of magnitude higher than the maximum PECsoil (i.e., 8.87 mg/kg). Although environmentally relevant risk data was not generated, the study did notably

observe avoidance behaviour (Giordano *et al*., 2010). Current toxicity guidelines omit exposure from food sources as well as avoidance behaviours, which may limit this route of exposure (Giordano *et al*., 2010). The exemption of this data may be significant and therefore the omission limits our understanding and the robustness of toxicity results (Giordano *et al*., 2010).

Standard toxicity tests with NOEC endpoints were not available for microbes and therefore microbes are not included in the SSD. The study by Rousk *et al*., (2008) applied tylosin specifically to observe the overlap of fungi and microbe function within ecosystems. They reported an EC50 value for growth data of 570 to 690 µg/g (Rousk *et al*., 2008). Their study indicated that the decrease in microbe population was compensated for by the increase in fungi and that the function of the microbe group within the ecosystem was preserved (Rousk *et al*., 2008). The impact of redundancy in the protection of ecosystem functioning is highlighted by this bacteria and fungi interaction.

Further evidence for microbe effects have been observed in manure lagoons (used for on farm manure storage and waste digestion). Antibiotics and antibiotic resistant genes have been measured in lagoons (Chee-Sanford *et al*., 2001). Microbe communities in manure lagoons convert complex organics to methane through multiple steps involving different types of microbes (Loftin *et al*., 2005). Loftin *et al*., (2005) measured partial inhibition of the methane production for applications of tylosin. The response of the microbe community was also found to be fairly stable over different dosages, including high dosages (i.e., 1, 5 and 10mg/L) (Loftin *et al*., 2005). The average inhibition in the two sites and over two time periods (i.e., 72h, and 336h) was 39.5%, and the highest of the 8 tested antibiotics (Loftin *et al*., 2005). Neither lagoon had a history of tylosin application, although one had more antibiotic application history than the other (Loftin *et al*., 2005). The implication of this inhibition was decreased efficiency of manure lagoons (Loftin *et al*., 2005).

The additional risks not considered here include resistance and plant uptake. Plant uptake and consequent human exposure is a health concern (Bhalsod *et al*., 2018). The risk of increased resistance from antibiotic exposure is also relevant to ecosystem and human health. A greater understanding of the contribution of antibiotics used in livestock is required (Zaheer *et al*., 2013).

Additional work with macrophytes and fish have concluded acceptable risk levels. Acute zebrafish embryo toxicity indicated that lower levels of tylosin (5mg/l) supported earlier hatchings while higher levels (25-100mg/l) had longer hatching times (Hu *et al*., 2010). However, these effects concentrations are higher than expected environmental

concentrations. Similar results were found for *Lemna gibba* and *Myriophyllum spicatum* indicating that growth promotion happened at lower levels (Brain *et al*., 2005). However, testing indicated that ecological effects are unlikely as measured endpoints changed less than 20% when exposed to tylosin (Brain *et al*., 2005). In the SSD modelling *Lemna gibba* was one of the more sensitive species (Figure 3.6). The positive responses observed in these tests are not currently considered in ecotoxicity testing. However, positive response alters the individual's resource use and potentially affects populations and communities (Giesy, 2001). Therefore, there are potential ecological impacts from positive changes in populations as well (Giesy, 2001).

The current risk assessment does not account for risk to sediment dwelling organisms. Limited data has been generated for the sediment compartment with only a few studies available. Available research suggests that the sediment compartment may be at risk from tylosin exposure. Detections of tylosin in sediment have been measured at $3.1x10^{-9}$ mg/kg (Pinckney *et al.*, 2013). Effects on benthic microalgae biomass and primary production have been measured for exposures of 11nmol (Pinckney *et al*., 2013). Shifts in primary production are of particular concern due to possible knock-on effects to ecological structure and function (Pinckey *et al*., 2013). Tylosin effects have also been measured for sediment dwelling marine diatoms (Swenson *et al.*, 2012). Therefore, the current limited data indicate that a risk to the sediment compartment is possible. Further effects data would support an SSD application and community estimate of risk. Modelling comparison with modelled exposure data would further the understanding of ecological risk to sediment ecology.

3.4.3 Risk

The cumulative evidence in this investigation indicates that some tylosin use scenarios have an ecological risk. However, there are uncertainties associated with both the exposure and toxicity profiles applied to calculate the ecological risk. Decision support tools applied to ecological risk data must be flexible in order to develop alongside the changing scientific tools and understanding. Decision tools are also necessary to support transparent decisions when risks are present. The application of previously described benefit-risk methodologies (Chapter 2) would support the authorization of tylosin treatment scenarios with indications of risk. In these cases methodologies that support benefit-risk evaluation are particularly relevant. The implementation of benefit-risk methodologies will support maximization of benefits and minimization of risk in the authorization process.

3.5 Conclusions

The cumulative data for tylosin clearly indicate that some scenarios pose a risk to both the terrestrial and aquatic environment. The identification of these scenarios highlights cases that would be supported by the benefit-risk methodologies described in Chapter 2. However, the exposure and effects results are subject to limitation and uncertainties. Additional toxicity data indicate that further development of the toxicity testing and RQ approach is necessary. This supports the discussion of benefit-risk assessment requiring flexibility to adapt to developments of ERAs. The availability of appropriate RMMs would also support the minimization of the environmental risks of tylosin.

4 Evaluation of environmental risk categories of benefit-risks assessment methods

There is clear evidence that in some cases VMPs have unacceptable environmental risks (e.g., tylosin, Chapter 3). However, VMPs also have apparent value for disease treatment that supports animal welfare and agricultural systems. Therefore the market authorization process for VMP entry to the European market requires that a favourable benefit-risk assessment is concluded from comparison of the treatment benefits against risks, including environmental risks (European Parliament, 2004a). Therefore methodologies were previously developed to integrate environmental risk data into the benefit-risk assessment process in order to support decision-making (Chapter 2). The methodologies are particularly valuable considering that currently benefit-risk comparison is only supported by a guidance document that offers vague advice rather than standardized methodologies (EMA, 2009). Development of proposed methodologies is required to operationalize methods and effectively integrate environmental risk data into the benefit-risk assessment process, in order to support transparent and standardized decision-making.

Development of the proposed methodologies will support progression towards practical application of benefit-risk methods. For example, a previous benefit-risk framework for benefits and adverse effects of human medicines presented by Coplan *et al.*, (2011) was subsequently supported by two different investigations. The first applied case study data for a hypothetical constructed drug, which combined data from different drugs within a specific class (Levitan *et al.*, 2011). The agglomeration of data was applied in order to assess the framework with a broad range of data (Levitan *et al.*, 2011). Subsequently, further development recruited pharmaceutical companies in order to make test applications of the framework (Noel *et al.*, 2012). The companies participated in a detailed post-use survey to inform on the experience of applying the framework (Noel *et al.*, 2012). This previous work demonstrates that further information and investigation is required to transition new frameworks from published ideas into tools that can be used in practice.

Similar to previous work, the case study testing of the proposed categorization methodologies will provide valuable insights into the practicality of their application. In this case, focused testing of environmental risk data in categorization methods is appropriate for three reasons: (i) the methodological aim; (ii) the developmental approach; and, (iii) support for method selection. First, the aim of the categorization methodologies is to integrate environmental risk data into a benefit-risk assessment and therefore methods must be appropriate for environmental risk data. Second, the approach to method development presented the environmental risk categories based on ERA requirements,

whereas the benefit categories were presented only to illustrate the benefit-risk comparison (Chapter 2). The further development of the benefits categories is recommended to apply veterinary expertise (Chapter 2). Third, the selection of a single approach based on the effectiveness of environmental risk categories will support efficient and focused development of benefits categorization.

Case study testing will demonstrate the differences in data representation between the different environmental categorization methodologies and therefore help to support method selection. Specifically, results will help to develop an understanding of how the three main differences between the approaches effect practical implementation. Firstly, case study rankings will inform differences between the more formulaic approaches (i.e. the summative categorization and comparative categorization) versus a more judgement-based approach (i.e. the visual scoring matrix). Secondly, data will support evaluation of independent approaches (i.e. the summative categorization and visual scoring matrix) versus the comparative categorization. Then finally, insights into the data handling of the three different categorization strategies will be examined. The three different categorization strategies were: (i) single level assignment based on the number and combination of set criteria thresholds exceeded (i.e. the summative approach), (ii) multiple levels within risk criteria based on magnitude (i.e. the visual scoring matrix), and, (iii) single level risk assignment based on a comparison of changes between products.

In order to effectively test categorization methodologies, measurements of unacceptable environmental risk are required. Therefore compounds that have previously been identified as compounds of concern are most appropriate for method testing. Additionally, the testing of the comparative approaches requires data from substitute compounds. Therefore the selection of high priority VMP compounds and potential alternatives is required for categorization testing.

This chapter applies data collected for case study and substitute compounds to test environmental risk categorization methods with data representing specific risks. Based on available data and models the specific environmental risks were evaluated for case study and substitute compounds. The primary objective of this exercise was to evaluate the environmental risk categorisation of the benefit-risk methodologies, not to make regulatory assessments and decisions regarding the environmental risks of the case study compounds. The results identify differences in data representation between the categorization methodologies and provide insights for the development and practical implementation of methods.

4.1 Case study compounds

Comprehensive testing requires case study compounds with diverse risk profiles. Different modes of action for different therapeutic classes will have different ecological effects (Brandt *et al.,* 2015). Therefore case study compounds were selected from three different therapeutic classes, each of which represent unique environmental concerns. The compounds selected were tylosin, ivermectin and diclofenac, which represent active ingredients from the antibiotics, anthelmintics and NSAIDs groups, respectively. Evidence of environmental risks has been previously presented for all three case study compounds and is described in the following sections. The final section describes the selection of substitute compounds.

4.1.1 Tylosin

Tylosin is an antibiotic that provides therapeutic treatments for bacterial diseases in major livestock species (i.e., chickens, pigs and cattle). Examples of tylosin indications include respiratory infections in chickens and pneumonia in pigs and calves (VMD, 2018). However, tylosin has been identified as a high priority compound in an environmental prioritization study (Boxall *et al.,* 2003a). Chapter 3 describes in detail the ecological risk data available for tylosin and identifies scenarios of unacceptable risk.

4.1.2 Ivermectin

Ivermectin is an anthelmintic compound applied for parasitic infections. Treatments are applied to three livestock species (i.e., cattle, pigs and sheep) (VMD, 2015). Example indications include gastro-intestinal roundworms and lungworms in all three livestock species.

Concern has been raised regarding the non-target effects of ivermetin and research since the 1980s has generated evidence to support the concern (Floate *et al.,* 2005). From existing data and additional testing, Liebig *et al.,* (2010) produced a comprehensive environmental risk assessment for ivermectin. The ERA follows the appropriate guidelines (i.e., VICH, 2000; VICH, 2004; EMA, 2008) and identifies unacceptable risk in the terrestrial, aquatic and sediment compartments (Liebig *et al.,* 2010). The specific risk to dung organisms is a result of pasture scenarios and inclusion of these scenarios will test a different environmental risk profile compared to tylosin.

4.1.3 Diclofenac

Diclofenac is NSAID applied to relieve inflammation, pain and fever (Todd and Sorkin, 1988). Additionally diclofenac treatments are applied for indications of lameness and other musculoskeletal disorders (EMA, 2014).

Diclofenac poses a unique risk to vulture populations, which was discovered after the collapse of vulture species in Asia (Oak *et al.,* 2004). Investigations of the unprecedented decline reported ill birds with drooping necks; consequently it was hypothesized that an infectious illness might be the cause (Prakash *et al.,* 2003). However, Oak *et al.,* (2004) investigated the vulture decline in Pakistan and provided evidence that vultures were suffering renal failure after ingestion of diclofenac.

The European concern regarding diclofenac was raised after two products containing diclofenac were authorized in Spain (EMA, 2014). The risk to vulture populations in Spain was assessed and the assessment published in a European Medicines Agency report (EMA, 2014). Therefore diclofenac inclusion in categorization testing will demonstrate how methodologies can be applied where there is a unique ecological risk.

4.1.4 Substitutes

Environmental risk categories of the comparative approach require substitute compounds to assign risk levels. Substitutes require the same therapeutic action and therefore must come from the same therapeutic class. However, different pharmaceutical classes will have different modes of action and potentially different risk profiles (Crane *et al.,* 2006). Therefore four substitute compounds were selected. Single compounds were selected as potential substitutes for tylosin and diclofenac (i.e., tiamulin and meloxicam, respectively). For ivermectin two compounds were selected (i.e. moxidectin and fenbendazole).

The three case study compounds represent three different therapeutic classes and have specific and divergent ecological concerns, as described in the above sections. Based on the specific concern different exposure scenarios are relevant for the environmental risk data and the testing of benefit-risk methodologies. Table 4.1 summarizes classification of the case study compounds and selected substitutes as well as the ecological concerns and relevant exposure scenarios.

Table 4.1 Summary of case study and substitute active pharmaceutical ingredients

Therapeutic Class	Active Pharmaceutical Ingredient	Active Pharmaceutical Ingredient Class	Identified concern	Exposure scenario of concern
Antibiotic	Tylosin[a]	Macrolide	Plants and algae	Intensively-reared
	Tiamulin	Pleuromutilin	Substitute	
Parasiticide	Ivermectin[a]	Avermectin	Dung fauna	Pasture direct entry
	Moxidectin	Milbemycin	Substitute	
	Fenbendazole	Benzimidazole	Substitute	
NSAIDs	Diclofenac[a]	Acetic acid derivatives	Vulture populations	Intensively-reared, Pasture
	Meloxicam	Enolic acid (Oxicam) derivatives	Substitute	

[a]Case study compound

4.2 Methods

4.2.1 Data collection

Data for case study compounds was collected from the public domain. Scientific literature was collected with searches for each compound. Searches were conducted on the Web of Science database and applied key words for toxicity and fate. Searches also combined key words for temporal and spatial risk for the evaluation of the summative approach. Information from reports was gathered when available from the U.S. Food and Drug Administration (FDA, 2016). The selection of high priority case study compounds was made to target compounds that have previous investigations. However, data availability limitations were encountered to different degrees with different compounds. Due to differences in data sets this evaluation focuses on methodology assessment and not compound evaluation.

4.2.2 Risk assessment methods

Exposure modelling applied dosage information, from summary of product characteristics, to models for PECsoil (EMA, 2008); PECsw (FOCUS, 2001); and PECgw (FOCUS, 2000). Modelling was based on the compound characteristics and exposure scenarios and is described for each case study compound in Appendix 2.

Data generated for this chapter supported project work done with a consortium. Colleagues working on the project contributed FOCUS modelling results and some PBT measurements.

Hazard evaluation was conducted with data collected from the public domain. Data were collected to assess ecological effects and PBT criteria (replicated in Appendix 2, Table A2.1). PNECs were calculated with appropriate assessment factors.

RQs were generated for environmental compartments and species depending on data availability. The worst-case scenarios were considered for all case studies in order to test the environmental categorizations of the benefit-risk methodologies. This application was chosen because the methodologies are especially relevant for cases where an environmental risk is indicated; therefore, assessing the greatest risk of the product could give the most insights into the data representation differences between categorizations. Specifics details of ERAs for individual compounds are included in Appendix 2.

For the tylosin case study, results from Chapter 3 were applied with additional data for PECgw and PBT characteristics. Consortium colleagues generated the additional groundwater data. The FOCUS model was parameterized differently than the model in Chapter 3. Differences in the inputted parameters and selected scenario are described in Table A2.3 (Appendix 2). The resulting PECgw was at least 3 orders of magnitude below the acceptable threshold (i.e., <0.001µg/L). Therefore, for the purpose of testing risk classifications the PECgw is assumed to be below the acceptable threshold (<0.001µg/L) and the worst-case RQs are applied from Chapter 3.

A Phase I assessment was applied for all compounds (VICH, 2000). If necessary, and data were available, Phase II was applied to either the Tier A or Tier B level depending on data availability (VICH, 2004). Benefit-risk method development recommended application of RMMs after benefits were found to be greater than risks (Chapter 3). Previous work highlighted that decreases in risk from RMMs were not guaranteed (Montforts *et al.*, 2004; EMA, 2012b; Liebig *et al.*, 2014). Therefore, the testing of the benefit-risk assessment focused on ERA data generated prior to RMM recommendation.

4.2.3 Environmental risk categorization testing

Testing of methodologies compared ERA results to criteria for the three proposed methods (i.e., the summative classification, the visual scoring matrix, and the comparative classification). Risk levels were assigned with the potential criteria used to illustrate the concepts in Chapter 2 (Table 2.1 - 2.3). The criteria for each benefit-risk method are summarized in Table 4.2. In the summative categorization, additional criteria for spatial and temporal risk are discussed (Section 2.3). In order to test the summative method, example criteria previously discussed were applied. Therefore spatial risk applied the

threshold of >5 scenarios with a RQ>1, and the temporal risk applied either treatment overlap with a sensitive species or treatment application in more than one season.

Table 4.2 Summary of criteria applied for the summative classification, the visual scoring matrix and the comparative classification. Detailed description in Tables 2.1 - 2.3.

Summative Classification			
Category	**Criteria exceeded**		
Level 5	All (PBT/vPvB, PECgw, RQ, Spatial risk, Temporal risk)		
Level 4	1 or 2 of PBT vPvB PECgw, RQ Both of Spatial, Temporal risk		
Level 3	1 or 2 of PBT vPvB PECgw, RQ Both of Spatial, Temporal risk		
Level 2	1 of PBT vPvB PECgw, RQ None of Spatial, Temporal risk		
Level 1	None		
Visual Scoring Matrix			
Category	**PBT**	**RQ**	**PECgw**
Very High	vPvB	RQ≥103	PEC ≥ 5
High	P, B, T	102≤ RQ≤ 103	1≤ PEC ≤ 5
Moderate	2 of 3	10≤ RQ ≤102	0.5≤ PEC ≤1
Low	1 of 3	1≤ RQ ≤10	0.1≤ PEC ≤0.5
Negligible	Not PBT	RQ ≤1	PEC≤ 0.1
Comparative Classification			
Category	**Changes in PBT/vPvB, PECgw, RQ**		
5 - Highly increased	≥2 increased, none decreased		
4 - Increased	2 increased, 1 decreased or 1 increased, 2 no change		
3 - No change	No substantial change 1 increased, 1 decreased		
2- Reduced	2 decreased, 1 increased or 1 decreased, 2 no change		
1 - Highly reduced	≥ 2 decreased, none increased		

4.3 Results and discussion

In the following sections, the ERA results, generated to test categorizations, are summarized and then these are used to evaluate the different environmental risk categorizations. Finally, comparisons of data representation are discussed and conclusions made.

4.3.1 ERA summarized results

The results of the ERAs for case study and substitute compounds, described in Appendix 2, are summarized in Table 4.3.

Availability of data varied significantly between compounds. Toxicity data for some of the case study molecules were limited and therefore it was not possible to fully characterize risks in all species and compartments (Appendix 2). Availability of acute, chronic and community test ecotoxicity data also varied between compounds and affected the

refinement of RQs. Consequently, the overall level of ERA assessment was varied as summarized in Table 4.3. Very limited data was available for the spatial and temporal categories proposed for the summative categorization (Table 4.3). Therefore outputs from the categorizations were not comparable across compounds due to the divergent datasets. However, the data is sufficient for the purposes of testing categorizations methodologies and comparing data representation between the categorization options.

Results from the ERAs indicate unacceptable environmental risks and therefore support categorization testing. All selected compounds indicate some level of threshold exceedance, with the exception of meloxicam (i.e., the substitute for diclofenac). Additionally, the environmental risk parameters applied in categorizations vary across the different compounds (Table 4.3). The most unique case is the risk results from diclofenac. In this case the phase I triggers were not exceeded (Appendix 2) however due to potential exposure to the highly sensitive species (i.e., vultures) a potential risk is indicated (Table 4.3).

Table 4.3 Summary of ERA data for case study compounds and substitutes. Criteria in columns as previously described in Table 2.1.

