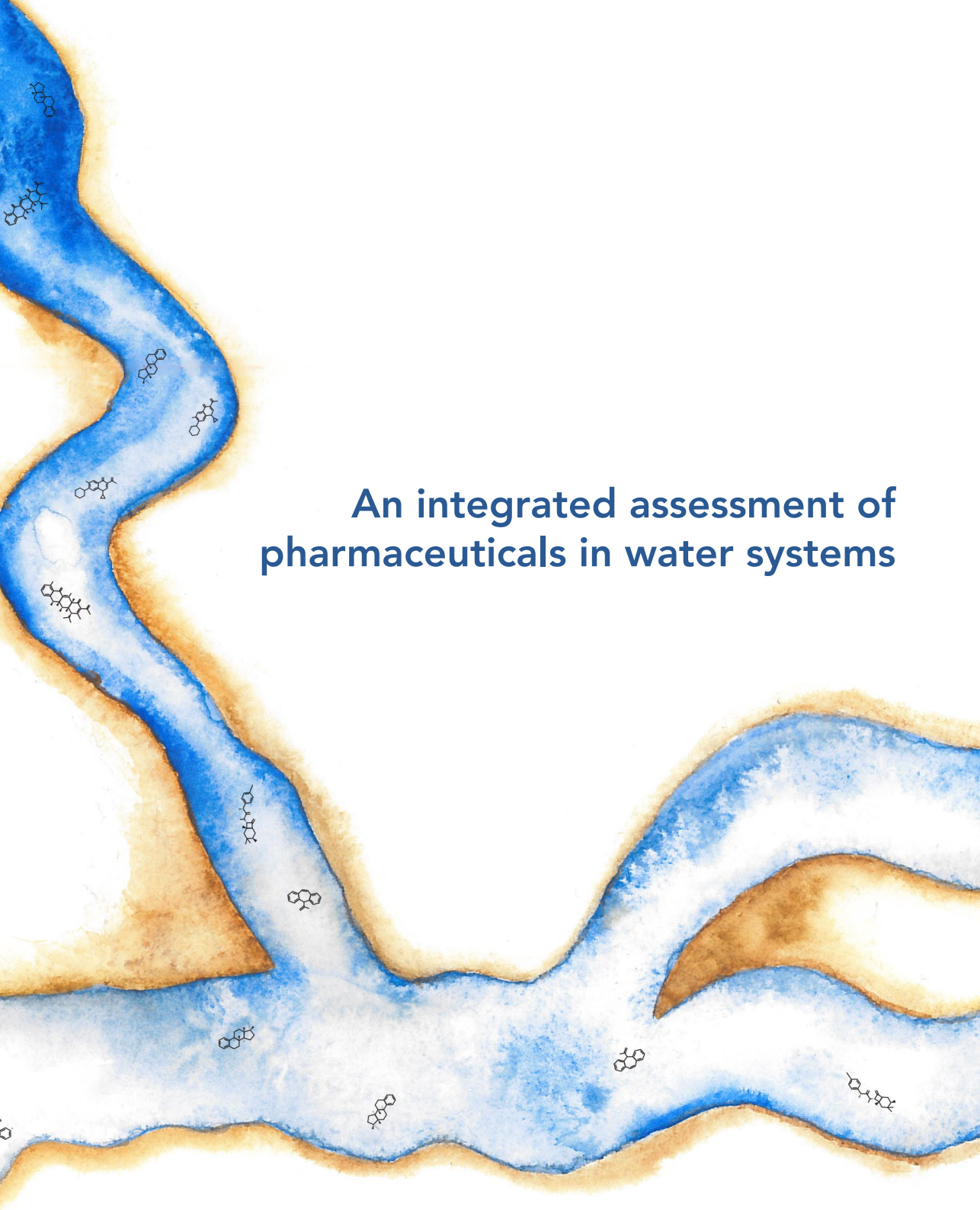

An integrated assessment of pharmaceuticals in water systems

Lara Wöhler

AN INTEGRATED ASSESSMENT OF PHARMACEUTICALS IN WATER SYSTEMS

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DISSERTATION

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on the authority of the rector magnificus,
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on account of the decision of the Doctorate Board
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by