Compound	Level of ERA Data	PBT or vPvB	Maximum ground water exposure (PECgw µg/L)	Maximum Risk Quotient (PEC / PNEC)	Spatial Risk	Temporal Risk	Reported additional risk
Ivermectin	Phase II Tier B + higher tier [a]	P, T (Not B)	<0.001µg/L	$9.7x10^5$	N/A	Yes[b]	None
Moxidectin	Phase II Tier B+[a]	Potentially B, Potentially T (Not P)	<0.001µg/L	$3.5x10^4$	N/A	Yes[b]	None
Fenbendazole	Phase II Tier A	Potentially T (Not P, Not B)	<0.001µg/L	187	N/A	Yes[c]	None
Tylosin	Phase II Tier A	Not P, Not B (screening data), T data N/A)	<0.001µg/L	38	Yes[d]	N/A	None
Tiamulin	Phase II Tier A	P, Potentially B,T data N/A	<0.001µg/L	153	N/A	N/A	None
Diclofenac	Phase I	T (Not P, Not B)	Negligible[e]	Negligible[e]	N/A	N/A	Possible risk to vultures[f]
Meloxicam	Phase I	Not P, Not B, Not T	Negligible[e]	Negligible[e]	N/A	N/A	None[g]

[a]Tested beyond recommendations in VICH (2004) for which Phase II Tier B is the maximum, higher tier is supported in EMA (2008); [b]Used during 2 or more seasons and overlaps with sensitive life stage (Boxall *et al.,* 2007); [c]Overlaps with sensitive life stage (Boxall *et al.,* 2007); [d]RQ>1 in more than 5 FOCUS scenarios; [e]PECsoil initial <100µg/kg dry weight exposure ERA stopped at Phase I; [f]LC_1=0.138 mg/kg feed with possible exposure routes (EMA, 2014); [g]Not toxic (Swan *et al.,* 2006; Swarup et al. 2007); N/A not available

4.3.2 Application of categorization methods to environmental risk data

Application of data to methodologies was successfully implemented. A description of the application process is given for the separate methodological approaches in the following sections.

Summative categorization

Testing of the summative method is described for all the case study compounds in Table 4.4. A basic comparison of values with thresholds and consequent tallying of exceedances resulted in assignment of a risk level. For example, in Table 4.4, tylosin is assigned two rows, the first gives the value of the environmental criteria and a second indicates if the criteria's threshold is exceeded (i.e., yes) or not (i.e., no). Based on the combination of criteria exceeded (Table 4.2) a risk level is assigned in the final column of Table 4.4. For tylosin the risk level is identified as level 3. The same risk level was assigned to ivermectin, moxidectin and fenbedazole, whereas diclofenac and tiamulin were ranked as a lower level 2 risk (Table 4.4). Meloxicam was the only compound ranked as a negligible risk in the level 1 category.

The application of data to example criteria successfully ranked the compounds although there were gaps in the datasets. The most visible gaps in this method are the categories where data was not available (i.e., N/A, in Table 4.4). Implications of the data gaps on resulting rankings are discussed further in Section 4.3.4.

Table 4.4 Evaluation of the case study data with summative categorization criteria.

Case study	Compound	Evaluation	PBT/vPvB[a]	PECgw[b]	RQ[c]	Spatial use	Temporal use	Category
Antibiotics	Tylosin	Value	Not PB[d], (T data N/A)	<0.001µg/L	38	Exceedance[e]	N/A	**3**
		Exceedance	No	No	Yes	Yes	N/A	
	Tiamulin	Value	P, Possibly B, (T data N/A)	<0.001µg/L	153	N/A	N/A	**2**
		Exceedance	No	No	Yes	N/A	N/A	
Anthelmintics	Ivermectin	Value	PT (Not B)	<0.001µg/L	$9.7x10^5$	N/A	Exceedance[e]	**3**
		Exceedance	No	No	Yes	N/A	Yes	
	Moxidectin	Value	Possibly BT (Not P)	<0.001µg/L	$3.5x10^4$	N/A	Exceedance[e]	**3**
		Exceedance	Yes	No	Yes	N/A	Yes	
	Fenbendazole	Value	Possibly T (not PB)	<0.001µg/L	187	N/A	Exceedance[e]	**3**
		Exceedance	No	No	Yes	N/A	Yes	
NSAIDs	Diclofenac	Value	T (not P,B)	Negligible	Negligible	N/A	N/A	**2**
		Exceedance	No	No	Potential risk	N/A	N/A	
	Meloxicam	Value	Not PBT	Negligible	Negligible	N/A	N/A	**1**
		Exceedance	No	No	No	N/A	N/A	

[a]Persistent,bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vPvB) criteria defined in EMA (2012a); [b]Predicted exposure concentration for groundwater; [c]Risk quotient (predicted exposure concentration / predicted no effects concentration);[d] Not B result based on screening data; [e] Explanation in Table 4.3

Visual scoring matrix

Application of the visual scoring matrices produced unique tables based on the compounds' datasets. An example matrix is presented in Table 4.5 and represents the tylosin maximum risk scenario from Chapter 3. In the tylosin example, the PBT criteria is categorized as a low risk due to the single criteria exceedance (i.e., exceedance of the T criteria). The ranking of the RQ results are divided into surface water and soil communities based on the availability of SSD results. Surface water was categorized as a moderate risk and soil as a low risk due to RQs of 64.8 and 8.9, respectively. The last criteria PECgw was ranked as negligible as the value was assumed to be below the 0.1µg/L threshold.

In this case the result is the visual scoring matrix (Table 4.5), however the supplementary score can support the understanding of the data when used with the table. The calculations of the scores were successfully applied as described in Section 2.1.2. The scoring of PBT and RQ for tylosin demonstrates the effects of applying a weighting to criteria with a different number of values. In the PBT criteria a single value is evaluated and the result is an assignment of a low risk and associated score of 0.5. Therefore the PBT criteria maximum score is 4 and the score is calculated by multiplying the weighting percentage by the fraction of compound score over total possible score (i.e., 33.3%(0.5/4) = 4.2%). Whereas in the RQ case the score for the surface water compartment (i.e., 1) is added to the soil compartment (i.e., 0.5) and the maximum score with two values is 8 instead of 4. The weighting percentage is again applied to the fraction representing the score over the maximum score (i.e., 33.3%(1.5/8) = 6.2%). The final adjusted score for tylosin is an exceedance of 10.4% of the possible risk.

The application of weightings applied 33.3% to equalize criteria. In the tylosin example the RQ has two categories and therefore a total possible score of 8 compared to the single categories of PBT or PECgw, which have a total possible scores of 4 (Table 4.5). In the case no weightings are applied, the percentage risk would be simply calculated as the total score of risk categories over the table's total possible score, and then multiplied by 100 to convert to a percentage. Tylosin's score without the weighting would be 12.5% (i.e., 100(2/16)). In this case the scores for PBT and RQ are 3.1% and 9.4% and diverge by 6.3%, which is more than when the weight was applied and PBT and RQ diverged by only 4%. This indicates that the weighting did successfully adjust categories so that representation was more even given the differences in number of categories for different criteria. However, depending on the goal of the weightings (i.e., to emphasize a criteria versus equalize) different weightings could be applied.

Table 4.5 Application of visual and scoring risk matrix (Figure 2.2) to tylosin ERA data. Colours indicate risk intensity from high (i.e., red) to moderate (i.e., yellow) to low (i.e., green).

				Risk Level	Very High	High	Moderate	Low	Negligible	Score	Weight	Adjusted Score
				Score	4	2	1	0.5	0			
Criteria	PBT[a]							T		0.5 / 4	33.3%	4.2
	RQ[b]	Compartment	Organism									
		Surface water	Community				38.29			1.5 / 8	33.3%	6.3
		Soil	Community					8.9				
	PECgw[c]								<0.1	0 / 4	33.3%	0
				Total						10.5%		

[a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vpvb) (Appendix 2, Table A2.1)
[b]Risk Quotient (PEC/PNEC)
[c]Predicted exposure concentration for groundwater (µg/L)

Comparative categorization

Application of the comparative categorization produced risk levels for comparative compounds (Table 4.6). In this approach the case study compounds were not ranked because they were set as the comparator. Additionally, no minimum level of change was set, but rather any difference was considered as a change. The testing in this approach generated relative results for combinations of compounds instead of results for individual compounds. For example, the results for the antibiotic comparisons are described in the first row of Table 4.6. The top two rows in this section describe the parameter values for tylosin and tiamulin (i.e., top row and second row, respectively). The third row (i.e., tylosin vs. tiamulin) evaluates if an increase or decrease is observed between the compounds (Table 4.6). In the case that no change is observed the criteria is assigned: “no significant change”. An example of no significant change for tylosin and tiamulin is the PBT and PECgw criteria (Table 4.6). Whereas the RQ is an example of an increase in the RQ in the case that tiamulin is authorized (Table 4.6). The final assignment of a risk category refers to the category rules summarized in Table 4.2. For tylosin one criterion is increased and 2 have not changed, therefore tiamulin is ranked as level 4 risk to show the increased risk compared to tylosin. All other comparisons of alternatives to case study compounds indicated level 2 risks, and therefore a decreased risk.

Table 4.6 Evaluation of the case study data with comparative categorization criteria.

Case study	Compound or comparison	Description	PBT/vPvB[a]	PECgw[b]	RQ[c]	Category
Antibiotics	Tylosin	Comparator data	Not PB*, (T data N/A)	<0.001µg/L	38	-
	Tiamulin	Alternative data	P, Possibly B, (T data N/A)	<0.001µg/L	153	-
	Tylosin vs Tiamulin	Evaluation of change	No significant change	No significant change	Increase	4 – Increased risk
Anthelmintics	Ivermectin	Comparator data	PT (Not B)	<0.001µg/L	9.7x10	-
	Moxidectin	Alternative data	Possibly BT (Not P)	<0.001µg/L	3.5x10	-
	Ivermectin vs Moxidectin	Evaluation of change	No significant change	No significant change	Decrease	2 – Reduced risk
	Fenbendazole	Alternative data	Possibly T (not PB)	<0.001µg/L	187	-
	Ivermectin vs Fenbendazole	Evaluation of change	No significant change	No significant change	Decrease	2 – Reduced risk
NSAIDs	Diclofenac	Comparator data	T (not P,B)	Negligible	Potential risk	-
	Meloxicam	Alternative data	Not PBT	Negligible	Negligible	-
	Diclofenac vs Meloxicam	Evaluation of change	No significant change	No significant change	Possible decrease	2 – Reduced risk

[a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vpvb) (Appendix 2, Table A2.1)
[b]Predicted exposure concentration for groundwater (µg/L)
[c]Risk Quotient (PEC/PNEC)

4.3.3 Adaptability of methodologies

The application of all methods to diclofenac data demonstrates the adaptability of methods to a unique dataset. Diclofenac's primary concern considered in this testing is the potential risk to vulture populations (EMA, 2014). However, avian testing is not required in current ERA guidelines (VICH, 2000; 2004; EMA, 2008). Therefore the potential exposure and risk to vultures is not represented in the species-specific data (i.e., RQs). Additionally, the risk assessment conducted for vultures in Europe did not result in a risk quotient, but rather a qualitative description of the potential exposure of vultures (EMA, 2014). Therefore the three methodologies were adapted appropriately.

Inclusion of the unique risk to vultures from diclofenac is included similarly in the summative and comparative categorizations (Table 4.4 and 4.6, respectively). In both approaches the inclusion of diclofenac's risk to vultures is made in the RQ criteria by evaluating it as a potential risk. In the summative case this is treated as an exceedance and therefore a level 2 risk is assigned instead of a level 1, which would have resulted without the adaptation. Similarly, in the comparative approach the potential risk for diclofenac is compared to no risk for meloxicam. Consequently the authorization of meloxicam is assigned a level 2 indicating a decreased risk for meloxicam compared to diclofenac (Table 4.6).

For the visual scoring matrix an adaptation possibility for diclofenac is presented in Table 4.7. In this matrix the risk to vultures is again included in the RQs section by adding a "special concern" division in the compartments section (Table 4.7). In this case no RQ is available and therefore instead of assigning a single category a qualitative warning is included across all the possible categories (i.e., "Risk highly toxic but low likelihood of exposure in most parts of Europe"). The risk is further highlighted with the use of colour, in this case red, due to the high toxicity of diclofenac (Oak *et al.*, 2004). Due to the possibility of vulture exposure the score for this criteria was assigned as greater than or equal to the low risk level (Table 4.7).

Table 4.7 Application of visual and scoring risk matrix (in text Figure 2.2) to diclofenac ERA data. Colours indicate risk intensity from high (i.e., red) to moderate (i.e., yellow) to low (i.e., green).

Risk Level				Very High	High	Moderate	Low	Negligible	Score	Weight	Adjusted Score
Score				4	2	1	0.5	0			
Criteria	PBT[a]						T		0.5 / 4	33.3%	4.2
	RQ[b]	Compartment	Organism								
		All	All					Negligible exposure assessment concluded at Phase I	≥0.5 / 8	33.3%	≥2.1
		Special Concern	Vultures	Risk highly toxic but low likelihood of exposure in most parts of Europe							
	PECgw[c]							Negligible exposure assessment concluded at Phase I	0	33.3%	0
Total									**≥ 6.3 %**		

[a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vpvb) (Appendix 2, Table A2.3)
[b]Risk Quotient (PNEC/PC)
[c]Predicted exposure concentration for groundwater (µg/L)

4.3.4 Sensitivity and data representation

Different sensitivities were found between the different methodologies. Table 4.8 describes the relative results for the compounds in different methodologies. Differences in sensitivity are best understood by considering the rankings of the anthelmintic compounds. In this case the three compounds were ranked the same in the summative approach, however in the comparative approach moxidectin and fenbendazole were preferred to ivermectin (Table 4.8). Finally, the scoring of the compounds in the visual scoring matrix resulted in a ranking of lowest risk to highest risk: fenbendazole < moxidectin < ivermectin. Therefore based on the relative results, differences in sensitivity are indicated from the least sensitive to the most sensitive as: summative < comparative < visual scoring matrix.

Table 4.8 Summary of case study results for absolute and comparative categorization and total matrix score from visual and scoring approach**.**

Compound	Compound	Summative Categorization	Comparative Categorization	Matrix Scoring[a]
Antibiotics	Tylosin	3	Comparator[b]	10.5
	Tiamulin	2	4 (Increased risk)	13.9[c]
Anthelmintics	Ivermectin	3	Comparator[b]	15.6
	Moxidectin	3	2 (Reduced risk)	30.5
	Fenbendazole	3	2 (Reduced risk)	14.2[c]
NSAIDs	Diclofenac	2	Comparator[b]	≥6.3
	Meloxicam	1	2 (Reduced risk)	0[c]

[a]Percentage of data indicating risk = (score/maximum score), scores are adjusted so PBT, RQ, and groundwater are given equal weighting. Further explained in text.
[b]Considered as the authorized product to which applicant products are compared to assess changes in risk levels.
[c]Additional visual scoring matrices included in Appendix 2, Table A2.22 – Table A2.24.

Data representation differences are also highlighted in cases where contrasting decisions would be supported. For example, in the antibiotics case study the summative categorization ranks tylosin as an increased risk compared to tiamulin. However, both the comparative and score from the visual scoring matrix indicate that tiamulin is a decreased risk. The difference in this case is the inclusion of a measurement for spatial risk in the summative method. Due to this measurement and availability of FOCUS results for tylosin and not tiamulin, the risk categorization of the summative method ranks tylosin's risk as higher. In the cases where spatial risk is not considered, the higher RQ and PBT criteria of tiamulin account for the higher risk.

Risk rankings of the anthelmintic compounds also vary in data representation. In this case the compounds are ranked equally in the summative approach due to the definition of criteria combinations in the levels (Table 4.2). All the compounds exceed the example

temporal criteria as well as 1 or 2 of the ERA criteria (i.e., PBT, PECgw, RQ) and are therefore ranked as level 3. However, the inclusion of 1 or 2 exceedances in the same level defines moxidectin with two exceedances (i.e., PBT and RQ) as equal to the other compounds with a single exceedance (i.e., RQ exceedance for ivermectin and fenbendazole). For this case the comparative method ranks both moxidectin and fenbendazole as reduced risk options compared to ivermectin due to a decrease in the maximum RQ (Table 4.6). However, a contrasting result is indicated from the score of the visual scoring matrices that indicate that both ivermectin and fenbendazole are lower risk options compared to moxidectin. In order to understand the conflict in the ranking of moxidectin, the visual scoring matrices for ivermectin and moxidectin are presented in Tables 4.9 and 4.10, respectively. Based on the matrices, the variation is due to differences in the incorporation of RQ results. In the visual scoring matrix all RQs are represented and therefore the scores for ivermectin and moxidectin consider one very high ranked RQ and 4 very high RQs, respectively (Tables 4.9 and 4.10). Due to the selection of only the highest RQ in the summative and comparative methods the single RQ higher by one order of magnitude is automatically considered a greater risk than many RQs an order of magnitude lower.

Sufficient data was available to test and compare categorization methodologies, however data representation is clearly impacted by data limitations. The most extensive dataset available was for ivermectin (Table 4.9) this is the only compound for which data considered the sediment compartment. Comparison of the ivermectin and moxidectin data sets (Table 4.9 and 4.10, respectively) show further differences in the species tested. The third anthelmintic, fenbendazole has fewer species data available (Appendix 2, Table A2.23). Differences in the datasets of antibiotic compounds include the previously mentioned availability of spatial data as well as application of SSDs for tylosin but not for tiamulin. In practical application of benefit-risk assessments at the authorization level, data requirements for ERAs will result in more consistent datasets and therefore differences in datasets will likely have less impact on results. The dataset differences require that results of this chapter are not applied to select preferred VMP compounds, but rather a preferred benefit-risk methodology.

The results of this section clearly indicate differences between categorization methodologies as well as the importance of category assignment with criteria and thresholds. This supports the discussion in Section 2.3, emphasizing the importance of setting meaningful criteria and thresholds.

Table 4.9 Application of visual and scoring risk matrix (Figure 2.2) to ivermectin ERA data. Colours indicate risk intensity from high (i.e., red) to moderate (i.e., yellow) to low (i.e., green).

Risk Level				Very High	High	Moderate	Low	Negligible	Score	Weight	Adjusted Score (%)
Score				4	2	1	0.5	0			
Criteria	PBT[a]					PT			1 / 4	33.3%	8.3
	RQ[b]	Compartment	Organism								
		Surface water	Algae					<1	7 / 32	33.3%	7.3
			Daphnia	$9.7x10^5$							
			Fish					<1			
		Sediment	Chironomids &Benthic communities			36					
		Soil	Earthworms					<1			
			Collembolans				5.7				
		Dung	Dung fly community			>40.9					
			Dung Decomposition				>3.03				
	PECgw[c]							<0.1	0 / 4	33.3%	0
Total									15.6		

[a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vpvb) (Appendix 2, Table A2.3)
[b]Risk Quotient (PEC/PNEC)
[c] Predicted exposure concentration for groundwater (µg/L)

Table 4.10 Application of visual and scoring risk matrix (Figure 2.2) to moxidectin ERA data. Colours indicate risk intensity from high (i.e., red) to moderate (i.e., yellow) to low (i.e., green).

Risk Level				Very High	High	Moderate	Low	Negligible	Score	Weight	Adjusted Score (%)
Score				4	2	1	0.5	0			
Criteria	PBT[a]					B&T			1 / 4	33.3%	8.3
	RQ[b]	Compartment	Organism								
		Surface water	Green Alga					<1	16 / 24	33.3%	22.2
			Daphnia	$3.5x10^4$							
			Fish	$6.6x10^3$							
		Soil	Earthworms					<1			
		Dung	Dung beetle progeny	$5.4x10^3$							
			Face Flies	$5.4x10^3$							
	PECgw[c]							<0.1	0 / 4	33.3%	0
Total									30.5		

[a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vpvb) (Appendix 2, Table A2.3)
[b]Risk Quotient (PEC/PNEC)
[c] Predicted exposure concentration for groundwater (µg/L)

4.3.5 Method assessment

Differences in key characteristics were identified through case study testing presented in the previous sections. Table 4.11 summarizes four characteristics (i.e., applicability, adaptability, sensitivity and transparency) and describes the differences between methodologies. First, applicability of the methods was considered good due to the success of implementation with case study data. However, difficulty with the data availability for the spatial and temporal criteria in the summative approach affected the ranking results. This suggests that eliminating the spatial and temporal aspect would support the applicability of this method until further work is conducted to support more consistent availability of data. Additionally, the applicability of the comparison categorization is limited because the current legislation supports individual assessment of compounds (European Parliament, 2004a). Second, the adaptability of all methods was ranked as good due to the successful adaptation to the unique risk of diclofenac (Section 4.3.3). Third, the sensitivity ranking was designated based on the discussion in Section 4.3.4. Finally, the transparency of environmental risk inclusion would be generally improved through the implementation of a standard structured approach, which is not currently implemented (EMA 2008). Therefore all approaches offer an improvement in transparency, however there are differences between the methodological approaches. In the case of the summative and comparative approach, transparency was described as moderate due to the summarization of RQ data. In comparison, the transparency of the visual scoring matrix was described as good due to the full representation of this data (Section 4.3.4).