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born on the 7th of March, 1991
in Osnabrück, Germany

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Acknowledgements

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Summary

Pharmaceutical pollution of freshwaters is occurring globally. A large variety of pharmaceutical substances enters the environment from different sources, i.e. manufacturing, human and animal excretion, or disposal into sewage or landfills. Once in the environment, pharmaceuticals pose diverse risks. They can be ecotoxic to flora and fauna, they can enter drinking water and food products and they are associated with resistances that can lead to failure of pharmaceutical treatment. While pharmaceutical pollution is mostly investigated from an environmental perspective – focussing on chemical processes, risk assessments or technical solutions – this thesis integrates the environmental dimension of impact assessment with the societal dimension of identifying drivers and exploring societal solutions. The research follows the rationale of the drivers-pressures-state-impact-responses (DPSIR) framework and presents investigations of pharmaceutical pollution from different sources (pressures, state, impact) as well as related societal elements (drivers, responses) in the chapters 2 to 5.

Chapters 2 and 3 analyse the pharmaceutical emission and their environmental pressure using the grey water footprint (GWF) as an indicator of water pollution. Chapter 2 presents the GWF for human and veterinary pharmaceuticals - from households, hospitals and livestock farming - at different geographical levels: global, national, catchment. Results show that pharmaceutical pollution contributes substantially to water footprints that were estimated in previous studies and did not consider pharmaceuticals. This highlights the significance of accounting for water pollution by pharmaceuticals when appraising humanity's appropriation of water resources. GWFs estimated for veterinary pharmaceuticals in the second chapter base on the precautionary assumption that all environmental emissions eventually end up in freshwater. In chapter 3 this assumption is refined by developing an approach to model veterinary pharmaceutical emissions from administration to surface waters with a specific focus on environmental fate and transport after field application. The developed approach is demonstrated for a number of antibiotics in the German-Dutch Vecht river catchment. Results indicate that only a minor fraction of the substance administered ends up in freshwater and thus GWFs are significantly smaller as those estimated in chapter 2. Still, the study warrants further awareness to pharmaceutical pollution from livestock due to the result's uncertainty, estimated soil accumulation and not assessed groundwater pollution.

Chapter 4 focusses on pharmaceutical pollution from different livestock production system. A framework is developed to assess differences in pharmaceutical pol-

lution from a variety of livestock types in conventional and organic production systems. A specific focus is set on factors influencing pharmaceutical pollution during administration, which were identified from expert interviews. The framework is applied in a pilot assessment for different livestock types and substances. The largely qualitative results reveal that pharmaceutical pollution is influenced by a series of factors, where some of them give tendency for more pollution in conventional systems and others in organic production. Combining these insights with quantitative information of pharmaceutical's pathway to and in the environment, identifies which substances, livestock types, production systems or the combination thereof is likely to have the highest or lowest pollution potential. If all systems adopted practices leading to less pollution, the sector's overall impact could be reduced.

Chapter 5 presents an investigation of the current societal system causing pharmaceutical pollution as well as exploring alternative future solutions. Transition research's multi-level perspective framework is used as a theoretical basis for the analysis. Empirical data is exploited from literature and interviews to present results that increase understanding of current dynamics and give decision makers indications for potential future pathways. The three identified alternative societal solutions are: 1) accepting pharmaceuticals in the environment - substantial changes to the system are not required; 2) reconfiguring the current system by implementing various innovations that reduce pharmaceutical emissions; 3) fundamentally changing the current system to (largely) avoid pharmaceutical emissions.

Pharmaceutical pollution is a global problem posing diverse risks to the environment and humanity. This research presents a novel integrated assessment that combines environmental with societal perspectives around pharmaceuticals in the environment – a valuable advancement to understanding cause-effect relationships of the topic. The results highlight the relevance of human and veterinary pharmaceutical pollution in the context of humanity's appropriation of freshwater resources. Major knowledge gaps around pharmaceutical pollution from livestock were addressed – including advances in emission modelling and comparing the relevance of substances, livestock types and production systems for pollution. Moreover, the study illustrates three concrete pathways for society to handle pharmaceutical pollution.

Samenvatting

Farmaceutische vervuiling van water komt wereldwijd voor. Een grote hoeveelheid geneesmiddelen komt in het milieu terecht uit verscheidene bronnen, bijvoorbeeld geneesmiddelproductie, menselijke en dierlijke uitscheiding, of directe lozing op riolen en afvalstort. Geneesmiddelen in het milieu kunnen verscheidene risico's vormen. Ze kunnen toxisch zijn voor flora en fauna, ze kunnen terecht komen in drinkwater en voedsel, en ze worden in verband gebracht met resistentie die kan leiden tot falen van medische behandelingen. In de huidige literatuur wordt farmaceutische vervuiling voornamelijk onderzocht vanuit een milieuperspectief met een focus op de chemische processen, risicoanalyse of technische oplossingen. Deze thesis integreert dit milieutechnische perspectief met een maatschappelijke dimensie die kijkt naar het identificeren van onderliggende oorzaken en het verkennen van oplossingen. Deze thesis past het concept toe van DPSIR (drivers, pressures, state, impact en responses) en bevat onderzoeken naar farmaceutische vervuiling uit verschillende bronnen (pressures, state, impact) en tevens naar gerelateerde maatschappelijke elementen (drivers, responses) in de hoofdstukken 2 tot en met 5.

Hoofdstuk 2 en 3 belichten de geneesmiddelemissie en de daaraan gerelateerde druk op het milieu door middel van de grijze watervoetafdruk (Grey Water Footprint, GWF) als indicator van watervervuiling. Hoofdstuk 2 bevat GWF-waardes voor menselijke en dierlijke geneesmiddelen – uit huishoudens, ziekenhuizen en veeteelt – op verschillende ruimtelijke schalen: globaal, nationaal, en stroomgebied. De resultaten laten zien dat farmaceutische vervuiling substantieel zijn ten opzichte van eerdere schattingen van watervoetafdrukken waarbij farmaceutica niet werden meegenomen. Dit toont de relevantie van geneesmiddelen bij de menselijke vervuiling van natuurlijke systemen. De GWF-waardes die in hoofdstuk 2 geschat worden voor diergeneesmiddelen zijn gebaseerd op de aanname dat alle geneesmiddelemissies uiteindelijk geheel in het water terecht komen. Deze aanname is verfijnd in hoofdstuk 3, waarin een model wordt ontwikkeld die de emissie van diergeneesmiddelen in water benadert door het emissiepad via landbouwgrond naar het oppervlaktewater te volgen. Dit model is toegepast op verschillende antibiotica voor het Duits-Nederlandse stroomgebied van de Vecht. De resultaten laten zien dat slechts een klein deel van de emissies van antibiotica uiteindelijk in het water terecht komt, waardoor GWF-waardes substantieel kleiner zijn dan gepresenteerd in hoofdstuk 2. Bewustzijn over farmaceutische vervuiling blijft belangrijk aangezien de resultaten onzeker zijn en het model vervuiling van grondwater niet meeneemnt. Ook laten resultaten zien dat de antibiotica – naast het

vervuilen van oppervlaktewater – kan ophopen in de bodem.

Hoofdstuk 4 focust op farmaceutische vervuiling uit verschillende soorten veeteelt. Een raamwerk is opgezet om geneesmiddelvervuiling van veehouderij in zowel conventionele als biologische productiesystemen te evalueren. Specifiek wordt hier gefocust op factoren die beïnvloeden hoe verschillen in het toedienen van diergeneesmiddelen leiden tot verschillen in farmaceutische vervuiling. Deze factoren werden door middel van expert-interviews geïdentificeerd. Het ontwikkelde raamwerk is toegepast om verschillen in dieren en substanties in kaart te brengen. De grotendeels kwalitatieve resultaten laten zien dat farmaceutische vervuiling beïnvloedt wordt door verschillende factoren, waarvan sommige tot meer vervuiling in conventionele systemen leiden, en anderen tot meer vervuiling in biologische productie. Het combineren van deze inzichten met kwantitatieve kennis over medicijnpaden laat zien welke geneesmiddelen, dieren, productiesystemen en combinaties hiervan meer of minder belastend zijn voor het milieu. Wanneer de verschillende productiesystemen (voor hun toepasbare) emissie-verminderende maatregelen toe zouden passen, zou de algehele impact van de sector verminderd kunnen worden.