Table 4.11 Summary of case study testing results for specific characteristic in environmental risk categorization methodologies.

Method	Applicability	Adaptability	Sensitivity ranking[b]	Transparency
Summative categorization	Possible with criteria change[a]	Yes	3	Moderate
Visual scoring matrix	Good	Yes	1	Good
Comparative categorization	Good[c]	Yes	2	Moderate

[a]Current application of spatial and temporal risk was not found to be supported by data availability; [b]Most sensitive = 1 and least sensitive = 3; [c]Not supported by current legislation

The results of the case study testing summarized in Table 4.11 identify differences between the categorization methodologies. Overall, the results suggest that the visual scoring matrix may be the appropriate method for continued development. This is due to the best combination characteristics (Table 4.11). The comparative method had the second

best combination of characteristics (Table 4.11). However, the main difficulty with the comparative method is that assessments are currently made based on individual product data (EMA, 2009). In the case that a substitution principle is adopted the comparative method could be more applicable, however, the visual scoring matrix can also be used for product comparison (e.g., Table 4.9 and 4.10). Finally, the summative approach ranked the lowest in the assessment of method characteristics. The main difference between the summative ranking and the comparative ranking is the applicability characteristic. In this case, the summative approach was found limited by data availability for two novel criteria (i.e., spatial and temporal risk). With further development it would be possible to include these criteria more effectively and possibly adapt the visual scoring matrix to consider this data. Overall, the findings of this chapter support selection and development of the visual scoring matrix.

The insights of into differences between benefit-risk methodologies can support further work to select an appropriate method through user consultation. The current testing supports selection of the visual scoring matrix, however pilot tests with users could be applied to confirm this finding. Previous work applied pilot testing to benefit-risk methods for human medicines considering benefits and side effects, the results were valuable insights into operationalizing methods (Noel *et al.*, 2012). Further work to operationalize the proposed benefit-risk methodologies for environmental risk integration will require discussion with regulators. The insights presented here would support methodology presentation and collection of regulator opinions.

4.4 Conclusions

The categorization of case-study data was the main aim of this chapter. All categorization methods were applied successfully, however they were limited by data availability. Insights were gained into the relative strengths and limitations of methodologies, which will provide direction for the further development of the ERA integration into benefit-risk decision-making. The insights into the implications of setting rules for levels (e.g., the summative method) are demonstrated and it is supported that these would require careful consideration in implementation. The results clearly demonstrate that ERA data can be successfully integrated into the categorizations for benefit-risk decision support and further work with regulator users will support operationalizing methods.

5 Environmental RMMS for VMPs from the user's perspective

5.1 Introduction

European market authorizations of VMPs require the inclusion of environmental risks in a favourable benefit-risk evaluation (EMA, 2009). In the case that environmental risks are unacceptable RMMs can be applied to decrease or remove the risk (EMA, 2008). In ERAs the risk of compounds is measured by combining the toxicity of the compound to test organisms and the predicted exposure concentration (VICH, 2004). The toxicity to non-target species will be specific to the compound being considered for authorization, therefore alterations to the risk level must focus on reducing the exposure (Liebig *et al.*, 2014). In order to reduce exposure, specific directions for use will be included in the SPCs in the "Special precautions for use" section (European Commission, 2006). An example RMM to decrease aquatic exposure and therefore risk to aquatic organisms is: "Do not allow treated animals to swim in water courses until at least …hours/days after administration." (European Commission, 2006).

Evaluation of RMMs for inclusion in ERAs follows four criteria recommended in the EMA (2008) guidance: (i) mitigation of exposure; (ii) agreement with agricultural practice; (iii) European and member state legislative agreement; and, (iv) ability to demonstrate risk reduction in ERA calculations. When it is not possible to identify RMMs for a VMP that meet the criteria, the unacceptable environmental risk is included in the benefit-risk assessment (EMA, 2008). However, no specific methods are available in guidance documents to support integration of unacceptable environmental risks into benefit-risk evaluation (EMA, 2009).

Benefit-risk methodologies have been developed in Chapter 2 to integrate environmental risks. The developed methodologies have suggested standard application of benefit-risk evaluation prior to assignment of risk mitigation measures (Chapter 2). The recommendation is primarily due to previous work supporting that RMMs are unreliable, and therefore may not actually decrease environmental risk (Montforts *et al.*, 2004; EMA, 2012b; Liebig *et al.*, 2014). However, if RMMs were improved and to the point that they were considered reliable it may be considered appropriate to apply them before the benefit-risk assessment. The development of RMMs would therefore potentially support capturing benefits by decreasing environmental risks in benefit-risk assessment.

Identification of appropriate RMMs would support their incorporation in the ERA process. Previous work by Liebig *et al.,* (2014) has catalogued a list of RMMs that were considered to adequately fulfil the criteria suggested by EMA (2008) as well as additional criteria suggestions. The additional criteria consider: (i) sustainability (i.e., long-lasting effects); (ii) addressing (i.e., directed to a specific addressee that would implement the RMM); and, (iii) a proportionality principle (i.e., RMM is suitable and reasonable to achieve goal and no less restrictive option is available) (Liebig *et al.,* 2014). Criteria were used to evaluate RMMs collected from product literature and novel RMM suggestions based on possible alterations to parameters included in exposure modelling (Liebig *et al.,* 2014). The resulting catalogue consists of 19 appropriate RMMs (Table 5.1). The RMMs are separated into the following 5 categories based on application scenario: (i) disposal; (ii) aquaculture; (iii) intensively-reared animals; (iv) pasture animals; and, (v) intensively-reared and pasture animals. The RMMs are addressed to veterinarians, farmers, animal holders, fish owners, and general users of the product.

Table 5.1 Catalogue of RMMs proposed in Liebig *et al.,* (2014) to fulfill criteria for appropriate and effective RMMs (see text).

Precautions for disposal	
1	Constraint to the user (fish owner): Prior to the use of the product, a discharge certificate is required from the relevant authority for the release of this product into the aquatic environment.
2	Constraint to the user (fish owner): Use only if the flow rate of untreated waters allows for an x-fold dilution of the volume of treated water before discharge into surface waters. Where the appropriate dilution of treated water cannot be achieved, the farm must have a discharge process to limit the release of product into the environment to within the parameters described. This can be achieved by the use of holding tanks and ponds, discharge lagoons and biofilters to clean treated water. Where this applies, the user must monitor the discharge concentration to ensure that the parameters are not exceeded.
Precautions for use in aquacultures	
3	Constraint to the user (fish owner): Prior to the use of the product, a discharge certificate is required from the relevant authority for the release of this product into the aquatic environment.
4	Constraint to the user (fish owner): Use only if the flow rate of untreated waters allows for an x-fold dilution of the volume of treated water before discharge into surface waters. Where the appropriate dilution of treated water cannot be achieved, the farm must have a discharge process to limit the release of product into the environment to within the parameters described. This can be achieved by the use of holding tanks and ponds, discharge lagoons and biofilters to clean treated water. Where this applies, the user must monitor the discharge concentration to ensure that the parameters are not exceeded.
Precautions for use in intensively reared animals	
5	Constraint to the farmer: Before spreading slurry (manure) from treated animals, it has to be stored for at least x days/months.

Table 5.1 Continued: Precautions for use in intensively-reared animals

6	Constraint to the farmer: Slurry (manure) from treated animals must not be spread on areas where run-off could occur (slope > 10%).
7	Constraint to the farmer: Slurry (manure) from treated animals must only be spread on arable land if it is x-fold diluted with slurry (manure) from untreated animals.
8	Constraint to the farmer: When spreading slurry (manure) from treated animals onto arable land, a safety margin of x meters to the water's edge has to be maintained.
9	Constraint to the farmer: When spreading slurry (manure) from treated animals onto arable land, the maximum nitrogen spreading limit must not exceed x kg N ha−1 yr−1.
10	Constraint to the farmer: Slurry (manure) from treated animals must only be spread on arable land in x portions of the maximum nitrogen spreading limit with minimum time intervals of y days.
11	Constraint to the farmer: Slurry (manure) from treated animals must not be spread on soils with an organic C content < x%
12	Constraint to the farmer: After spreading of slurry (manure) from treated animals, soil must be ploughed to a depth of at least x cm (>5 cm).
Precautions for use in pasture animals	
13	Constraint to the veterinarian/animal holder: Strategic treatment of stock is only allowed after the fly or dung beetle season in autumn or in early spring.
14	Constraint to the animal holder: Animals [animal group] from free-range husbandry must be kept indoors during treatment and x days following treatment.
15	Constraint to the animal holder: During treatment and x hours/days following treatment animals [animal group] must be kept away from watercourses.
16	Constraint to the animal holder: [Product] is toxic to dung organism (flies, beetles). Therefore, animals [animal group] must not be kept on the same pasture every season.
Precautions for use in intensively reared and pasture animals	
17	Constraint to the veterinarian/animal holder: Only treat affected animals [animal group] when required. For correct diagnosis and development of an appropriate treatment schedule, a veterinarian should be consulted. Fecal worm (worm egg) counts can be used as an indicator of whether treatment is needed or not.
18	Constraint to the user of the product: During the use of the teat dipping or spraying, dripping residues must be collected and disposed of separately (cf. special precautions for disposal, SmPC, Section 6.6).
19	Constraint to the farmer: Dirty water must only be spread with a maximum spreading rate of x L (<50,000) ha−1 onto arable land or pastures.

Communication of RMMs to addressees (i.e., users) is vital to support implementation (EMA, 2012b). However assessments of VMP RMMs have focused on criteria evaluation rather than user input regarding practicality of RMMs (EMA, 2012b; Liebig *et al.,* 2014). The previous investigations aimed at VMP users (e.g. veterinarians and famers) have focused on disease management, prescribing, and health system description (Alarcon *et al.,*

2014; Speksnijder *et al.,* 2014; Rojo-Gimeno *et al.,* 2018, respectively). Additionally, prevention of exposure from farming situations has previously investigated RMMs for pesticides and measured their efficacy (Reichenberger *et al.,* 2007). The previous investigations of users' perspectives of the environmental concerns from pharmaceuticals have focused on human medicines. For example, monetary valuations of possible wastewater treatment measures to mitigate human pharmaceuticals entering the environment have been supported with survey tools (Logar *et al.,* 2014; Wang *et al.,* 2016). Interviewing has also been applied to human medicine users' with the aim to increase the understanding of consumption and disposal (Interreg IV BN). However, no investigations have been conducted to understand the VMP users' perspectives of environmental RMMs.

In this chapter the understanding of VMP users' environmental attitudes and perspectives of VMP environmental risks and mitigation options are developed. The VMP users recruited represented both the veterinarians and farmers. Semi-structured interviews collected data on the VMP users' attitudes as well as perspectives of suggested RMMs and ideas for improvement. A template analysis was applied to identify themes that emerged from the interview data. Presentation of a novel narrative of users attitudes and experience with VMP environmental RMMs emerged. Additionally, results identified factors affecting RMM practicality and ideas for improvement. The discussion of the results compares this work with previous work and presents recommendations for RMMs application in the authorization process.

5.2 Methods

Developing an understanding of the user's narrative regarding RMMs requires application of social science survey methodologies. Specifically, interviews are a valuable tool and a method that creates rich, in depth narrative output (Bryman, 2016). Facilitating interviews with a flexible questionnaire is considered a semi-structured interviewing approach (Bryman, 2016). In this case the discussion is guided by a questionnaire and there is flexibility to explore the topics raised with further questioning (Bryman, 2016). The recording and transcription of interviews provides textual data to inform on social research questions. The analysis of textual data can take either a deductive or inductive approach. The deductive approach applies previously developed theory to the data (Bryman, 2016). The second is inductive, which develops theory from the data (Bryman, 2016). The combination of deductive and inductive approaches has been found to be effective in previous studies (Alacron *et al.,* 2014; Fereday and Muir-Cochrane 2016a,b).

5.2.1 Questionnaire development

Semi-structured interviews were guided with questionnaires included in Appendix 3. Separate questionnaires were designed for the two groups of VMP users (i.e., veterinarians and farmers). Approval of the questionnaire and research study was received from the University of York Environment Department Ethics Committee. The open-ended questions were aimed to understand perceptions, attitudes, the practicality of VMP RMMs, and finally to collect ideas to improve RMMs. Risk mitigation measures suggested by Liebig *et al.,* (2014) were the basis of the practicality sections (Table 5.1).

Recruitment of two groups of VMP users was applied to create a broad understanding of the users' perspectives. Selection of veterinarians and farmers was based on the majority of the previously suggested RMMs addressing veterinarians and livestock farmers, whom would also be animal holders (Liebig *et al.,* 2014). Differences between the two groups were considered in questionnaire development. Veterinarians, as animal health experts and farm consultants, provided experience of multiple farming establishments. Data collection started with the development and implementation of the veterinarian questionnaire and therefore initial responses were applied to the development of the farmer questionnaire. One adaptation of the farmer's questionnaire was application of the term management instead of RMMs. This was applied due to veterinary participants suggesting the RMMs term was unlikely to have meaning for farmers. The farmer's questionnaire captured insights for the suggested RMMs that were more detailed and specific to the operations of single farm units.

5.2.2 Participants

VMP users were targeted from veterinarian and farming backgrounds. Purposive sampling aimed to recruit veterinarians either currently practicing or having previous experience with livestock practice. A two-pronged approach was applied to recruit veterinarians. Research advertisement was made through willing veterinary networks to recruit volunteers. Additionally, a snowballing approach was applied by asking participants if they knew of colleagues whom might be interested in volunteering for the study. The recruitment of farmers relied solely on snowballing. Recruited farmers were currently running farming businesses. Participation was voluntary and permission to record interviews and use data was confirmed at the beginning of interviews. Participant details were removed to make data anonymous.

5.2.3 Data collection

Interviews were conducted either by phone or in person between October 2015 and November 2016. Interviews were recorded with the participants' consent. The audio recordings of interviews were later transcribed verbatim. After 17 interviews (10 veterinarian and 7 farmer interviews) no new themes were emerging and sampling was concluded.

5.2.4 Data analysis

The focus of this research was to understand RMMs from a VMP user perspective. Therefore famer and veterinary data was combined in the analysis.

The application of template analysis combining deductive and inductive coding was applied to support the research aims. The defined research aim was to collect data describing VMP user attitudes, perceptions of suggested RMMs and collect ideas for improvement. Support of these specific categories required organization and therefore deductive coding to guide thematic development. The addition of inductive codes to this approach would support capturing the unique insights provided from participants. This is especially supportive of defining the factors important from a user's perspective since it has not been previously done and therefore there is no work to inform formulation of strictly deductive codes. Finally, in previous survey work with farmer participants, the investigation of disease management was successfully informed by template analysis (Alarcon et al. 2014).

Deductive codes were applied to organize the initial coding and were based on questionnaire prompts (King, 2004). The three main categories supporting our aims were applied (i.e., Attitudes, VMP RMMs and improvements). An additional category was added for the collection of general participant information. Divisions based on the prompts in the main sections were included as lower-order codes to guide and focus coding. A more minimalistic initial template was deemed appropriate for this research in order to capture emerging factors (Figure 5.1).

1. General information
    a. Livestock type
    b. Region
2. Attitudes towards environment
    a. Environmental attitudes
    b. Perceptions of VMP RMMs
        i. RMM implementation
3. Practicality of RMMs
    a. Practicality
    b. Cost-effectiveness
    c. Additional benefits
4. General improvements
    a. Suggestions
    b. Communication

Figure 5.1 Initial coding template of deductive codes based on questionnaire prompts.

Careful and iterative reading was applied in the coding exercises and inductive codes were added to the initial template to describe data. NVIVO software was used to apply exploratory codes to interview transcripts. Inductive coding resulted in a large set of 267 codes. Subsequently, to assist with the identification of themes and organization of the dataset, descriptive summaries of interview data were generated. Refinement and re-organization of descriptive data and supporting quotes resulted in the identification of themes across the coded data. Emerging themes and final template were refined and different categorizations were applied in an iterative process to test organization and find the best description of findings based on the research objectives. Final results were verified by comparison to the initial coding to confirm thorough representation of data and findings. Results were circulated to participants for comments, which were considered in result finalization.

5.3 Results

The final template resulted in five top-level divisions (Figure 5.2). The first top-level category contains information describing the participants. The following four codes contain themes and factors describing the specific category (Figure 5.2). The thematic sections below (sections 5.3.2 – 5.3.5) present the final template for the section and subsequent description of the supporting data. In the descriptions of themes, quotes are identified with veterinarians and farmers with either a “v” or “f”, respectively.

1. Participants
2. Attitudes and perceptions
3. Awareness of VMP environmental concerns
4. Practicality of RMMs
5. Improvements

Figure 5.2 Top level categories of final thematic template.

5.3.1 Participants

Discussions with participants ranged in duration from a minimum of 18.09 minutes to a maximum of 84.32 minutes. A summary of the livestock expertise and the region of each interviewee are included in Table 5.2. In the case of two of the farmer interviews more than one farm representative (i.e., 3 and 2 representatives) contributed to the discussion. In these cases the interview data was considered as a single response for the farm. In the longest interview the recorder failed at question 18 (Farmer Questionnaire, Appendix 3) after an hour and a half discussion. In this case, it was agreed that the final questions, mostly related to improvements, had come up in the extensive conversation of the questions prior to the recording failure. The questionnaire was adjusted after the pilot interview to include a question regarding the number of animals on the farm. Therefore, this data is not available for the first farm. Four farms had between 250 and 350 animals. The highest number of animals was 2700 including breeding animals and offspring. The smallest had less than 100 animals of different species.

Table 5.2 Participant livestock expertise and region

Variable	List of participant results
Veterinarian livestock expertise	Sheep Primarily sheep, some cattle Primarily sheep, with overview of livestock production systems Primarily dairy and pigs, a small amount of sheep and poultry Cattle and sheep Cattle (2 participants) Ruminants Primarily sheep, secondarily cattle Dairy cattle
Farmer livestock expertise	Dairy (3 participants) Sheep Pigs Mixed (breeding sheep, horses, chickens) Beef

Table 5.2 Continued

Variable	List of participant results
Veterinarian regions	Whole U.K, North, Northwest England Across U.K. and Northern Ireland East Anglia Yorkshire North Yorkshire Shropshire Southern Scotland Majority Southwest England, other work around U.K. Southwest U.K.
Farmer regions	North Yorkshire all participants

5.3.2 Attitudes and perceptions

The thematic template for attitudes and perception is summarized in Figure 5.3. The below sections describe the themes identified in analysis.

I. Attitudes and perceptions
   a. Caring and positive attitude
   b. Variability of attitudes
   c. Focus on animal health
      i. VMP use

Figure 5.3 Thematic template for result of attitudes and perceptions.

Caring and positive attitudes

Generally a caring and positive attitude towards the environment, animal health and supporting regulation was expressed during interviews. Farmers generally supported the aims of regulations (i.e., to maintain environmental or animal health).

"A lot of the regulations we want to do anyway, it's not something that we won't want to do, cause it's all about animal welfare and keeping the environment as well as we can, so a lot of it's for positive reasons" [F]

Veterinarians also considered that the majority of farmers "have a great deal of care" and would want to avoid damage to their farm. Motivation for environmental care was also described to come from maintaining farm productivity and therefore profits.

Difficulties with regulation. Although there was general support of the aims of environmental regulation there was recognition of difficulties in their application. A significant challenge for farmers was the complexity of regulations, which were reported to be "duplicated" across a number of organizations involved in farm regulation. Some organizations and regulations mentioned by participants included the Department for

Environment, Food and Rural Affairs (DEFRA), the Environmental Agency, farm assurance (e.g., Red Tractor), nitrate vulnerable zones (NVZs) regulation, and stewardship schemes. Record keeping and inflexible restriction were also considered challenging:

"The impact is on the book keeping and the recording and the red tape side of it which is, […] a bit too keen at times." [F]

Variability of attitudes

The caring and positive theme was supported by the study participants, however there was also recognition of variation in the perceptions of environmental issues across the agriculture industry. The attitude towards the environment was reported as dependent on "the individual and their personal beliefs" and therefore would be variable. Additionally, participants observed the existence of a "bad" or "lower" fraction of the industry.

"We have 10% of really bad people. Really bad people. Who you know are so bad, that they are always going to contaminate the environment, and they don't take notice of what their told or what to do and they don't want to see a vet." [V]

Focus on animal health

The attitudes of veterinarians were very focused on animal health. Through the implementation of health plans with farmers, veterinarians described supporting farm specific health management. Meetings with veterinarians and farmers were applied to develop plans that were described as "balancing" different aspects like animal health and stress as well as farm practicalities. Plans were considered to focus on disease prevention that would consider the environment more from a disease transmission perspective.

VMP use. VMP application was highlighted as applied by veterinarians in response to illness or risk assessments with consideration of safety measures. The priority safety considerations were reported as the withdrawal times (i.e., the hold time post-treatment before acceptable for the market) and proper application. Environmental safety was described as a lower priority concern and often not necessary based on the product.

"So, it depends on the category of medication that you are dealing with as to whether or not there is a risk to the environment" [V]

5.3.3 Awareness of VMP environmental concerns

A diversity of perceptions and levels of awareness were collected regarding the environmental risks of VMPs. There were some reports of high awareness of the environmental issues of VMPs and many highlighting uncertainty. The template for this section is illustrated in Figure 5.4.

I. Awareness of VMP environmental concerns
   a. Specific VMP cases of environmental risk
      i. Insecticides
      ii. Anthelmintics
      iii. Baycox
      iv. Topical versus excreted
   b. Uncertainty
      i. Antibiotics
      ii. No risk

Figure 5.4 Thematic template for result of awareness of VMP environmental concerns.

Specific VMP cases of environmental risk

The discussions clearly indicate that there are cases of environmental risks that have higher awareness, however even high awareness cases were not necessarily known to all participants. The variation appeared to be effected by differences in livestock diseases and therefore product use.

Insecticides. Some veterinarians and farmers discussed the environmental concerns of sheep dips and pour-on insecticides. This case was considered to be a risk that was "known" and the avoidance of watercourse exposure to have been "flagged up over the years". The awareness was reported as high in this case and described as extending to "everyone". Penalties were described as in place to enforce environmental caution and use required obtaining a license.

"Certainly for things like sheep dips in particular, you know you're very much aware, because you need to be licenced to use them." [F]

Anthelmintics. Concerns regarding anthelmintic use were described as resistance and environmental risks. The problem of resistant parasites was reported from overuse of anthelmintic products. The environmental concern in this case, was also described to have high awareness as an "obvious" case with effects to fish. In this case, the reported RMM would be allowing the animal to "dry out" (i.e., allowing topical applications to dry for appropriate amount of time before exposure to a watercourse). The risk to dung beetles was also discussed and different opinions were given. In one case the effects were described as "short-lived and temporary" and therefore "not a problem". Other opinions observed that certain active ingredients and long-acting products would have higher concern. However, justification for the use of these products could be based on the farming situation or the farm's resistance profile.

“But we are aware of particular products, with particular impact on, for example the dung beetle population. So, would there be consideration in the selection maybe based on that […] It would depend on the resistance picture with the spectrum on that particular farm.” [V]

Baycox. Two veterinarians highlighted this specific VMP as having a RMM in the summary of product characteristics.

“If you go and read the data sheet for baycox, you know, it specifically says it shouldn’t be used in cows over 80 kilos. And there’s some wording on there about the animals under treatment must only represent a certain proportion of animals within the herd.” [V]

Topical versus excreted. A division in the concern for topical versus treatments metabolized by animals was reported. Discussions highlighted that veterinarians would advise for treatments applied topically, a specific example was given as footbath applications, which would be given with specific disposal instructions. In the case of footbath treatments advice could be given that animals stand on concrete post application to prevent product being “wiped off on the grass” but also to prevent “too much […] run off into a watercourse”. Additionally, footbath advice would consider the potential for splashing during application and the placement was considered an approach to minimize entry to the “water table for instance”. In contrast to the footbath example applications through injection or oral preparations were reported to have less environmental consideration as well as a level of uncertainty.

“I don’t think we give much consideration to, when you give an injection to a cow, what the knock-on effect might be” [V]

Uncertainty

There were many indications of uncertainty regarding the environmental concerns of VMPs outside of specific cases. In some cases this uncertainty was attributed to a lack of research and evidence for environmental risks of VMPs. The consequence of limited research was limited communication and consideration of environmental concerns. In other cases the uncertainty reflected that participants were not aware if the research was required or it was a case of communicating the research.

“I don’t know whether the research has been done [in] the first instance […]or [it’s] just knowledge transfer really.” [F]

Antibiotics. Environmental concerns for antibiotics were presented as uncertain and extended to the concern of antibiotic selection for resistance. In the discussions of antibiotic resistance there were perceptions of inequality between human medicines and

veterinary medicines. Additionally, there were reports of pressure to decrease antibiotic use, specifically from milk buyers in the dairy industry.

No risk. Reports that participants didn't know of environmental risks linked to perceptions that VMPs didn't pose a risk. Some discussion points that supported the perception of no risk included the compound breakdown and dilution in the case of residuals entering the slurry or dirty water systems. Also highlighted was the low usage of VMPs.

"I'll freely admit I don't know the full impact of what we're using. We don't use very much to be honest" [F]

5.3.4 Practicality of RMMs

Based on discussions of RMMs previously suggested by Liebig *et al.*, (2014) three main thematic categories emerged, that described: (i) disposal; (ii) RMM limitations; and, (iii) situational dependence. The thematic template of this section is presented in Figure 5.5.

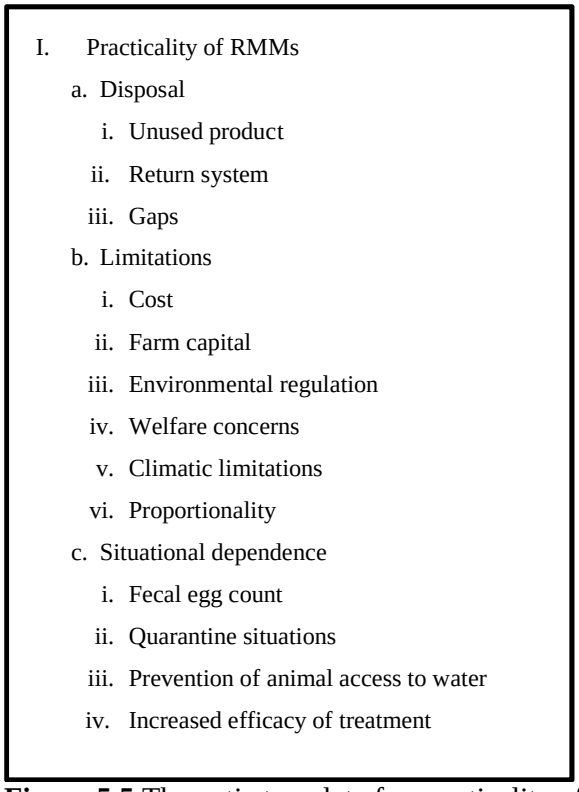

Figure 5.5 Thematic template for practicality of RMMs.

Disposal

Disposal discussion data indicated two dominant themes. The first was that unused product was rare. The second was that return systems are currently in place, however with some gaps.

Unused product. The first theme indicated that the need to dispose of unused product was considered uncommon by both veterinarians and farmers. This was motivated by the expense of the products and could even support use beyond the expiration date.

"Most farmers would only buy what they need and what they are going to use. So, a situation where some was left at the end, it doesn't occur very often and farmers being farmers would generally probably keep it and use it next time even if it went out of date." [F]

"I've never seen a farmer pay what they consider to be quite a, quite a high cost for a product and not use it." [V]

Return system. Data indicated the implementation of return systems was occurring in many instances. Commonly, veterinarians reported that their practices would collect unused product and empty bottles by supplying a collection container and applying a cost to cover disposal. The system of return to the veterinary practice was considered "highly organized" by one veterinarian and noted by another veterinarian to be "in everybody's health plan". Veterinarians also reported that in some cases return systems were organized through contractors. In addition, four farmers reports supported that return systems were in place on their farms. The system was reported as a regulatory requirement and was generally supported. The disposal through veterinary practices was described to give one farmer confidence the disposal was "done properly".

Gaps. Cases of gaps in the implementation of return systems were also reported. For example, one veterinarian specified that return systems were implemented on "most of our farmers". A veterinarian also observed a product specific gap in their report that their practice did not collect products not sold by veterinarians to the farmers, for example wormers. The exclusion of some farms was further supported by three farmer reports indicating that no return system was implemented. Additionally, burning waste on farm specifically on November 5th, when bonfires are common, was highlighted as an instance of improper disposal.

The exclusion of farms seemed to be related to livestock type and associated VMP use and veterinary contact. The farms without a return system had sheep and beef cattle stock. One farm noted that their "farming situation" produced a waste level considered "very very negligible" however, they considered that the situation might be different in a different type of farm, for example they specified a pig farm. Specifically they perceived the VMP usage as higher:

“maybe a pig farm that uses a lot more vaccines and a lot more in feed antibiotics there’s maybe, yeah, there’s maybe a situation there” [F].

Further elaboration by another farmer highlighted that beef and sheep farmers have less interaction with veterinarians compared to dairy farmers, with the perception that: “some farmers have a good working relationship with the vets and so a sort of return, sort of a policy or whatever is sort of happening now”. However, in the sheep farming the main products usage was considered to be wormers and vaccines, picked up by the farmer according to need.

Limitations

Limitations to RMMs emerged from discussions of suggested RMMs. The limiting factors for RMMs were identified as costs, farm capital, environmental regulation, welfare concern, climatic factors and proportionality. The below sections give examples of RMM discussion supporting the importance of limiting factors.

Cost. Importance of cost-effectiveness was a clear theme for the successful implementation of RMMs. Low prices for livestock products were a consistently identified problem in the discussions of possible RMMs for VMPs. The low product prices motivated high awareness of costs within the farming industry and high business consequences if costs couldn’t be kept down. Therefore RMMs with associated costs would likely be impractical or require payment support.

“it’s costing them more to produce something than […] what they are being paid for it […] the more that they [farmers] are told to do things, they think well that’s fine either pay us to do it, or give us a return on our product, and if that’s not forth coming then, let’s say it’ll simple level us through the floor.” [V]

Farm capital. Farm capital was highlighted in discussions regarding changing slurry and manure practices as a potentially limiting factor. One veterinarian described the limited storage space in combination with restrictions on spreading slurry and manure as a potential “big problem”. Specifically, in discussions regarding the separation of treated and untreated animals a need to expand slurry or manure storage space was considered a limitation. Additionally, the expansion of storage space would have health and safety as well as cost considerations. Capital would also be required to separate animals in different housing and support feeding of different groups. Based on capital constraints one veterinarian summarized their opinion as: “I don’t think that’s a practical one”. Farmers agreed that separation of animals was unpractical. Farmers described separating animals as “a real problem” and “difficult”.

Capital constraints were also discussed in terms of the RMM to avoid repeated use of pasturelands. In this case the quality and amount of land were a limitation. It was commonly observed that farms did not have enough land to avoid repeated pasture use. The quality of the land would also affect how it was utilized. For example, in the case of young sheep it was reported that "favoured" pastures would be used due to favourable characteristic, such as having more shelter. Discussions with farmers also reported lands were used repeatedly each year. The time of year also affected the grazing pattern, as one farmer pointed out: "at this time of year we actually have sheep in absolutely every field we've got".

Environmental regulation. The environmental limitation was highlighted in discussion of RMMs referring to slurry and manure. In this case conversation repeatedly mentioned regulatory constraints. Slurry and manure application was observed to have "standard constraints" which vary between local authorities and would potentially consist of limits to the time of spreading, the distance to watercourses, and the specific fields. Several veterinarians highlighted farms in NVZs as farms with heavy restrictions. Farmers mentioned DEFRA's involvement with slurry and manure practices as well a restriction in the NVZs, cross-compliance, entry level stewardship (ELS), the water framework directive and farm assurance programs (e.g., Red Tractor). Even in the case that manure was sent to another farm it was remarked by a farmer that the supplier needed to also provide information on how much manure or slurry could be spread on what fields. One veterinarian succinctly summarized the discussion by highlighting that any RMM for slurry and manure would have to integrate with the current constraints.

"Whatever mitigations are put in place, would have to be operable within that existing framework." [V]

A further example of a regulatory limit was given for the RMM suggestion to hold free-range animals indoors post treatment. In this case it was pointed out that consideration would have to be given to the length of holding time permitted to qualify as free-range animals.

Welfare concern. Participants often highlighted the welfare of animals as the priority in livestock systems and reported regulatory support. The concern for welfare was observed to be an important limit for the RMM, "strategic treatment of stock only after fly or dung beetle season in autumn or early spring". The implications of this RMM to animal healthcare were considered impractical, because it was considered "essential" that treatments could be applied when animals were clinically assessed as unwell.

“You tend to treat when it’s necessary, you don’t treat indiscriminately. And therefore if it’s necessary it’s usually an animal welfare issue to treat it […] You can’t just [say]: oh, sorry there’s dung beetles, your animal has to suffer for another two months before I’m allowed to give it this medication.”[V]

Additionally, financial impacts from withholding treatments would be very high. This was described in one veterinarian’s response when asked if this RMM was cost-effective:

“No, no. You’re talking thousands of kilos of potential grow.” [V]

Another example of an animal health consideration was given for RMMs, which would require separation of animals. In this case specific stress from separation was reported for grazing cattle.

“Obviously they [cattle] are herd animals, and it’s pretty stressful for them to be separated from the herd. […] I do feel like, [it’s] one of the main things that you can do to stress a cow which is a herd animal is, […] mixing its social group. It’s something that I always advocate, it’s something that should be kept to a minimum.” [V]

Climatic limitations. The climatic factors must also be considered for any RMMs specific to slurry and manure. Specifically, the necessity of the correct weather conditions at the right time of year for slurry and manure spreading was summarized by one veterinarian:

“The calendar and the weather are the two biggest things that drive farmers. […] if it’s a frosty day, they’ll be out spreading slurry, and that’s got to be done then because, if they can’t do it on that frosty day the ground is too heavy and they damage it too much with the tractors, so there will be a practical limitation there. So, very dependent on the year and the elements.” [V]

Proportionality. Discussion of capturing teat dip separately highlighted the need to consider the proportion of risk compared to the RMM suggested. In this case dip was described as applied after milking and a “small amount” would drip onto the floor and be collected with the slurry. No risk was perceived based on the perceived low hazard of the compound used, the dilution of drops within the slurry, and potential compound breakdown. Therefore the effort and impracticality of trying to capture drops to separate from manure was not considered justified.

Situational dependence

The final theme that emerged from practicality discussions of RMMs was situational dependence. No RMMs were identified as fully practical in all situations, but rather practical depending on farm and business characteristics. For example one veterinarian

pointed out variation based on the risks and practicalities of the farm, and another the topography and climate of the farm.

“It depends on the risks and practicalities on each farm.” [V]

“Depends on the individual topography and the climate of that farm.” [V].

Dependent on the farm situation there may be opportunities or other drivers, which would support the RMMs discussed. These cases are explored in the following sections.

Faecal egg count. Many, but not all veterinarians, expressed strong support for the implementation of treatment after faecal egg count (FEC) tests. This was described as, “the gold standard” and “good practice” for parasite control. It was considered to reduce product use and therefore have the additional benefits of timesaving, reducing animal stress, and maintaining effectiveness of products.

“Less work, less stress on the animals, less expense.” [V]

“It also means that you give these other products a longer life in the field as being effective. By using more strategically.” [V]

The generalization of the practice to all farms was considered by some veterinarians to not be fully practical and a case-by-case approach was preferred. This opinion highlighted that both practicality and cost-effectiveness were discussed as dependent on farm type and the “particular business’s ability to implement a treatment protocol based on the results of the test.” Additionally, one veterinarian considered that the focus of FEC tests on number of worm eggs was discussed as potentially “misleading”. A movement away from FEC testing was described due to new evidence supporting the importance of pathogenicity of the worm over the quantity of eggs found in faecal samples. An additional limitation highlighted for FEC by a veterinarian was the lag time between animal symptoms and egg appearance in faeces.

Farmers’ reports supported differences in perceptions of the usefulness of FEC tests. Some farmers reported it as an available option; other farmers reported it as an implemented and effective tool.

“We’ve used faecal egg counts for the last 5 or 6 years, something like that, and some years we sell quite a lot of lambs without ever having wormed them at all.” [F]

Quarantine situations. Quarantine practices were viewed as possibly synergistic with the RMM suggestion to separate treated and untreated slurry or manure. For example, new livestock may be held in quarantine situations before joining the farm’s stock. The quarantine was described to support parasite resistance management by providing an

opportunity to separately treat animals. After treatments, parasites excreted from animals would not enter the farm's pasture, but rather manure or slurry would be disposed of separately. Additionally, in the case of free-range animals it was remarked that the practice of quarantine and holding animals indoors for treatment was advantageous to monitor the animal's response to the treatment.

"If you're dealing with free range animals, then having them indoors after treatment makes sense because you need to have them at least contained so that you know that they are responding to the treatment you're using." [V]

Prevention of animal access to water. In more intensive farming practices common to lowland areas, water bodies were reported as fenced off for disease management. The inclusion in health plans was described for "a lot of people" by a veterinarian. The fencing off of water bodies prevented animals drinking from them and potentially contracting a disease. Additionally for dairy, tuberculosis regulations were reported as specifying that animals were not allowed to drink from water bodies. Prevention of animals drinking from water bodies was also reported to reduce transmission of worms and leptospirosis

Some farmers with pasture animals reported already having implemented fences to prevent animals accessing water bodies. One farmer highlighted that preventing animals entering water bodies also prevented disease, drowning, and pollution. Discussion of possible change was limited. In the case of regulatory requirements no modification could be made. Additionally, change wasn't desirable as the fencing of water bodies was viewed positively as a way to protect the environment and animal health.

"No, I think we need, [...] to keep the water clean, and drinking water needs to be clean and I think that one of the things that you have to do" [F]

However, the full restriction of sheep from water bodies would not be practical in highland areas or with extensive situations. In these areas the pasture was described as "open access" and a situation where animals are drinking from water on the land.

"Huge numbers of grazing systems will be relying on watercourses to provide drinking water, the minority of enclosures would be supplied with, or my perception would be, the minority would be supplied with tanked water, piped water. So, access to, free access to natural watercourses is, is essential for a lot of enclosures" [V]

Increased efficacy of treatment. An example of increased efficacy of treatment and possible reduction in direct environmental exposure was given for teat dip application. The avoidance of direct entry to pastures by holding animals on concrete yards after treatment was reported as "practical" and "doable". Veterinarians reported that they encouraged

farmers to let cows stand on concrete for 15 minutes after teat dip application. The holding of animals after treatment was considered cost-effective due to its benefit of making treatments more effective. The holding of animals would prevent direct entry of dripping residuals to pasture environments. Instead residuals would enter a waste collection system. This advice is motivated by animal health due to the advantage of reduced infection risk.

“By letting them stand for 15 min after milking, it closes the teat orifice and there’s less risk of infection getting in.” [V]

Reports also highlighted avoiding rain post treatment as an opportunity to increase efficacy and decreased environmental risk for topical treatments. For this case, one veterinarian thought that avoiding treatment on a wet day was an implemented RMM, however couldn’t find it in SPC information. There was another report that farmers might be less aware or “forget” about avoiding rain exposure post treatment. However, one farmer indicated they were aware of the consequences of rain exposure and would apply treatments accordingly.

“We wouldn’t normally start doing that [apply treatments] if we felt there was a risk of a heavy rain shower you know, because obviously it’s a waste of product as well as the risk of contamination really.” [F]

5.3.5 Improvements

The template representing the results of the improvement section is described in Figure 5.6.

- I. Improvements
  - a. Awareness
    - i. Environmental risk research
    - ii. Communication
    - iii. Enforcement
    - iv. Incentives
  - b. RMM implementation
    - i. Consultation
    - ii. Labeling
  - c. Decreased and responsible VMP use
    - i. Health planning and vaccination
    - ii. Disease education
    - iii. Prescription
    - iv. Supply chain management
    - v. Other possibilities

Figure 5.6 Thematic template for result of the improvement section.

Awareness

The lack of awareness identified in the attitudes discussion was again a theme in improvement conversations.

“I think, make people more aware, I think I’ve said that already” [V]

“Well as I keep saying, I don’t know, I’m not saying there isn’t a problem, I don’t know whether there is a problem. If there is, I suppose the first thing, the first thing to do is make the farmers aware of it.” [F]

Additionally, farmers particularly expressed that focusing on problem cases would support awareness. For example one farmer summarized their opinion as: “I’m a great believer, if it’s not broke don’t try and fix it”. The focused approach would support farmers in being able to manage the many demands of farm business management.