Hoofdstuk 5 analyseert het huidige maatschappelijke systeem waarin farmaceutische vervuiling plaatsvindt, en onderzoekt oplossingen in toekomstige scenario's. Het *multi-level perspective framework* uit het onderzoeksveld van transitiemanagement is gebruikt als een theoretische basis voor deze analyse. Empirische data uit de literatuur en interviews zijn gebruikt om inzicht te verschaffen in het huidige systeem en om beleidsmakers kennis te laten maken met toekomstige scenario's. Drie maatschappelijke oplossingsrichtingen die hierin worden geïdentificeerd zijn: 1) het accepteren van farmaceutica in het milieu – hiervoor zijn substantiële veranderingen niet nodig; 2) het systeem herzien door verscheidene innovaties toe te passen die de emissie van farmaceutica verminderen; 3) fundamentele herziening van het systeem door (grotendeels) emissies van farmaceutica te vermijden.

Farmaceutische vervuiling is een wereldwijd probleem dat het milieu en de mensheid blootstelt aan verscheidene risico's. Dit onderzoek presenteert een nieuwe integrale beoordeling waarin maatschappelijke perspectieven rondom farmaceutica in het milieu onderzocht worden, en is een waardevolle toevoeging aan het begrip van oorzaak-gevolgrelaties in dit onderwerp. De resultaten laten de relevantie zien van menselijke en dierlijke farmaceutische vervuiling in de context van de menselijke invloed op de natuurlijke watercyclus. Kennishiaten rondom farmaceutische vervuiling zijn geïdentificeerd en deels gedicht, zoals vooruitgang van modellering van emissie, en het vergelijken van emissies van verschillende geneesmiddelen, dieren en productiesystemen. Als laatste laat deze thesis drie oplossingarichtingen zien voor de maatschappij om met farmaceutische vervuiling om te gaan.

CHAPTER ONE

INTRODUCTION

Introduction

1.1. Pharmaceuticals as lifesavers or threat to global freshwater systems?

Using natural products with pharmacologically active characteristics for disease treatment has been practiced in various ancient cultures, going back to the year 2900 B.C. (Dias et al., 2012). The development of manifold pharmaceuticals used in modern medicine roots in molecule structures of natural products such as plants or fungi (Dias et al., 2012). Pharmacological research and modern pharmaceutical development began in the late 18th century and slowly evolved further during the following century (Dias et al., 2012). Several notable advances such as the development of salicylic acid (a precursor of acetylsalicylic acid, commonly known as aspirin), penicillin and insulin were achieved in the end of the 19th and beginning of the 20th century (Taylor, 2016). Since then, the development and production of pharmaceuticals has evolved into a global industry with immense levels of innovation, growth and profitability (Malerba and Orsenigo, 2015). Indisputably, pharmaceuticals have increased societies' wellbeing and life expectancies during the past century (Taylor, 2016); they can certainly be perceived as life-easing and life-saving compounds.

Despite these societal benefits, pharmaceuticals are concurrently revealed as environmental threats. First concerns about the use of pharmaceuticals arose in the 1940s, i.e. due to unintentional poisoning of humans (Daughton, 2016) or antibiotic residues in food (Kirchhelle, 2018). In the 1970s it was first reported about the presence of steroid hormones in waste water and related interest about their biodegradability in different media (Tabak, 1970). Since then, an extensive research field around the (environmental) emissions and effects of pharmacologically active substances emerged and continues growing (Daughton, 2016). During the 1990's a vulture population collapse due to their intoxication with the non-steroidal anti-inflammatory substance diclofenac through carcass consumption of treated cattle livestock in India and Pakistan ultimately highlighted the topic's relevance (Green et al., 2004, Oaks et al., 2004).