“We don’t particularly want to burden the farmers with another layer of… […] it’s partly the time it takes to [do] all the form filling, and all the reading up and keeping up to date with it but it’s also the fact that you know, you sort of… […], your brain is busy enough trying to run the business and then to try and remember to do all these things, or not do this and do that then and do this now, and you just get to the stage where… heads full of it.” [F]

Environmental risk research. The state of uncertainty and unawareness regarding the environmental risks of VMPs was considered to stem from a lack of knowledge and research on the subject.

“If there is a problem there in the first place, […] the research needs to be done to sort of find out where there is a real problem.” [F]

“We don’t really know what the degree of environmental consequences are for the vast majority of products we use.” [V]

Justification of RMMs with research-based evidence was also considered as necessary to encourage uptake. For example, in discussing communication of RMMs on products, one veterinarian responded that symbols might be useful in the case that there was evidence of both risk and effectiveness of the RMM.

“If there was something that had a decent evidence base that would really mitigate a real, real evidence risk.” [V]

One description from a veterinarian suggested an important contributing factor to the lack of VMP risk knowledge was authorization before environmental risk assessment requirements.

“A lot of these products have been registered a very long time again, at which point they won’t have had to do a particularly detailed environmental risk assessment, it’s only the more recently licensed products that have actually been done.” [V]

In the case that the risks were high the option to remove the VMP from the market was identified.

“If the medicines are a particularly big problem withdraw them in the first place, […] if they are doing serious damage to the environment.” [F]

Communication. Another theme for improvement was the inclusion of environmental risk for VMPs in existing schemes and communication structure. Suggestions for communication are summarized in Table 5.3.

Table 5.3 Summarized communication possibilities and description for ideas to support awareness of VMP environmental concerns and RMMs

Communication Possibility	**Description**
Health plans	Opportunity to include or add emphasis to RMMs in specific farm health management plan
Farmers press	Publications with good readership. Specifically the Farming press was considered "one of the best ways to inform the farming public"
Veterinarian practice's newsletter	A monthly newsletter reported to accompany veterinarian bills
Farm assurance	Inclusion in the criteria in the standards and inspections already in practice
Client meetings	Suggestion to make environmental concerns a habitual topic for veterinary and farmer client meetings
Farmers' meetings	Discussion at hosted meetings for farmers
Conferences	Specific to the livestock industry and likely to have pharmaceutical representatives
Levy boards for agricultural industry	Possibility to support research and dissemination
Farmer organizations	For example the National farmers union (NFU)
Veterinary organizations	For example the British Veterinarian Association (BVA)
Education requirement	Inclusion in the undergraduate curriculum for veterinarians
Online platforms	Dissemination through social media or webinars
TV	Possibility of introduction of farmer specific programming

Enforcement. Discussions surrounding implementing RMMs highlighted different opinions regarding enforcement. There were some reports of VMP misuse being highly publicized with large consequence.

In some discussions it was suggested that, for the potential RMMs discussed, enforcement would be required.

“Someone has to, is going to have to, enforce it if they want it to actually happen.” [V]

Whereas in other cases RMMs “imposed” on farmers were thought to likely lead to a negative attitude, especially if an explanation of importance was not provided.

Incentives. Farmers did not suggest enforcement but rather expressed that environmental regulation generally could involve “ridiculous monitoring and penalties”. Therefore discussions expressed a preference for an approach that focused on the communication of incentives.

“It’s about having that… not soft approach, but I think telling the farmers that, you know this is going to improve your business by this and this rather than saying you’ve got to do this.” [F]

RMM implementation

Consultation. Considering the variability of on farm practicality (Section 5.3.4), discussions with farmers would be useful to understand how risks could be minimized. Adding in financial support was also suggested as a way to “go further”. One farmer highlighted the need to improve consultation process specifically with regards to changes to the ELS scheme that they were participating in:

“That’s where the communication can be improved in the development of environmental schemes, you know, and a consultation process, you know, farmers feel at the moment that we have just not been listened to at all, with the new scheme, this mid-tier scheme, that’s available, and I think that’s a real shame you know, I think it’s just, […] too onerous and the rewards aren’t enough to, to tempt farmers to… to sign” [F]

Labelling. Contrasting opinions were presented regarding product labelling. In some cases product labels were considered sufficient.

“Most of the labels are fairly clear […] that, it’s […] toxic to, you know, for water courses and things like that.” [F]

However, in other cases labels were considered to need more clear instructions.

“Being more specific. And being more […] direct. You know: do, don’t.” [V]

More general challenges with communication through product literature were reported. Challenges included the tendency to skim through and potentially not appreciate RMMs, if included. In other cases, leaflets with VMPs may have been previously disposed of.

Finally, a farmer suggested improvements to better communicate any changes to a VMP's handling instructions, and specific inclusion on labels instead of in literature was suggested.

To support RMM awareness, an interesting suggestion was the application of colour coding to support discussions of environmental risks.

"Maybe, as a consideration, there should be a panel on medicinal products giving a visual or coded colour as to the relative risk of the use of this product to the environment. Which would give you a base to discuss the use of it with your client." [V]

Decreased and responsible VMP use

From discussions of possible improvements with veterinarians, one of the most prevalent emergent themes was implementation of health management focusing on responsible VMP usage and minimizing treatment need. The minimization of VMP use was strongly supported and described as "the ultimate mitigation". Several factors were identified as possible support of product minimization and are presented in this section.

Health planning and vaccination. VMP minimization was considered to be part of health planning implemented for individual farmers through veterinarian consultation. Within these plans veterinarians applied management of the environment to prevent disease as well as vaccination. The improvement of on farm management and the development of vaccinations were therefore recommended. Additionally, minimization of VMPs with health planning and vaccination was preferred to the RMMs discussed in the practicality section.

"I would say you will, you are more likely to reduce the impact in the environment by putting in place vaccination or herd management practices, that reduce the need for the product, than you are to try and keep animals off pasture or to create a separate waste stream for the handling of faeces let's say." [V]

Disease education. Education aimed to inform VMP users about the diseases treated was suggested to improve appropriated VMP use.

"We had a farmer meeting last night and I made the comment that, how often have you been told to use this product because it treats all stages of fluke. And everybody around the table went, yeah. They'd all been told that. Whereas actually a greater understanding of the disease of fluke would say that you would only use that product at certain times of year and you would use different products at different times of year" [V]

The idea of adding certification requirements to treat animals was discussed to possibly promote training and education requirements. Disease understanding was also reported as supported on one farm by reports received from their abattoir on animal condition and disease. They reported that this supported their herd management and described it as "handy, that information, very".

Prescription. Some veterinarians advocated for "tightening up" of prescription practices. Discussions of prescription improvement highlighted two sources of prescription the first being veterinary practices, and the second being suitably qualified people. Improved justification for prescription and monitoring of subsequent use was suggested.

Supply chain management. Challenges in supply chain management were reported as contributing factors to poor medicine use. For example one veterinarian remarked, "there's a commercial requirement to sell the product, so that.. frequently overrides the, […] animal health reasons to sell the product." [V]

Sales by merchants of non-prescription based products were also described as "very poorly evidenced based". Contribution to increase in resistance specifically to anthelmintics was highlighted as a consequence of this poor practice.

Other possibilities. Another possibility to decrease VMP usage would be "breeding animals that are more resistant". This was reported to already have genomic testing occurring and viewed to be a future possibility supportive of VMP minimization. Additionally the development and improvement of diagnostic techniques would support effective and minimal treatment use.

5.4 Discussion

The results of this chapter develop the VMP users' narrative regarding the environmental concerns of products. This is an area that has not been previously investigated and therefore offers important insights into the RMM awareness and implementation as well as the practicalities of previously suggested RMMs (Liebig *et al.,* 2014). This work contributes a critically important first step towards understanding the health and farm management context surrounding RMMs. The following sections further discuss the study results.

5.4.1 Environmental knowledge

Factors and themes described in this work suggest that on farm attitude and knowledge of environmental issues could support RMMs. The caring attitude observed by veterinarians and reported by farmers is important to support willingness to consider RMMs aimed to

protect environmental quality. The environmental awareness necessary for the regulations already in place on farms provides a base level of knowledge regarding environmental contamination that could be built upon to support an understanding of the risks of VMPs. Additionally, evidence collected also supported that previously identified risks have been successfully communicated to VMP users in some instances of specific risks (Section 5.1.3). However, the identification of products with environmental risks was not consistent across participants, indicating that improvements could be made. Further reports highlighted that a fraction of the industry was recognized as operating suboptimal practices and therefore would be unlikely to implement RMMs.

5.4.2 RMM practicality

Disposal

The return system for VMP disposal was often described as already implemented. However, the environmental exposure from disposal is not actually considered in ERA models (VICH, 2000; VICH, 2004; EMA, 2008). Therefore RMMs for disposal will not actually contribute to the level of environmental risk in ERAs and authorization considerations. However, the interview data on this point is valuable to demonstrate the success and gaps of this system and can guide future efforts to improve return systems.

RMM limits and scenario dependence

The themes of RMM practicality requiring consideration of limitations and situational factors indicate similar findings to the EMA (2012b). The evaluation by EMA (2012b) compared the eight RMMs for livestock against the four criteria suggested by EMA (2008). Only two RMMs were found to fulfil the criteria. In both these cases the criteria requiring RMMs to “be in line with agricultural practices” was considered to be scenario dependent. This supports the theme that practicality of RMMs is situational dependent.

The six cases of RMMs found to not fulfil the criteria are also supportive of the situational theme, and additionally supportive of the limitations theme. In this case a division between RMMs under control of the veterinarian and farmer were separated from those not under control of these two VMP user groups. For the two RMMs under veterinarian or farmer control two criteria were indicated as dependent upon and conflicting with animal welfare. Further capital constraints were identified as barriers to fulfilling criteria. The four cases not under control of the veterinarian or farmer related to the spreading of manure. In one case identified by EMA (2012b), an RMM was indicated but would already be accounted for in exposure modelling. In the other cases the primary concern was the transfer of manure to another party and the potential that the RMM would not be communicated.

Further support for difficulties applying RMMs to traded manure was highlighted by Montforts *et al.*, (2004) as an area that would not be legally enforceable. This investigation also found the RMMs targeting manure were highlighted as areas of environmental regulations and potentially very limited (Section 5.3.4).

5.4.3 Communication

The evidence suggesting participants were uncertain or unaware of environmental concerns for VMPs is an important finding, especially given this theme was first recognized in the attitudes section and then repeated in the improvements section. An increase in the general awareness of VMP environmental exposure and potential risk would support communication of risk management.

A consultation process aimed to identify RMM opportunities and limitations would support a more realistic application of RMMs. Identification of treatment scenarios where RMMs are unlikely to be applied could be factored in as a change in risk magnitude. An increase in realism and transparency would be accomplished compared to the previous consideration of RMMs that, subject to some criteria, could convert an unacceptable risk to an acceptable risk. Discussions with VMP users to gather opinions on effective RMMs would have the added advantage of increasing user awareness through the discussions. Opportunities to implement consultation could work with existing networks that were highlighted by participants (Table 5.3). Implementing a consultation process would increase the regulator and user knowledge of RMMs.

Further, this investigation indicates that effective communication of RMMs requires justification and clear communication of risk evidence, which is also recognized by the EMA (2012b). This further supports the need for an increased scientific understanding of the environmental risks of VMPs that is a continually developing field of scientific and regulatory knowledge (Küster and Adler, 2014).

5.4.4 Further research

The current investigation focused on livestock and dominantly represents ruminant species. Further investigations into fish farms as well as chicken and poultry production would add to the understanding of RMMs in agriculture.

5.4.5 Recommendations

This investigation and previous work (Montforts *et al.*, 2004; EMA, 2012b) highlight the difficulties in RMM implementation. Therefore improvements are required to realistically consider RMM impacts on environmental risks and support integration into benefit-risk

assessment. Challenges and recommendations for improvements are summarized in this section.

The challenge of finding practical RMMs was highlighted in the interview data. Discussions of RMM practicality highlighted that limitations and situational variables would greatly impact RMM practicality (Section 5.3.4). Additionally, it was observed that RMMs could be omitted either due to unawareness (Section 5.3.3) or due to poor attitude (Section 5.3.2). Therefore, it is recommended that RMMs applied in environmental risk calculations should decrease risk by a realistic factor rather than completely shifting environmental risk to an acceptable level. This adjustment would better inform the amount of risk accepted in benefit-risk assessment. Further work with RMM users and development of a consultation process would support developing an understanding of reasonable factors for application to environmental risk calculations based on specific RMMs.

Another main challenge for RMMs was the general lack of awareness regarding the environmental risks of VMPs (Section 5.3.5). In order to improve awareness, a number of existing networks were suggested for information dissemination (Table 5.3) and the need for evidence of environmental risk was highlighted (Section 5.3.5). The previously mentioned implementation of a consultation process would have the added benefit of directly educating consultants who could consequently disseminate information. Another possibility to improve awareness is to include environmental safety statements when no risk is identified with either a phrase (e.g., “No evidence of environmental concern”) or potentially a colour system (e.g., different colours for different levels of environmental risks). These recommendations have the potential to support a more consistent consideration of environmental risk in VMP selection and improving communication in differences between products.

5.4.6 Conclusions

The novel research conducted in this study highlights the diversity of factors at play in livestock production and environmental maintenance. This research contributes to an area not previously investigated and begins to develop the understanding of the user context surrounding VMP RMMs. The investigation presents a diversity of considerations required for successful implementation of RMMs and identifies unique opportunities. Based on the work presented here and previous work recommendations have been outlined for RMMs in the authorization process. Finally, this investigation presents further evidence to support identification of favourable benefit-risk VMPs before application of RMMs in the authorization process.

6 Discussion

6.1 Summary of thesis aims and results

In this thesis, the integration of environmental risk and mitigation into the benefit-risk assessment for VMPs within the European authorization process was investigated. The work began with the development of possible benefit-risk methodologies based on current European authorization regulations. Subsequently, an in-depth investigation of the risks of a higher concern antibiotic (i.e., tylosin) provided insights into the available data and uncertainties. Application of environmental risk assessment data from case-study compounds and substitutes developed the understanding of differences between the benefit-risk methodologies. Finally, novel qualitative data illustrated the perspectives and attitudes of VMP users towards RMMs.

Chapter 1 introduced the background regulatory framework for European VMP authorizations and reviewed previous work. Background information included an introduction to VMPs, their use, subsequent emission to the natural environment and potential ecological effects. This background information also described the regulatory requirements for ERA and risk mitigation within benefit-risk assessment for VMP authorization in Europe. The main difficulty in implementing a benefit-risk assessment is the comparison of benefits (i.e., for the treated animal) and risks (i.e., to the environmental health). A review of work attempting to compare the benefits and risks highlighted that few studies have been implemented for VMPs or pharmaceuticals more broadly. Further the methodologies previously applied were not benefit-risk approaches and therefore would not support the authorization process requirements.

Chapter 2 developed three methodological options to support the integration of environmental risk into benefit-risk assessment. Methodologies are currently developed for application prior to RMMs due to previous work suggesting that implementation is not reliable (Montforts *et al.,* 2004, EMA, 2012b, Liebig *et al.,* 2014). A categorization approach was applied in all three methodologies in order to address the main challenge of incomparable benefits and risks. Two approaches for the individual evaluation of VMPs were proposed (i.e., the summative categorization and the visual scoring matrix) and the third approach was based on differences between VMPs (i.e., the comparative approach). The application of benefit-risk methodologies to support market authorizations is critical in the case of ERAs identifying unacceptable risk.

Application of a full ERA with cumulative available data was conducted for the antibiotic tylosin. Treatment scenarios for the U.K. market were applied in the exposure modelling

which resulted in different level of risk for the soil compartment. Some usage scenarios (i.e., 23%) indicated an unacceptable risk to the soil compartment. Previous FOCUS modelling by Guo *et al.,* (2016a) was adapted to the maximum, the average and the minimum PECsoil values. Resulting risk estimates for European surface water exposure scenarios varied based on the exposure scenario and the rate of application of tylosin to soils. Surface water risk was identified in some scenarios. A comparison with previous work discussed uncertainty in risk estimates. Therefore potential future adaptations of ERAs could be made to address uncertainties and this supports the need for adaptable benefit-risk assessments. The unacceptable risk measurements are appropriate for the application of the benefit-risk methodologies. Additionally, the availability of effective RMMs would support tylosin use in cases with unacceptable environmental risks.

Testing of the environmental risk categorization methodologies was applied for the proposed benefit-risk methodologies. Testing applied different risk profiles of unacceptable environmental risks from case study compounds of high concern (i.e., tylosin, ivermectin and diclofenac). To support the comparative categorization alternative compounds were also investigated (i.e., tiamulin, moxidectin, fenbendazole and meloxicam). Application of ERAs was limited by data availability and therefore testing cannot support recommendations on the case study compounds. However, data was suitable for the testing of benefit-risk methodologies and the comparison of data representation between the approaches. The results identified differences between the approaches in terms of applicability, adaptability, sensitivity and transparency. A comparison of the differences suggested that the visual scoring matrix had advantages in these categories. The identification of a single strategy to develop can draw on these results and is suggested to investigate the preferences of regulators. In this application the consideration of risk mitigation measures was not made due to the uncertainty previously identified (Montforts *et al.,* 2004, EMA, 2012b, Liebig *et al.,* 2014).

Refinement of unacceptable risk with RMMs is an important method to minimize risk and capture VMP benefits (EMA, 2008). Therefore an understanding of the user perspective is required to understand practicality of RMMs and include realistic and effective RMMs into the benefit-risk assessment. Accordingly, the final investigation collected interview data from VMP users (i.e., veterinarians and farmers). Application of a thematic template analysis was conducted on the data to identify emerging attitudes and experiences as well as identify factors affecting the practicality of proposed RMMs. The results highlight the perception that the majority of the farming industry has a positive and caring attitude towards both animals and the environment. Specific to VMPs application focus on animal

health concerns, but some environmental risks were identified as well-known cases by some respondents. Uncertainty regarding the environmental concerns of VMPs was also discussed more generally. Specific to practicality, disposal return systems were reported as often already in place. With regards to other RMMs important limiting factors would require consideration. When RMMs were practical it was considered to likely be dependent on the scenario. The results were compared to a previous evaluation by the EMA (2012b) that also supported that RMMs would be effective depending on the situation.

Overall, the thesis contributed significantly to the development of ERA and mitigation integration into benefit-risk assessment of VMPs. Methodology development supports realistic identification and discussion of three scenarios: (i) benefits are greater than environmental risks; (ii) environmental risks are greater than benefit; (ii) benefits are equal to environmental risks (Figure 6.1). In the first scenario products will be authorized whereas in the second scenario realistic risk mitigation will be a valuable tool to potentially alter the benefit-risk balance. Finally, the case that benefits are equal to environmental risks would require regulator judgement but could also be adjusted if realistic RMMs were identified and communicated. The sequential investigations of this thesis establish a foundation for the integration of ERA data and RMMs into benefit-risk evaluations to better identify the scenarios described in Figure 6.1. However, the preliminary nature of this research has limitations and requires further research, which is discussed in the next section.

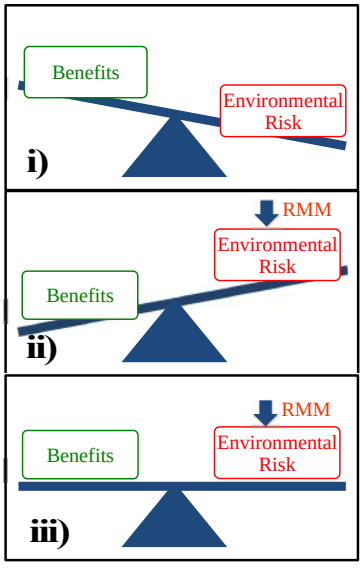

Figure 6.1 Benefit risk possible scenarios: i) benefits greater than environmental risks; (ii) benefits less than environmental risks; (iii) benefits equal to environmental risks. RMM: risk mitigation measures.

6.2 Limitations and further research

6.2.1 Application of benefit-risk assessment

Following the current European guidance the development of benefit-risk methodologies focused on the integration of environmental risks into benefit-risk evaluation. However, the risk profile of a VMP will be diverse and require consideration of other direct risks (i.e., for the target animal, the user, and the consumer of animal derived foodstuff) and indirect risks (i.e., antimicrobial resistance development, unintended spread of vaccine strain, and reversion to virulence) (EMA, 2009). For this work an assumption was implemented that a VMP would meet the acceptable risk level in the other risk categories in order to be considered for authorization. Realistically, VMPs could have trade-offs in terms of both benefits criteria and different risk categories. Further research to support the expansion of methods to represent full benefit and risk profiles of VMPs will support optimal decision-making. The benefits categories were also presented to illustrate methodologies, however further work is required to assign meaningful criteria and thresholds and veterinarian consultation is advised (Chapter 2).

In the case of European authorization of VMPs, benefit-risk is the required methodology (European Parliament, 2004a). Therefore the current study focused on benefit-risk methodologies due to regulatory requirements, however other methodologies are available to make comparisons. One approach to compare benefits and risks is to convert impacts to monetary units so that a direct cost-benefit can be applied. Another available approach is multi-criteria decision analysis.

Applications of cost-benefit approaches simplify the comparisons and answer the question: are benefits greater or less than costs. This approach is similar to the summative categorization method (Section 2.1.1) and comparative classification (Section 2.1.3) as both simplify benefits and risk data into levels to implement a greater than or less than comparison. The application of a formulaic approach requires agreement on decision-rules that will define the amount of risk acceptable for a benefit level. It would be assumed that the defined categories would facilitate recognition of cases that regulators would consider animal welfare benefits to be greater than environmental damage. In order to define the levels and the rules of comparison (e.g., benefits 1 level higher than risks is required for authorization) further work to gather expertise is required.

Limited work has been applied to monetize the environmental impacts of VMPs (Section 1.3.1). The example of a direct monetization study by Markandya *et al.*, (2008) was conducted to measure impacts, mainly on human health impacts, after diclofenac caused vulture populations to collapse. In this case the focus of the monetization impacts were

only measurable after exposure of vultures to the VMP diclofenac. In order to support the authorization process and avoid negative impacts, benefit-risk assessment considers predicted risk values. Therefore the monetization strategies applied by Markandya *et al.,* (2008) would not be applicable for novel VMPs applying for authorization. Further work would be required to apply monetization and cost-benefit to VMPs.

Another tool previously applied to wastewater treatment decisions is multi-criteria decision analysis. In this case, both stakeholder perspectives and ecotoxicology information was successfully integrated (Schuwirth *et al.,* 2012). A main result from implementing a multi-criteria decision analysis in the investigation of wastewater treatment options for a hospital was that discussion between stakeholders was supported (Schuwirth *et al.,* (2012). Facilitating discussion was also the main objective of the visual scoring matrix method (Section 2.1.2). The ranking of alternatives in multi-criteria analysis is also similar to the comparative approach (Section 2.1.3), which is the only approach to take into account the benefits and risks of other available VMPs. However, the visual scoring matrix of two VMPs could be compared to gain more insight into the differences of VMP environmental risk profiles and avoid simplification to a single level that is applied in the comparative approach. Adoption of a comparative method would require changes to legislation, which currently require individual evaluations of VMPs (European Parliament, 2004a).

6.2.2 Environmental risk data

Integration of environmental risks into benefit-risk assessment is limited by the available data. The two chapters investigating environmental risks demonstrated some of the limitations for ERAs and consequently benefit-risk assessment. The accumulation of available data for the antibiotic tylosin contributed to a comprehensive understanding of the current evidence for environmental risk in this case (Chapter 2). In the scientific literature only one other compound (i.e., ivermectin) has had a cumulative evaluation of the available evidence to evaluate the level of environmental risk (Liebig et al., 2010). The results of Chapter 2 highlighted data gaps as well as uncertainties regarding both exposure and effects data for tylosin. Additionally, the variation in environmental risk level was dependent on the scenario for both the terrestrial and aquatic risk. Limitations were also identified in the case study data applied for method testing in Chapter 4. In this case method testing was possible, however results could not support VMP compound decisions due to significant differences in datasets.

Development of the scientific understanding of environmental risks of VMPs occurs over time. For example, Brandt *et al.,* (2015) recommended that ERAs of antibiotics be adjusted to effectively protect ecosystem services. Measuring ecosystem services has developed to

recognize the value derived from natural ecosystems (Costanza *et al.,* 2017). The evaluation by Brandt *et al.,* (2015) focused on four categories of ecosystem, that have been supported by different agencies (Constanza *et al.,* 2017). Identification of microbial contributions were described for the three categories: (i) provisioning services (e.g., genetic resources); (ii) regulatory services (e.g., carbon sequestration); (iii) supporting services (e.g., agricultural soil formation and fertility). Effects in the fourth category of ecosystem services (i.e., cultural services) were considered negligible. In most cases of excotoxicological endpoints were advised and standard tests available, therefore providing clear direction for ERAs. However, some endpoints were uncertain and therefore tests are not available. In other cases endpoints were advised but standardized tests not available. For this example, it was specified that the development of microbial ecological knowledge will lead to further suggestions for improvement. This study demonstrates that over time ERAs will require adaptation and consequently so will benefit-risk assessment.

The application of spatial and temporal criteria was discussed for benefit-risk assessment. These criteria are not currently required for VMP ERAs (VICH 2000, 2004; EMA 2008). The results of the cumulative ERA of tylosin indicated variation across treatment scenarios as well as European surface water exposure scenarios (Chapter 3). Specifically the differences across Europe support spatial variation in risk. Brandt *et al.,* (2015) provided further support by noting variability in microbial communities in different environments as a challenge for standardized ERA application. In Chapter 4 the testing of temporal risk applied survey data for the anthelmintic case study from Boxall *et al.,* (2007). The evaluation applied criteria for length of application and possible overlap with sensitive species. However, without input from farmers reporting usage, this type of data is not available. Therefore in an ERA conducted before authorization the temporal risk would have to consider disease predictions to estimate treatment timings. Further variation may be expected from varying VMP user preference and knowledge. Currently, neither temporal nor spatial risk criteria were found to have substantial data for benefit-risk application in the testing conducted in chapter 4. Further work to develop understanding of spatial and temporal variation will support more accurate ERAs and consequent benefit-risk assessment.

Evaluation of ERA data is restricted to the authorization process and as a result has limitations. Benefit-risk balance is evaluated when products are authorized and renewed (European Parliament, 2004a). Renewals require reports of changes to authorization data including safety (European Parliament, 2004a). Renewals occur after five years and will not be required after the initial renewal unless the competent authorities considers it

justified to require a second renewal after five years (European Parliament 2004a). Based on these requirements the initial authorizations can only consider predicted data subject to uncertainties and that require assumptions to model environmental exposure and ecological effect. However, the renewal is an opportunity for benefit-risk to adapt to environmental knowledge collected during VMP use (e.g., environmental monitoring data). Therefore there is an opportunity to incorporate spatial and temporal monitoring data at the renewal time. However, current monitoring data is limited and further work is required to support this area (Küster and Adler, 2014).

Overall, it is clear that the development of compound specific knowledge is required for ERAs. Additionally ERAs have uncertainties that need to be addressed with flexible and adaptable benefit-risk assessment.

6.2.3 Inclusion of RMMs

Practical knowledge of VMP user perspectives and attitudes has not been previously considered. Previous work with RMMs has highlighted, from a theoretical perspective, that RMMs are not reliable (Montforts *et al.*, 2004; EMA 2012b; Liebig *et al.*, 2014). However, the VMP user is critically important to the management of VMP environmental risk. Figure 6.2 illustrates how the knowledge, action and outcome function for the three groups: scientists, regulators and users. The level of environmental risk requires communication across these three groups (Figure 6.2). In the case that there is an environmental risk and a RMM is required, the VMP user will determine the level of environmental exposure and risk (Figure 6.2). The preliminary investigation to develop the VMP user narrative was therefore a foundational step in understanding how RMMs can be incorporated successfully into the ERA and benefit-risk assessment of VMPs.

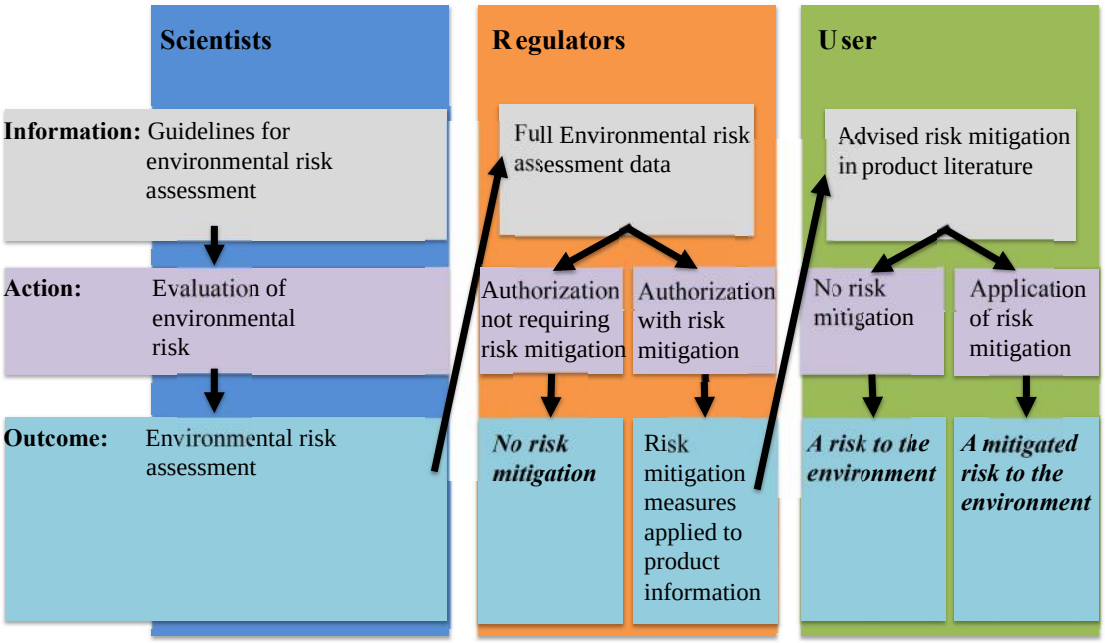

Figure 6.2 Schematic of the actors (i.e., scientists, regulators and users), the information available to each actor, the possible actions and outcomes of these actions. The black arrows indicate the flow of between information, action and outcome as well as movement of information to other actors.

The collection of VMP user insights provided evidence that the application of RMMs in the authorization process cannot assume RMM implementation, and therefore an elimination or reduction of environmental exposure. In order to be protective, the current approaches presented in Chapter 2 suggest the consideration of RMMs after benefit-risk assessment ensures that benefits are greater than risks. However, increasing the amount of cases that benefits are greater than risks could be accomplished through the development of reliable RMMs and application prior to benefit-risk assessment. In order to further the understanding of RMM reliability and the realistic level of implementation, VMP user consultation is necessary.

The ideas and evidence presented in Chapter 5 provide a basis for the further development and reliable integration of RMMs into the ERA and benefit-risk assessment. This work focused on the U.K. and collected veterinarian and farmer opinions. However, suitably qualified people can also advise on VMP use and could be included in further work. Further work with interviews and thematic understanding could focus on the poultry and pig sectors of the industry that were not thoroughly represented in this study. Additionally, more quantitative surveys could be built off of this research to understand some of the variation in practicality and attitudes amongst VMP users.

7 Conclusions

VMPs have high usage in livestock agricultural systems and are valuable to animal health and care, however as a consequence of use, environmental exposure and risk can occur. Therefore benefit-risk assessment is applied in the regulatory European authorization decisions for VMPs and requires the consideration of environmental risks (EMA, 2009). However, the guidelines on the methods of integration of environmental risks and risk management are not specific (EMA, 2008; EMA, 2009). Additionally, previous work aimed to compare the environmental risks to benefits of pharmaceuticals is not appropriate to inform the development of this procedure. Therefore a foundational work for the integration of environmental risk and risk mitigation was a large knowledge gap.

The research presented in this thesis has implications for the support of livestock production by highlighting the weaknesses and advancing the knowledge and implementation of ERA as part of the VMP market authorisation process. Livestock production is a growing industry and an important food source for the global population (Aiking, 2014; Tilman *et al.*, 2002) and VMP use is an integral part of the success in this industry. However, environmental risks from VMP usage have been identified, for example the indirect exposure of vultures to diclofenac through scavenging of cattle carcasses, leading to population collapse (Oaks *et al.,* 2004). Environmental risk assessment is a component of the benefit-risk assessment required for VMP market authorisation; however, the environmental risk assessment result is binary (i.e., acceptable or unacceptable) and likely an oversimplification. This binary approach leads to trade-offs between benefits and risks being poorly represented. Categorization methods are proposed to better capture the complexity of both the benefits and risks with the aim of making environmental risks comparable (Chapter 2). Improved comparison of benefits and risks would support decision-making to balance trade-offs of complex benefits and risks, to maintain animal and environmental health.

The evidence from an in-depth cumulative ERA suggests that these approaches require flexibility to consider the evolving science. The consequent specific testing with ERA data within benefit-risk assessment provides further development and understanding of how methodologies capture the complexity of ERA data.

Finally, consideration of RMMs from a user perspective offers insights into attitudes and experience as well as the practicality of these measures. The qualitative data supports that RMMs are not guaranteed, however there are possibilities to improve RMMs, and therefore capture more VMP benefits compared to lessened environmental risks.

The novel research presented in this thesis supports an initial development of benefit-risk methodologies for the European authorization process. The investigations develop methodological options for benefit-risk assessment and support the understanding of environmental risk assessment data within these methods. The final consideration of RMMs from a user perspective offers insights into attitudes and experience as well as the practicality of these measures. Overall, this research supports a movement towards more realistic inclusion of the complexity of environmental risk and risk management in benefit-risk assessment. The novel work supports moving towards incorporating complexity and measuring trade-offs in the decision-making for VMP authorization.

Appendix 1 Tylosin investigation supporting data

Table A1.1 Parameter applied in previous FOCUS modeling replicated from Guo *et al.* (2016a)

Parameter	Value
Molecular weight (g/mol)	916.12
Log Kow	1.63[a]
DT50water (days)	9.5[b]
DT50soil (days)	54[c]
DT50sediment (days)	1000[d]
Vapour Pressure (pa)	2.65x10^-32[d]
Water solubility (mg/L)	5[e]
Enthalpy of vaporization (J/mol)	95000
Molar enthalpy of dissolution (J/mol)	27000
Koc	553[f]

[a]Loke *et al.*, 2002, [b]Brain *et al.*, 2005, [c]Boxall *et al.*, 2006, [d]Data predicted by EPI Suite (EPA, 2014), [e]EPA, 2014, [f]Rabolle and Spliid, (2000).

Table A1.2 Treatment scenarios and PEC soil initial for tylosin; in text Figure 3.3.

Treatment scenario[a]	PEC mg/kg
Broiler (D:200, T:5)	8.87
Broiler (D:100, T:5)	4.43
Broiler (D:127, T:3)	3.38
Broiler (D:50, T:5)	2.22
Replacement layer (D:200, T:5)	1.96
Broiler (D:20, T:7)	1.24
Laying hen (D:200, T:5)	1.04
Replacement layer (D:100, T:5)	0.98
Replacement layer (D:127, T:3)	0.75
Broiler breeder (D:200, T:5)	0.56
Broiler (D:20, T:3)	0.53
Laying hen (D:100, T:5)	0.52
Replacement layer (D:50, T:5)	0.49
Laying hen (D:127, T:3)	0.39
Broiler breeder (D:100, T:5)	0.28
Replacement layer (D:20, T:7)	0.28
Laying hen (D:50, T:5)	0.26
Broiler breeder (D:127, T:3)	0.21
Laying hen (D:20, T:7)	0.15
Broiler breeder (D:50, T:5)	0.14
Replacement layer (D:20, T:3)	0.12
Broiler breeder (D:20, T:7)	0.08
Laying hen (D:20, T:3)	0.06
Broiler breeder (D:20, T:3)	0.03
Weaner pig (to 25 kg) (D:5.3, T:140)	6.45
Fattening pig (25-125 kg) (D:5.3, T:140)	4.37
Weaner pig (to 25 kg) (D:25, T:10)	2.17
Weaner pig (to 25 kg) (D:20, T:10)	1.74

Table A1.2 Continued

Treatment scenario[a]	PEC mg/kg
Sow (with litter) (D:5.3, T:140)	1.55
Fattening pig (25-125 kg) (D:25, T:10)	1.47
Fattening pig (25-125 kg) (D:20, T:10)	1.18
Weaner pig (to 25 kg) (D:6, T:21)	1.09
Weaner pig (to 25 kg) (D:5, T:21)	0.91
Fattening pig (25-125 kg) (D:6, T:21)	0.74
Fattening pig (25-125 kg) (D:5, T:21)	0.62
Weaner pig (to 25 kg) (D:10, T:7)	0.61
Sow (with litter) (D:25, T:10)	0.52
Sow (with litter) (D:20, T:10)	0.42
Fattening pig (25-125 kg) (D:10, T:7)	0.41
Sow (with litter) (D:6, T:21)	0.26
Sow (with litter) (D:5, T:21)	0.22
Sow (with litter) (D:10, T:7)	0.15
Weaner pig (to 25 kg) (D:10, T:3)[b]	0.13
Fattening pig (25-125 kg) (D:10, T:3)[b]	0.09
Weaner pig (to 25 kg) (D:20, T:1)[b]	0.09
Fattening pig (25-125 kg) (D:20, T:1)[b]	0.06
Sow (with litter) (D:10, T:3)[b]	0.03
Sow (with litter) (D:20, T:1)[b]	0.02
Calf (D:40, T:14)	3.20
Calf (D:14, T:14)	1.12
Cattle (>2 years) (D:10, T:3)[b]	0.09
Calf (D:10, T:3)[b]	0.09
Cattle (0-1 years) (D:10, T:3)[b]	0.08
Dairy Cattle (D: 10, T:3)[b]	0.05

[a]Livestock category and in parenthesis D = dosage mg/kg bodyweight, T= times applied
[b]Application by injection

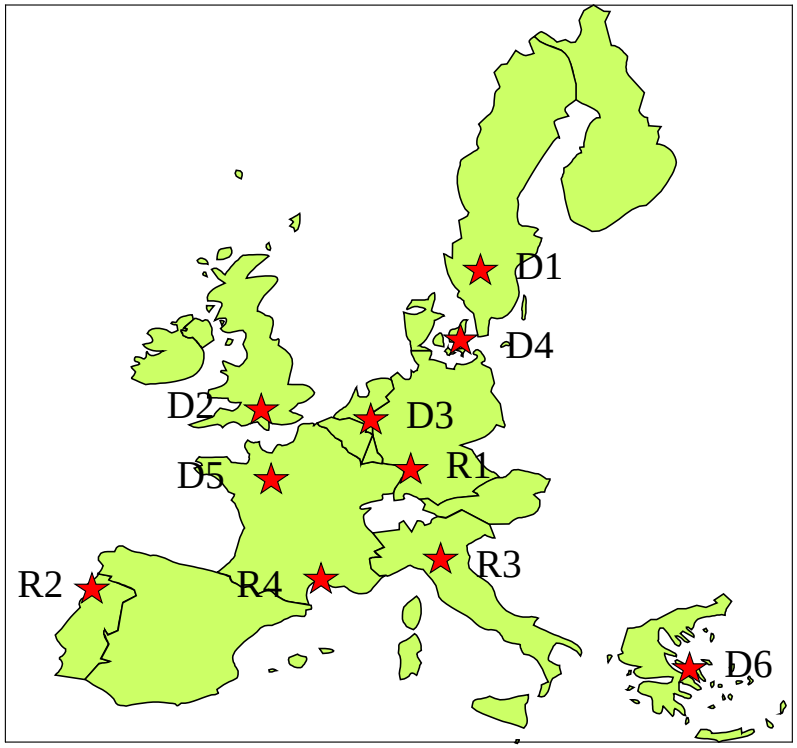

Figure A1.1 Replicated figure of 10 surface water FOCUS scenarios across Europe (D = Drainage, R = run-off) (FOCUS (2001).

Table A1.3 Replicated table of scenario variables for EU FOCUS scenarios (D = Drainage, R = run-off) (FOCUS (2001).

Name	Mean annual Temp. (°C)	Annual Rainfall (mm)	Topsoil	Organic carbon (%)	Slope (%)	Water bodies	Weather station
D1	6.1	556	Silty clay	2.0	0 – 0.5	Ditch, stream	Lanna
D2	9.7	642	Clay	3.3	0.5 – 2	Ditch, stream	Brimstone
D3	9.9	747	Sand	2.3	0 – 0.5	Ditch	Vreedepeel
D4	8.2	659	Loam	1.4	0.5 – 2	Pond, Stream	Skousbo
D5	11.8	651	Loam	2.1	2 – 4	Pond, stream	La Jailliere
D6	16.7	683	Clay loam	1.2	0 – 0.5	Ditch	Thiva
R1	10.0	744	Silt loam	1.2	3	Pond, stream	Weiherbach
R2	14.8	1402	Sandy loam	4	20[a]	Stream	Porto
R3	13.6	682	Clay loam	1	10[a]	Stream	Bologna
R4	14.0	756	Sandy clay loam	0.6	5	Stream	Roujan

[a]terraced to 5%.