Today, in the EU alone several thousand pharmaceutical substances are on the market (European Medicines Agency, 2020, Kümmerer, 2008a). Their environmental emissions either result from manufacturing waste (Larsson, 2014) or from use and consumption (Kaczala and E. Blum, 2016, Kümmerer, 2009). After human or animal administration most pharmaceuticals are (partially) metabolized by the target body (Kümmerer, 2008a). Non-metabolized fractions are excreted as parent compound,

mostly via urine and faeces, whereby renal excretion is generally dominant (Winker et al., 2008). Once excreted, human pharmaceuticals enter the sewage system from where they are discharged into the aquatic environment as a point source either through direct piping or via a waste water treatment plant (Hughes et al., 2013). Substances administered to food producing animals are either entering the environment directly (e.g. by pasture emissions (Boxall, 2008) or as feed in aquacultures (Schar et al., 2020)) or are collected in manure first that is then applied to fields as fertilizer (Boxall, 2008). Common pathways for these diffuse emissions into waterbodies are overland transport and groundwater leaching (Kemper, 2008).

Today close to 800 different substances have been detected in different environmental media around the globe (Dusi et al., 2019). Aus der Beek et al. (2016), whose study bases on the same database, show that more substances are found in regions that have been investigated more intensively, leading to the conjecture that more compounds could be detected in other regions if they were to be investigated.

The potential risks from environmental presence of pharmaceuticals are diverse and have only been partially understood and researched to a limited extent. First, immediate ecotoxicological effects on different species such as fish or amphibians have been observed (Kidd et al., 2007, Peltzer et al., 2017). Second, concern arose over the fact that different compounds have been detected in drinking water and food products (Li et al., 2017, Pullagurala et al., 2018). Generally, concentrations in these consumption products are at such low levels that no acute toxicity is expected for humans (Bruce et al., 2010, de Jesus Gaffney et al., 2015), but there are no studies that assess effects from long term exposure of pharmaceuticals at sub-therapeutic concentrations in humans. Third, concerns associated with environmental pharmaceutical emissions are resistances that evolve in microorganisms, inter alia through their exposure to antimicrobials as well as their ability to develop resistance genes (Davies and Davies, 2010). This is especially relevant for the substance group of antibiotics as antibiotic resistant bacteria have been detected in waterbodies around the globe (Singh et al., 2019). The WHO declares antimicrobial resistances to be among the top 10 major health threats to humanity (WHO, 2021).

Klein et al. (2018) estimate a global increase of up to 202% from 2015 to 2030 for human antibiotic consumption. Antibiotic use in livestock and aquaculture is expected to grow by 67% (from 2010 to 2030) and 33% (from 2017 to 2030), respectively (Schar et al., 2020, Van Boeckel et al., 2015). Potential risks associated with pharmaceutical emissions are thus likely to gain importance towards the future.

1.2. State of the art

1.2.1. Pharmaceutical emission modelling

Besides detecting pharmaceuticals in the environment with analytical chemical methods, a common way to predict the environmental state is emission modelling (Cunningham, 2008). Emission models conceptualize pharmaceuticals' lifecycles to ultimately estimate environmental loads or concentrations (Cunningham, 2008). For the prediction of emissions resulting from human and veterinary pharmaceutical use, models generally take consumption amounts as a starting point and assess their pathways to the environment considering relevant lifecycle stages, taking empirical data as a basis (Cunningham, 2008, Di Guardo et al., 2008).

Various models exist to estimate human pharmaceutical emissions resulting from consumption – with geographical levels ranging from regional to global (see e.g. Font et al. (2019), Lämmchen et al. (2021), Oldenkamp et al. (2019), Schwab et al. (2005)). Approaches to model diffuse pollution and specifically veterinary pharmaceutical emissions exist as well (e.g. Bailey (2015) Hollander et al. (2016), Mackay et al. (2005), Pereira et al. (2017)). All of these, however, come with certain shortcomings and/or challenges: 1) identifying the origin of veterinary pharmaceutical emissions (different livestock types and production systems) is convoluted; 2) modelling diffuse emissions is more complex compared to point source modelling; 3) models not developed for pharmaceuticals specifically require adaptation; 4) not all approaches are methodologically well described and reproducible; 5) several approaches do not capture the veterinary pharmaceutical lifecycle from source (administration) to sink (different environmental compartments).

Besides these methodological hurdles, empirical data for veterinary pharmaceutical emission modelling is sparse. In particular, consumption data – the foundation to emission modelling – is not comprehensively available. While scattered and partially aggregated data is available for the substance group of antibiotics (e.g. in Van Boeckel et al. (2015), Van Geijlswijk et al. (2018), or Wallmann et al. (2018)), no data is currently accessible for other substance groups. Moreover, information is lacking about which fractions of the total pharmaceutical amounts are used by different livestock production systems. This makes an environmental assessment of pharmaceutical pollution that compares different production systems challenging.

1.2.2. Pharmaceutical pollution in integrated assessments of freshwater systems

Integrated assessments combine interdisciplinary knowledge and methods to understand cause-effect relations and to outline options for action. Frequently used in environmental science, they are useful to understand the interconnection between societal activities and (finite) natural resources.

One of these finite natural resources is freshwater. Assessing the status of global freshwater systems and developing water management strategies is essential to provide sufficient and clean freshwater resources for human life and nature (Pahl-Wostl et al., 2013, Srinivasan et al., 2012). While the planet's water resources are finite in quantity and quality terms (van Vliet et al., 2017), humanity's freshwater demands are rising due to, i.e. population growth, increasing living standards, changing consumption patterns and more irrigated agriculture (Mekonnen and Hoekstra, 2016). The largest water withdrawals are (partially competingly) used for agriculture, followed by industry and domestic supply (UNESCO, 2021). The same sectors are majorly responsible for multi-pollutant hotspots in various river basins around the globe, contributing to more precarious water scarcity through insufficient water quality (Kroeze et al., 2016, Strokal et al., 2019). Conducting quantitative assessments indicate the extent of environmental stressors and their influence on the environmental state. The rivalling water demands for human activities as well as their resulting degradation in water quality highlight the relevance to integrate quantitative assessments about environmental aspects with (societal) assessments that help to understand the system's dynamics and to give future (policy) recommendations.

An advocated approach to do so is the DPSIR (drivers, pressures, state, impact, response) framework (Kristensen, 2004, Smeets and Weterings, 1999). Due to its integrative nature the framework assists to analyse causal links between environmental problems (pressure, state, impact) and human actions (drivers and responses) (Kristensen, 2004). The DPSIR framework has been widely applied in water management (Gari et al., 2015) to structure cause-effect relationships (e.g. Borja et al. (2006) Niemeijer and de Groot (2008), Troian et al. (2021)) and support decision making (e.g. Mysiak et al. (2005), Pyrgaki et al. (2021), Romanelli et al. (2021)). In this thesis the framework is used as a structural frame to contextualize the environmental pharmaceutical pollution and its anthropogenic drivers as well as societal responses in an integrated assessment (see Figure 1-1).

Research and literature on pharmaceutical pollution is extensive, but existing studies mostly concentrate on environmental, chemical and technological aspects of pharmaceuticals in the environment, rather than societal ones (Daughton, 2016).

This indicates that despite the undisputable anthropogenic origin of pharmaceuticals in the environment, their drivers and potential responses are not thoroughly discussed in the scientific discourse. In terms of responses, many studies investigate the efficiency of technical standalone measures which have proven to capture a limited selection of substances from only some sources, but will not tackle the issue as a whole (Kosek et al., 2020, Kümmerer, 2008b, Voigt et al., 2020). An investigation about potential societal responses from an integrative perspective is lacking even though different concepts to acquire insights to such processes are available, see e.g. Binder et al. (2013) or Geels (2010).