Table A1.4 Terrestrial NOEC dataset for tylosin analyzed in Figure 3.5.

Species	Effects concentration (mg/kg)	Endpoint	Acute / Chronic	Reference
Earthworm (Aporrectodea caliginosa)	5000	NOEC survival	Acute	Baguer *et al.*, 2000
Earthworm (Aporrectodea caliginosa)	3000	NOEC reproduction	Acute	Baguer *et al.*, 2000
Earthworm (Aporrectodea caliginosa)	3000	NOEC growth	Acute	Baguer *et al.*, 2000
Earthworm (Aporrectodea caliginosa)	3000	NOEC hatchability	Acute	Baguer *et al.*, 2000
Springtails (Folsomia fimetaria)	5000	NOEC survival	Acute	Baguer *et al.*, 2000
Springtails (Folsomia fimetaria)	3000	NOEC reproduction	Acute	Baguer *et al.*, 2000
Enchytraeids (Enchytraeus crypticus)	2000	NOEC survival	Acute	Baguer *et al.*, 2000
Enchytraeids (Enchytraeus crypticus)	3000	NOEC reproduction	Acute	Baguer *et al.*, 2000
Rice (Oryza sativa L.)	500	NOEC seedling height (plant growth)	Acute	Lui *et al.*, 2009
Cucumber (Cucumis sativus L.)	50	NOEC seedling height (plant growth)	Acute	Lui *et al.*, 2009
Rice (Oryza sativa L.)	500	NOEC root length (root length)	Acute	Lui *et al.*, 2009
Cucumber (Cucumis sativus L.)	50	NOEC root length (root length)	Acute	Lui *et al.*, 2009
Onion (Allium cepa)	27.8	NOEC biomass	Acute	Richter *et al.*, 2016
Onion (Allium cepa)	250	NOEC emergence	Acute	Richter *et al.*, 2016
Onion (Allium cepa)	83.3	NOEC post-emergence survival	Acute	Richter *et al.*, 2016
Onion (Allium cepa)	27.8	NOEC shoot length	Acute	Richter *et al.*, 2016
Oat (Avena sativa)	27.8	NOEC biomass	Acute	Richter *et al.*, 2016

Table A1.4 Continued

Species	Effects concentration (mg/kg)	Endpoint	Acute / Chronic	Reference
Oat (Avena sativa)	800	NOEC emergence	Acute	Richter *et al.*, 2016
Oat (Avena sativa)	800	NOEC post-emergence survival	Acute	Richter *et al.*, 2016
Oat (Avena sativa)	200	NOEC shoot length	Acute	Richter *et al.*, 2016
Oat (Avena sativa)	50	NOEC biomass	Acute	Richter *et al.*, 2016
Red clover (Trifolium pratense)	83.3	NOEC emergence	Acute	Richter *et al.*, 2016
Red clover (Trifolium pratense)	48.1	NOEC post-emergence survival	Acute	Richter *et al.*, 2016
Red clover (Trifolium pratense)	16	NOEC shoot length	Acute	Richter *et al.*, 2016
Red clover (Trifolium pratense)	16	NOEC biomass	Acute	Richter *et al.*, 2016

Table A1.5 Aquatic NOEC dataset for tylosin, chronic NOECs analyzed in Figure 3.6.

Species	Effects concentration (mg/L)	Endpoint	Acute / Chronic	Reference
Green Algae (Pseudokirchneriella subcapitata)	0.5	NOEC growth inhibition	Chronic	Guo *et al.*, 2016b
Algae (Desmodesmus subspicatus)	<8.6	LOEC growth inhibition	Chronic	Guo *et al.*, 2016b
Algae (Chlorella vulgaris)	>74.4	NOEC growth inhibition	Chronic	Guo *et al.*, 2016b
Green Algae (Pseudokirchneriella subcapitata)	<0.064	LOEC Biomass	Acute (72 hours)	Yang *et al.*, 2008
Green Algae (Pseudokirchneriella subcapitata)	0.206	NOEC population growth rate	Acute (72 hours)	Eguchi *et al.*, 2004
Diatom Algae (Navicula pelliculosa)	0.5	NOEC growth inhibition	Chronic	Guo *et al.*, 2016b
Diatom Algae (Phaeodactylum tricornutum)	0.3	NOEC growth inhibition	Chronic	Guo *et al.*, 2016b
Cyanobacteria (Anabaena flos-aquae)	0.03	NOEC growth inhibition	Chronic	Guo *et al.*, 2016b
Cyanobacteria (Synechococcus leopoliensis)	0.008	NOEC growth inhibition	Chronic	Guo *et al.*, 2016b

Table A1.6 Continued

Species	Effects concentration (mg/kg)	Endpoint	Acute / Chronic	Reference
Water Flea (Daphnia magna)	45	NOEC progeny counts/numbers	Chronic	Wollenberger *et al.,* 2000
Rotifer (Brachionus plicatilis)	22.4	NOEC Lifespan	Chronic	Araujo and McNair, 2007
Rotifer (Brachionus plicatilis)	22.4	NOEC progeny counts	Chronic	Araujo and McNair, 2007
Rotifer (Brachionus calyciflorus)	22.4	NOEC progeny counts/numbers	Chronic	Araujo and McNair, 2007
Rotifer (Brachionus calyciflorus)	22.4	NOEC Lifespan	Chronic	Araujo and McNair, 2007
Inflated Duckweed (Lemna gibba)	0.3	NOEC Chlorophyll A concentration	Chronic	Brain *et al.,* 2004
Inflated Duckweed (Lemna gibba)	0.3	NOEC Chlorophyll B concentration	Chronic	Brain *et al.,* 2004
Inflated Duckweed (Lemna gibba)	0.1	NOEC Biomass	Chronic	Brain *et al.,* 2004
Inflated Duckweed (Lemna gibba)	1	NOEC carotenoid content	Chronic	Brain *et al.,* 2004
Inflated Duckweed (Lemna gibba)	1	NOEC progeny counts	Chronic	Brain *et al.,* 2004
Rainbow trout (Oncorhynchus mykiss)	96	NOEC mortality/adverse effect	Acute	Elanco, 2012

Appendix 2 PBT table and Case study ERAs

Table A2.1 PBT classification criteria

Property	**PBT-criteria**	**vPvB-criteria**
Persistence criterion (any of the situations)	- T½ > 60 days in marine water, or - T½ > 40 days in fresh or estuarine water, or - T½ > 180 days in marine sediment, or - T½ > 120 days in fresh or estuarine sediment, or - T½ > 120 days in soil	- T½ > 60 days in marine, fresh or estuarine water, or - T½ > 180 days in marine, fresh or estuarine sediment, or - T½ > 180 days in soil.
Bioaccumulation criterion	Bioconcentration factor > 2000 l/kg	Bioconcentration factor > 5000 l/kg
Toxicity criterion (any of the situations)	NOEC (long-term) < 0.01 mg/l for marine or freshwater organisms, or (H350), mutagenic (H430), or toxic for reproduction (H360, H361)*, or toxicity**	

EMA, 2012a - Guidance on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicine

Case study environmental risk results

Antibiotics

The full results of the antibiotic case study are summarized. Results include groundwater exposure, a PBT criteria evaluation (i.e. persistence, bioaccumulation and toxicity) and RQs for taxonomic groups

Phase I

The compounds considered in this case study are antibiotics. Intensively-reared livestock scenarios were modelled for standard treatment dosages. The initial PECsoil worst-case exposure scenario for tylosin and tiamulin is summarized in Table A2.2. Exposure data for tiamulin and tylosin PECgw presented below, are based on these scenarios.

Table A2.2 Phase I PECsoil worst case scenarios for tylosin and tiamulin.

Compound	**Exposure scenario**	**Treatment group**	**Application**	**Dose mg/ kg BW**	**Days**	**PEC soil initial[b]**
Tylosin	IR[a]	Broiler	oral	86 (tartrate :100)	5	3814 (4435)
Tiamulin	IR[a]	Broiler	oral	25	5	1109

[a]Intensively-reared; [b]µg/kg

Exposure

The exposure data for different environmental compartments are summarized in Table A2.3. FOCUS modelling applied the PECsoil from scenario in Table A2.2. Differences between the Chapter FOCUS model and the FOCUS model applied for groundwater calculations are included in Table A2.3. Comparison of PECsw results for the Chapter 2 model and the model in Table A2.3 are within an order of magnitude (Figure A2.1).

Table A2.3 PECgw and PECsw estimates for tylosin and tiamulin scenarios.

Compound	**Dose mg/kg BW**	**Days** [a]	**PECgroundwater (µg/L)**		**PECsurfacewater (µg/L)**		**Properties**	
			TGD [b]	**FOCUS-PEARL**	**TGD** [b]	**FOCUS-SW**	**Koc**	**DT50 soil**
Tylosin [c]	86 (tartrate: 100)	5	16.6	0.000000	5.5	5.38	3252 [d]	50 d
Tiamulin [c]	25	5	28.9	0.000000	9.6	4.6	536[e]	100 d

[a] Number of days of application
[b] Technical guidance document (EMA, 2008)
[c] Exposure scenario for intensively reared broiler chickens given oral applications
[d]Chapter 2 Koc = 553
[e]Chapter 2 DT50 soil = 54d

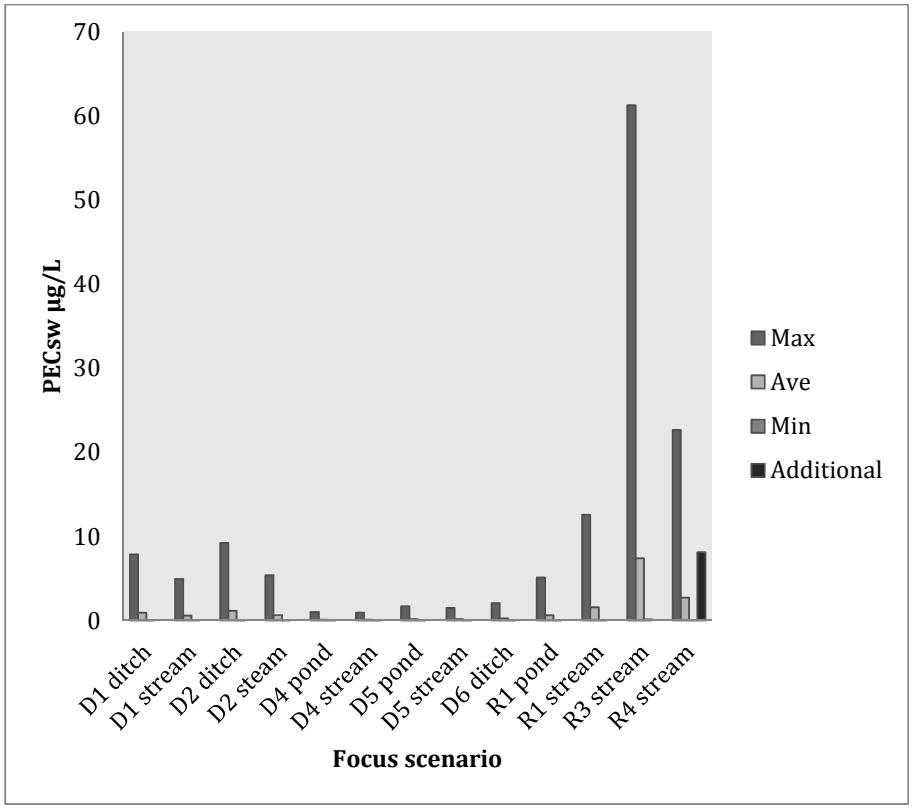

Figure A2.1 PECsw data (in text Figure 3.4) with additional scenario based on FOCUS model presented in Table A2.3.

PBT

Tables A2.4 and A2.5 classify the case-study compounds terms of the PBT criterion.

Table A2.4 PBT assessment of tylosin.

Criterion	Parameter	Trigger	Tylosin Value	Fulfils criteria?	Reference
P	Half-life in soil	>120 d	8.1 d	N	Boxall *et al.*, 2011
B	log Kow	≥ 4	2.5	N	De Liguoro, 2003
T	Acute EC50 (freshwater or marine)	< 0.1mg/L	34µg/L (EC50 blue-green algae)`	N/A[a]	Halling-Sørensen, 2000

[a] NA – not available, data for blue-green algae is important for antibiotics and not available

Table A2.5 PBT assessment of tiamulin.

Criterion	Parameter	Trigger	Tiamulin value	Fulfils criteria?	Reference
P	Half-life in soil	>120 d	301 d	Y	Boxall *et al.*, 2011
B	log Kow	≥ 4	5.9	Potentially	Halling-Sørensen, 2000
T	Acute EC50 (freshwater or marine)	< 0.1mg/L	40 mg/L	N/A[a]	Wollenberger *et al.*, 2000

[a] NA – not available, data for blue-green algae is important for antibiotics and not available

Risk assessment

Table A2.6 summarizes the results for calculations of risk quotients for different biological taxa for tiamulin. Exposure values from Table A2.3 are applied. Currently, risk to sediment has not been considered. The risk assessment for tylosin is presented in Chapter 3.

Table A2.6: Summary of risk assessment for tiamulin for different compartments

Compartment	Species	Test	EC50	AF	PNEC	PEC	RQ
Surface Water	Green alga (*Selenastrum capricornutu*)	72 hours Growth rates EC50	0.165 mg/L [a]	100	1.65 µg/L	4.6 µg/L	2.8
	Freshwater cyanobacteria (*Microcystis aeruginosa*)	7 days Growth rates EC50	0.003 mg/L [a]	100	0.03 µg/L	4.6 µg/L	153
	Water Flea (*Daphnia magna*)	48 hours Immobilization EC50	40 mg/L [b]	1000	40 µg/L	4.6 µg/L	0.115

Table A2.6 Continued

Compartment	Species	Test	EC50	AF	PNEC	PEC	RQ
Soil	Springtails (*Folsomia fimetaria*)	21 days Reproduction EC50	475 mg/kg dwt [c]	10	47500 µg/kg dwt	1109 µg/kg dwt	0.023

[a](Halling-Sørensen, 2000); [b](Wollenberger *et al.*, 2000); [c](Jensen *et al.*, 2003); bolded value is maximum value

Anthelmintics

Anthelmintic exposure

The compounds considered in this case study are anthelmintics applied to pasture animals and therefore must proceed to Phase II (VICH, 2000). The initial PECsoil for standard applications of ivermectin, moxidectin and fenbendazole are summarized in Table A2.7. The exposure data for ivermectin were extracted from (Liebig *et al.*, 2010).

Table A2.7 Phase I PECsoil scenarios for ivermectin, moxidectin and fenbendazole

Compound	Exposure scenario [a]	Treatment group	Application	Dose mg/kg BW	Days	PEC soil initial[b]
Ivermectin	IR[c]	Weaner pig	oral	0.1	7	6.08
	P[d]	Beef Cattle	topical	0.5	1	2.09
Moxidectin	IR[c]	Cattle (>2 years)	injection	1.0	1	5.83
	P[d]	Beef Cattle	injection	1.0	1	4.18
Fenbendazole	IR[c]	Weaner pig	oral	5	1	43.4
	P[d]	Beef Cattle	oral	7.5	1	31.4
	IR[c]	Horses	oral	60	1	311
	P[d]	Horses	oral	60	1	144

[a]Percentage of herd treated assumed to be 100% EMA(2008); [b]µg/kg; [c] Intensively-reared; [d]Pasture

Anthelmintic exposure

The exposure data for different environmental compartments are summarized in Table A2.8. The initial estimates for surface water, ground water and dung follow the calculations in the technical guidance document (EMA, 2008). The minimum Koc values were used for moxidectin and fenbendazole (18666 and 3938, respectively) as this approach was taken in Liebig *et al.*, (2010) for ivermectin. The refinement of groundwater and surface water results was conducted with FOCUS modelling.

Table A2.8 Phase II Exposure results for ivermectin, moxidectin and fenbendazole (dose and number of days in Table A2.7)

Compound [a]	**Exposure scenario**	**Treatment group**	**Application**	**PECgroundwater [µg/L]**		**PECsurfacewater [µg/L]**			**PECdung [µg/kgwwt]**
				TGD [b]	FOCUS-PEARL	TGD [b]	FOCUS-SW	direct entry / refined d.e.	TGD [b]
Ivermectin Koc = 4000[c]	Intensively reared	Weaner pig	oral	0.021	0.000000	0.0072	0.0073	N/A	N/A
	Pasture	Beef Cattle	topical	0.0074	**0.000000**	0.0025	0.0022	0.522 / **0.029**	**12 692**
Moxidectin Koc = 18666[d]	Intensively reared	Cattle (>2 years)	injection	0.0044	0.000000	0.0015	0.0024	N/A	N/A
	Pasture	Beef Cattle	injection	0.0032	**0.000000**	0.0011	0.0016	1.045 / **0.013**	**25 385**
Fenbendazole Koc = 3938[e]	Intensively reared	Weaner pig	oral	0.156	0	0.052	0.053	N/A	N/A
	Pasture	Beef Cattle	oral	0.133	0.000000	0.038	0.038	7.8 / 0.445	190 000
	Pasture	Horses	oral	0.517	0.000000	0.172	0.187	N/A	**1 440 000**
	Intensively reared	Horses	oral	1.117	0.000000	0.372	**0.423**	N/A	N/A

[a] DT50soil= 1000 days; [b]Technical guidance document (EMA, 2008); [c] Liebieg *et al.*, 2010; [d] Fort Dodge, 1997; [e] Hoechst-Roussel Agri-Vet Co., 1995; d.e. = direct entry ; N/A = Not applicable

Anthelmintic PBT assessment

Tables A2.9 to A2.11 classify the case-study compounds terms of the PBT criterion.

Table A2.9 PBT assessment of ivermectin.

Criterion	Parameter	Trigger	Ivermectin value	Fulfils criteria?	Reference
P	Degradation half-life in freshwater sediment	>120 d	130 d	Y	Liebig *et al.*, 2010
B	BCF	> 5000 L/kg	56L/kg (Bluegill sunfish)	N	Van de Heuvel, 1996
T	Chronic NOEC (freshwater or marine)	< 0.01mg/L	NOEC (21 d reproduction daphnia) 0.0003 ng/L	Y	Garric *et al.*, 2007

Table A2.10 PBT assessment of moxidectin

Criterion	Parameter	Trigger	Moxidectin value	Fulfils criteria?	Reference
P	Half-life in soil	>120 d	~ 60 d	N	Fort dodge, 1997
B	log Kow	≥ 4	6.0	Potentially	Prichard *et al.*, 2012
T	EC50 (freshwater or marine)	< 0.1mg/L	EC50 (48 hour Daphnia) 30 ng/L	Potentially	Fort dodge, 1997

Table A2.11 PBT assessment of fenbendazole.

Criterion	Parameter	Trigger	Fenbendazole value	Fulfils criteria?	Reference
P	Half-life in soil	>120 d	54 d	N	Kreuzig *et al.*, 2007
B	BCF	≥ 5000 L/kg	580x (Bluegill sunfish)	N	Hoechst-Roussel Agri-Vet Co., 1995
T	EC50 (freshwater or marine)	< 0.1mg/L	Acute EC50 daphnia 12 µg/L	Potentially	Hoechst-Roussel Agri-Vet Co. ,1995

Anthelmintic risk assessment

Tables A2.12 to A2.14 summarize the results for calculations of risk quotients for different biological taxa. Different tiers of the risk assessment were realized depending on data availability. The ivermectin assessment was extensive and fulfilled the Tier B recommendations. Data for ecotoxicity tests required for Tier B were not available for moxidectin and fenbendazole; therefore, these assessments proceeded to Tier A.

Table A2.12 Results where a risk is indicated for the environmental risk assessment Phase II Tier B for ivermectin conducted by Liebig *et al.,* (2010) with additional scenarios from Table A2.8.

Compartment	Species or biological parameter	Endpoint	AF	PNEC[a]	Scenario[b]	PEC[c]	RQ[d]
Surface water	D. magna	EC50	1000	0.0057 ng/L	P d.e.	1.0 ng/L	175
	D. magna	NOEC 21 day reproduction	10	0.00003 ng/L	P d.e.	10.3 ng/L	$3.4x10^5$
					P	12.9 ngL	$4.3x10^5$
					IR	0.70 ng/L	$2.3x10^4$
					P d.e.[e]	29 ng/L	**$9.7x10^5$**
	D. magna (2-species)	NOEC 96 hour reproduction	10	<0.1 ng/L	P d.e.	10.3 ng/L	>103
Sediment	C. riparius	NOEC 10 day larval growth	10	0.31 µg/kg sed. dwt	P d.e.	2.17µg/kg dwt	7
					IR	0.65 µg/kg dwt	2.1
	Benthic communities	NOEC 224 days	10	0.06 µg/kg sed. dwt	P d.e.	2.17 µg/kg dwt	36
					IR	0.65 µg/kg dwt	10.8
Soil[e]	F. fimetaria (2-species test)	EC10 21 day reproduction	10	2 µg/kg soil dwt	P	4.8 µg/kg dwt	2.4
					IR	11.4 µg/kg dwt	5.7
					IR[f]	6.08 µg/kg	3.04
Dung	Dung fly community (field)	NOEC 28 days	[e]	<310 µg/kg dung dwt	P	2365 µg/kg dung dwt	>7.629
					P[f]	12692 µg/kg	40.942
	Dung decomposition (field)	NOEC 86 days	[e]	<780 µg/kg dung dwt	P	2365 µg/kg dung dwt	>3.032

[a]Predicted no effects concentration; [b]P d.e. = pasture direct entry, P = pasture, IR = intensively reared; [c] Predicted exposure concentration; [d] Risk quotient (PEC/PNEC); [e]Earthworm risk assessment concluded at Tier A RQ<1 (Liebig *et al.,* 2010); [f] Exposure from results in Table A2.8; bolded value is maximum value.

Table A2.13 Summary of risk assessment for moxidectin for different environmental compartments

Compartment	Species or biological parameter	Endpoint	Effects concentration	AF	PNEC[ab]	Scenario[c]	PEC[d]	RQ[e]
Surface water	*D. magna*	48 hour LC50	30 ng/L	1000	0.03 ng/L	P	1.1 ng/L	36.7
						P d.e.	1.05 µg/L	**35000**
						IR	2.4 ng/L	80
	Oncorhynchus mykiss	96 hour LC50	0.16 µg/L	1000	0.00016 µg/L	P	1.1 ng/L	6.9
						P d.e.	1.05 µg /L	6562.5
						IR	2.4 ng/L	15
Dung	*Onthophagus gazella* (dung beetle) adult	EC50	2567.7 µg/kg	100	25.7	P d.e.	25385 µg/kg wwt	988
	Euoniticellus internedius (dung beetle) progeny	EC50	469.3 µg/kg	100	4.7	P d.e.	25385 µg/kg wwt	5401
	Musca autumnalis[f] (Face Flies)	EC50	465 µg/kg dw	100	4.7	P d.e.	25385 µg/kg wwt	5401

[a]Predicted no effects concentration; [b]Fort Dodge, 1997; [c]P d.e. = pasture direct entry, P = pasture, IR = intensively reared; [d] Exposure from results in Table A2.8; [e]Risk quotient (PEC/PNEC); [f]Blackenhorn *et al.,* 2013; bolded value is maximum value

Table A2.14 Summary of risk assessment for fenbendazole for different environmental compartments.

Compartment	Species or biological parameter	Endpoint	Effects concentration	AF	PNEC[ab]	Scenario[c]	PEC[d]	RQ[e]
Surface water	*D. magna*	48 hour EC50	12 µg/L	1000	0.012 µg/L	P	0.19 µg/L	15.8
						IR	0.42 µg/L	35
	Scenedesmus vacuolatus (Algae)	72 hour EC50	> 1000 µg/L	100	10 µg/L[f]	P	0.19 µg/L	0.019
						IR	0.42 µg/L	0.042
	Lepomis macrochirus (Bluegill)	21d LC50	> 40 µg/L	1000	0.04 µg/L	P	0.19 µg/L	4.75
						IR	0.42 µg/L	10.5
Soil	*Lumbricus terresfris* (Earthworm)	28 day LC50	180000 µg/L	1000	180 µg/L	P	0.19 µg/L	0.001
						IR	0.42 µg/L	0.002
Dung	*Onthophagus gazella* (dung beetle) adult	7 day LC50	>77000 µg/kg	100	770 µg/L	P d.e.	1440000 µg/kg wwt	**1870**

[a]Predicted no effects concentration; [b] Hoechst-Roussel Agri-Vet Co., 1995; [c]P d.e. = pasture direct entry, P = pasture, IR = intensively reared; [d] Exposure from results in Table A2.8; [e]Risk quotient (PEC/PNEC); [f]Wagil *et al.*, 2015; bolded value is maximum value

Non-steroidal anti-inflammatory drugs (NSAIDs)

The full results of the NSAID case-study are summarized. Results include, a Phase I ERA, a PBT criteria evaluation and discussion of unique risk to vultures.

PBT

Tables A2.15 and A2.16 classify the case-study compounds terms of the PBT criterion.

Table A2.15 PBT assessment of diclofenac

Criterion	Parameter	Trigger	Diclofenac value	Fulfils criteria?	Reference
P	Degradation half-life in soil	>120 d	20	N	Xu et al., 2009
B	BCF	>2000 l/kg	147 (whole fish estimate)	N	EQS 2011
T	Chronic NOEC (freshwater or marine)	< 0.01mg/L	1 µg/L	Y	EQS 2011

Table A2.16 PBT assessment of meloxicam

Criterion	Parameter	Trigger	Meloxicam value	Fulfils criteria?	Reference
P	Half-life in soil	>120 d	7.5d soil	N	EPISUITE, fugacity model
B	log Kow	≥ 4	3.54 (EPISUITE estimation)	N	Fick *et al.*, 2010
T	EC50 (freshwater or marine)	< 0.1mg/L	13 mg/L (72 hour Algal IC50)	N[a]	Brit. Pharmacopeia, 2013

[a]Based on screening criteria

ERA Phase I NSAIDs

Table A2.17 to A2.20 summarize the results for the Phase I risk assessments for Diclofenac and meloxicam.

A Phase I exposure assessment was conducted according to the VICH (2000) guidelines. As diclofenac is not available in the U.K. product details were therefore taken from the online sources of one of the market authorization holders for diclofecac (Vibrac, 2008). Calculations and default values for soil predicted environmental concentration (PEC_{soil}) were taken from EMA (2008). The soil $PEC_{initial}$ are compared to a trigger level

of100µg/kg. None of the exposure scenarios exceeded this trigger (Tables A2.17 to A2.20) therefore groundwater exposure and risk to biological taxa were not required.

Table A2.17 Initial PEC estimations for diclofenac (administration route: injection) in soil based on the intensively reared exposure scenario, treatment group, pharmaceutical form, dose and number of applications.

Treatment group	Percentage of herd treated*	Dose (mg/kg bw)	Number of applications	PEC soil initial (µg/kg)
Cattle (>2 years)	100%	2.3	3	40.22
Cattle (0-1 years)	100%	2.3	3	34.76
Calf	100%	2.3	3	39.41
Dairy Cow	100%	2.3	3	22.16
Weaner pig (to 25 kg)	100%	2.3	3	59.95
Fattening pig (25-125 kg)	100%	2.3	3	40.66
Sow (with litter)	100%	2.3	3	14.44
Horses	100%	2.3	5	59.58

*No percentage of herd recommended in EMA (2008) therefore used 100% as a conservative value, which would result in protective PECs.

Table A2.18 Initial PEC estimations for diclofenac (administration route: injection) in soil based on the pasture exposure scenario, treatment group, pharmaceutical form, dose and number of applications.

Treatment group	Percentage of herd treated*	Dose (mg/kg bw)	Number of applications	PEC soil initial (µg/kg)
Beef Cattle	100%	2.3	3	28.84
Dairy Cow	100%	2.3	3	19.32
Calf	100%	2.3	3	2.32
Horses	100%	2.3	5	27.60

*No percentage of herd recommended in EMA (2008) therefore used 100% as a conservative value, which would result in protective PECs.

Table A2.19 Initial PEC estimations for meloxicam (administration route: injection) in soil based on the intensively reared exposure scenario, treatment group, pharmaceutical form, dose and number of applications.

Treatment group	Percentage of herd treated*	Dose (mg/kg bw)	Number of applications	PEC soil initial (µg/kg)
Cattle (>2 years)	100%	0.5	1	2.91
Cattle (0-1 years)	100%	0.5	1	2.52
Calf	100%	0.5	1	2.86
Dairy Cow	100%	0.5	1	1.61
Weaner pig (to 25 kg)	100%	0.4	2	6.95
Fattening pig (25-125 kg)	100%	0.4	2	4.71
Sow (with litter)	100%	0.4	2	1.67
Horses	100%	0.6	1	3.11

*No percentage of herd recommended in EMA (2008) therefore used 100% as a conservative value, which would result in protective PECs.

Table A2.20 Initial PEC estimations for meloxicam (administration route: injection) in soil based on the pasture exposure scenario, treatment group, pharmaceutical form, dose and number of applications.

Treatment group	Percentage of herd treated*	Dose (mg/kg bw)	Number of applications	PEC soil initial (µg/kg)
Beef Cattle	100%	0.5	1	2.09
Dairy Cow	100%	0.5	1	1.40
Calf	100%	0.5	1	0.17
Horse	100%	0.6	1	1.44

*No percentage of herd recommended in EMA (2008) therefore used 100% as a conservative value, which would result in protective PECs.

Risk to vultures

Risk characterization requires characterization of exposure and toxicity. Table A2.21 summarizes the exposure and toxicity for diclofenac and meloxicam. The exposure scenarios are possible, but to contribute to a quantitative risk characterization, would require consideration of probability of the exposure.

Table A2.21 Summary of qualitative toxicity and exposure of diclofenac and meloxicam to vultures.

Criterion	Diclofenac[a]	Meloxicam
Toxicity	LD_1 = 0.138 mg/kg	Non-toxic[b]
Exposure	1. Vulture feeding stations 2. Fallen livestock in extensive farming	N/A

[a](EMA, 2014)
[b](Swan *et al.,* 2006; Swarup *et al.,* 2007

Visual scoring matrices

The visual scoring matrices not included in the chapter text are presented in tables A2.22-A2.24.

Table A2.22 Application of visual and scoring risk matrix (in text Figure 2.2) to tiamulin ERA data. Colours indicate risk intensity from high (i.e., red) to moderate (i.e., yellow) to low (i.e., green).

Risk Level				Very High	High	Moderate	Low	Negligible	Score	Weight	Adjusted Score
Score				4	2	1	0.5	0			
Criteria	PBT[a]					P&B, T = N/A			1 / 4	33.3%	8.3
	RQ	Compartment	Organism								
		Surface water	Freshwater cyanobacteria		153				2 / 12	33.3%	5.6
			Daphnia					<1			
			Springtails					<1			
	PECgw[c]							<1	0 / 4	33.3%	0
Total									13.9		

[a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vpvb) criteria defined in Table A2.1.
[b]Risk Quotient (PNEC/PC)
[c] Predicted exposure concentration for groundwater (µg/L)

Table A2.23 Application of visual and scoring risk matrix (Figure 2.2) to fenbendazole ERA data. Colours indicate risk intensity from high (i.e., red) to moderate (i.e., yellow) to low (i.e., green).

Risk Level				Very High	High	Moderate	Low	Negligible	Score	Weight	Adjusted Score
Score				4	2	1	0.5	0			
Criteria	PBT[a]						T		0.5 / 4	33.3%	4.2
	RQ[b]	Compartment	Organism								
		Surface water	Algae					<1	6 / 20	33.3%	10.0
			Daphnia			35					
			Fish			10.5					
		Soil	Earthworms					<1			
		Dung	Dung beetle progeny	$1.9x10^4$							
	PECgw[c]							<0.1	0 / 4	33.3%	0
Total									14.2		

[a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vpvb) criteria defined Table A2.1.
[b]Risk Quotient (PEC/PNEC)
[c] Predicted exposure concentration for groundwater (µg/L)

Table A2.24 Application of visual and scoring risk matrix (in text Figure 2.2) to meloxicam ERA data. Colours indicate risk intensity from high (i.e., red) to moderate (i.e., yellow) to low (i.e., green).

Risk Level				Very High	High	Moderate	Low	Negligible	Score	Weight	Adjusted Score
Score				4	2	1	0.5	0			
Criteria	PBT[a]							Not PBT	0 / 4	33.3%	0
	RQ[b]	Compartment	Organism								
		All	All					Neglible exposure assessment concluded at Phase I	0 / 8	33.3%	0
		Special Concern	Vultures					Not toxic			
	PECgw[c]							Neglible exposure assessment concluded at Phase I	0 / 4	33.3%	0
Total									0		

[a]Persistent, bioaccumulative, toxic (PBT)/very persistent, very bioaccumulative (vpvb) criteria defined in Table A2.1.
[b]Risk Quotient (PNEC/PC)
[c]Predicted exposure concentration for groundwater (µg/L)

Appendix 3 Questionnaires for VMP users

Veterinary Medicinal Products Risk Mitigation Measures Survey

Overview

Authorisation and availability of veterinary products requires that any identified environmental risk should be assigned mitigation measures to decrease risks. This questionnaire is aimed to support work to improve the effectiveness of environmental risk mitigation measures (RMMs) for veterinary medicinal products.

Objectives:

1. To gain a better understanding of the current use and attitudes towards environmental RMMs for veterinary medicinal products.
2. To gain insights into the practicality and cost-effectiveness of RMMs for veterinary medicinal products.
3. To gain ideas for improved RMMs for veterinary medicinal products.

Questionnaire

General Questions

1. Which type of livestock do you primarily work with?
2. In which region of the U.K. do you work?

Use and Attitudes

3. Do you think environmental RMMs for veterinary medicinal products are widely implemented?
    a. Why?
4. When administering veterinary medicinal products are environmental risks considered?
5. When prescribing veterinary medicine and/or creating animal health plans are the environmental risks considered?
    a. Is this communicated to the people that will be administering the veterinary medicine?
        i. If so how?

6. In your opinion what is the attitude of farmers towards the environmental issues of veterinary medicinal product use?
    a. Do you think farmers generally apply environmental RMMs for veterinary medicinal products?
    b. How practical do you think they find limitations to the following:
        i. Constraints to spreading slurry/manure.
        ii. Requirements to keep free-range animals indoors after treatment.
        iii. Requirements to keep animals away from watercourses.
        iv. Requirement to avoid using the same pasture each season.
    c. How do you think farmers perceive these RMMs?
        i. Are there additional benefits to the farmers or vets from following the RMMs?

Practicality

Below is a list of possible RMMs targeted at veterinarians (Liebig 2014). The RMMs are labelled alphabetically under headings specifying the where RMMs will be applied. For each I'd like to discuss whether the RMM is practical and/or cost-effective as well as the rational, other possible benefits and ideas for improvement. The questions under 1.a. will therefore be repeated for each specific RMM.

7. RMM for disposal aimed to avoid contamination of water or other areas of the environment.
    a. Avoid disposal of unused product in sewage.
        i. Is this limit practical?
        ii. Is it cost-effective?
        iii. Why?
        iv. Are there additional benefits besides environmental protection?
        v. Do you have any ideas for improvement?
    b. Returning unused medicine and empty containers to appropriate facilities.
8. RMMs for pasture animals.
    c. Strategic treatment of stock only after fly or dung beetle season in autumn or early spring.
9. RMMs for intensively-reared and pasture animals

d. Treatment of only infected animals when required, established through veterinary consultation or faecal worm (worm egg) count.

e. For teat dipping or spray the collection and separate disposal of dripping residues.

Improvements

10. How would you improve the use of RMMs for veterinary medicinal products?

11. Do you think communication of environmental issues to farmers and/or vets could be improved?

    a. For example, would including pictures instead of text on labels and product literature be a helpful idea in your opinion?

    b. Are there other opportunities besides the labels and product literature that could be used to communicate RMMs?

12. Do you have any suggestions for new RMMs for either veterinarians or famers applying medicines?

13. Do you have any further thoughts or ideas you'd like to share?

Thank you very much for your input!

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Liebig M, Floeter C, Hahn T, Koch W, Wenzel A, Römbke J. 2014. Risk mitigation measures: An important aspect of the environmental risk assessment of pharmaceuticals. Toxics 2:35-49.

Veterinary Medicinal Products Environmental Management Survey

Overview

To sell new veterinary medicines testing is required, including tests of the effects of residues in the environment. If the tests indicate that effects are likely, then management strategies for the usage of products are suggested. This questionnaire aims to discuss environmental management of veterinary medicine based on strategies suggested in Liebig et al. (2014). The objectives are described below.

Objectives:

4. To gain a better understanding of the current use and attitudes towards environmental management for veterinary medicinal products.
5. To gain insights into the practicality and cost-effectiveness of environmental management for veterinary medicinal products.
6. To gain ideas for improved environmental management for veterinary medicinal products.

Questionnaire

General Questions

14. Which type of livestock do you farm? How many animals do you have?
15. In which region of the U.K. are you located?
16. How long have you been farming?

Use and Attitudes

17. Do environmental regulations impact your farm business?
    a. How so? (positively / negatively)?
    b. Do you think environmental regulations are a good thing? Why / why not?
    c. How do environmental regulations affect the way you farm?
18. Are you aware of any management you are advised to use during or after veterinary medicine application?
19. How have you been informed about the environmental management (e.g. from vets, product literature, health plans, etc.)?
20. Do you think environmental management for veterinary medicinal products are widely implemented?

b. Why?

Precautions for disposal

21. How do you dispose of veterinary medicine and empty containers?
22. Would it be practical and cost effective to return medicines and containers to veterinarian practices?
    a. Would there be other benefits for you to return medicines and containers?
    b. Do you have any ideas on how this could be improved?

Management for spreading slurry/manure for pasture and arable land

23. How do you use your slurry / manure? Could you change this? Why / Why not?
    a. How long you store slurry? Could you change this? Why / Why not?
    b. Do you spread on slopes? Could you change this? Why / Why not?
    c. Do you only spread on specific soils? Could you change this? Why / Why not?
    d. How are applications applied? Could you change this? Why / Why not?

The following are specific to arable land:

    e. Could slurry (manure) from treated animals be mixed with untreated animals before application? Why / Why not?
    f. How far from water bodies is manure spread? Could you change this? Why / Why not?
    g. Is a maximum nitrogen limit followed? Could you change this? Why / Why not?

Management for pasture animals.

24. Can animals access water bodies during and after treatment? Could you change this? Why / Why not?
25. Are the same pastures used each season? Could you change this? Why / Why not?

Management for intensively-reared and pasture animals

26. How are treatments normally given?
    a. Are veterinarians regularly consulted? Why / Why not?
    b. Do you use tests like the fecal worm (worm egg) count test? Why / Why not?

27. How are teat dips or spray that drip during application disposed of? Could this be changed? Why / Why not?

28. Is there any opportunity for medicines to enter water during treatment? If so how is water disposed of?

Improvements

29. How would you improve the use of environmental management for veterinary medicinal products?

    a. Do you think communication of environmental issues could be improved?

    b. Are there other opportunities besides the labels and product literature that could be used to communicate environmental issues?

30. Do you have any suggestions for other environmental management for applying medicines?

31. Do you have any further thoughts or ideas you'd like to share?

Thank you very much for your input!

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List of Abbreviations

AF	Assessment factor
CVMP	Committee for Medicinal Products for Veterinary Use
DEFRA	Department for Environment, Food and Rural Affairs
DT50	Degradation time for 50% of original compound concentration
dwt	dry weight
EC50	Effects concentration at which 50% of tested individuals are affected
EICaquatic	Environmental introduction concentration for aquatic environment
ELS	Entry level stewardship
EMA	European Medicines Agency
ERA	Environmental risk assessment
EU	European Union
FEC	Faecal egg count
FOCUS	Forum for Pesticide Fate Models and their Use
HC5	Hazard concentration effecting 5% of species
Koc	Organic carbon normalized adsorption coefficient
Kow	n-Octanol/water partitioning coefficient
LOEC	Lowest-observed-effects concentration
NOEC	No-observed-effects concentration
NSAID	Non-steroidal anti-inflammatory drug
NVZ	Nitrate vulnerable zone
PBT	Persistent, bioaccumulative and toxic
PECgw	Predicted exposure concentration for groundwater
PECsoil	Predicted exposure concentration for soil
PECsw	Predicted exposure concentration for surface water
PNEC	Predicted no effects concentration
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals

RMM	Risk mitigation measures
RQ	Risk quotient
SEA	Social-Economic Assessment
SPC	Summary of product characteristics
SSD	Species sensitivity distribution
VICH	International cooperation on harmonisation of technical requirements for registration of veterinary medicinal products
VMP	Veterinary medicinal product
VMD	Veterinary Medicines Directorate
vPvB	Very persistent, very bioaccumulative
wwt	wet weight

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