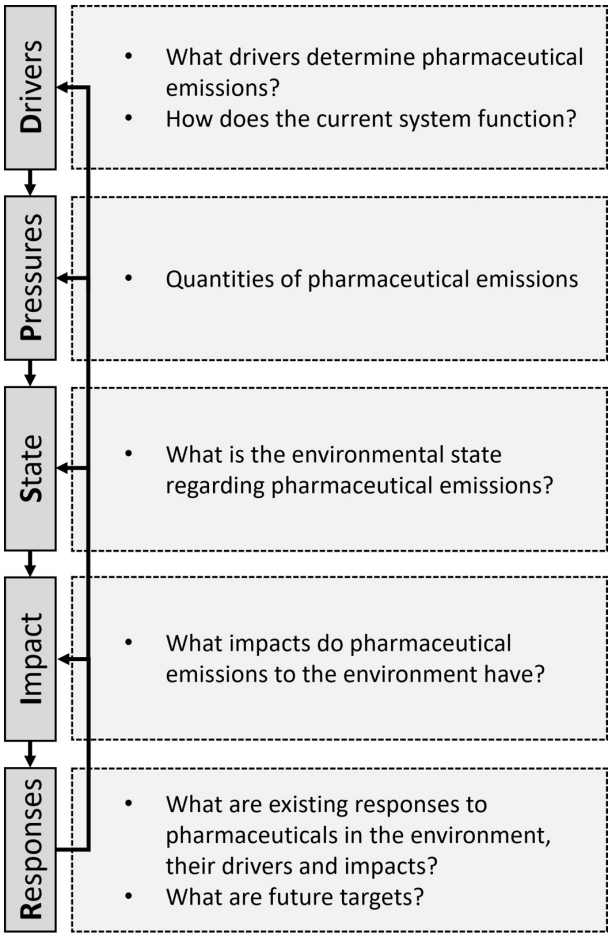

Figure 1-1. The conceptual overview of an integrated assessment of pharmaceutical pollution following the DPSIR framework as described by Smeets and Weterings (1999) and Kristensen (2004).

1.2.3. Water footprint assessment

An established tool to assess consumptive as well as degradative water consumption is the water footprint (WF) (Hoekstra, 2017). The consumptive element refers to the use of rainwater, described as green WF and the use of ground- and surface water, named blue WF. Degradative use is understood as grey WF and defined as the water volume required to dilute polluted water volumes to an extent that water quality standards are not violated (Hoekstra et al., 2011). The WF serves as an indicator that measures water use over the entire value chain of a product or service (Hoekstra et al., 2011). Consequently it is possible to attribute a WF to products (Gerbens-Leenes et al., 2018, Mekonnen and Hoekstra, 2012) or sectors (Cazcarro et al., 2014, Palhares and Pezzopane, 2015). Besides the WF that indicates a production perspective of water use, the concept is also used to attribute water use to consumers, regions or nations based on consumption patterns (Da Silva et al., 2016, Hoekstra and Chapagain, 2007).

During almost 20 years of WF research since the concept was developed in 2002 , numerous studies have been published (Hoekstra, 2017). The grey WF was assessed for a diverse set of pollutants such as nitrogen (Aldaya et al., 2020, Chukalla et al., 2018, Hu et al., 2018, Mekonnen and Hoekstra, 2015, Muratoglu, 2020), phosphorus (Mekonnen and Hoekstra, 2018), pesticides (Barreto et al., 2020, Vale et al., 2019), heavy metals (Yan et al., 2021) or for combinations of different contaminants (Borsato et al., 2018, Bustamante-Silveira et al., 2021, Feng et al., 2021, Morera et al., 2016) as well as across geographical levels from regional (Lamastra et al., 2014, Wang et al., 2019) to global (Liu et al., 2012, Mekonnen and Hoekstra, 2015, Mekonnen and Hoekstra, 2018). Assessing the grey water footprint (GWF) of pharmaceuticals is however new. Besides the work presented in this thesis, only one study exists that assesses human pharmaceuticals using the grey WF (Martinez-Alcala et al., 2018).

The beforementioned diverse facets of pharmaceutical emissions from production and consumption highlight the relevance of assessing their pollution potential at different geographical levels, for various sources and in relation to pollution by other contaminants as well as water availability. Hereto a multi-dimensional indicator that evaluates pollution in volumetric terms, such as the grey WF, is beneficial. Furthermore, including the pharmaceutical-related grey WF in WF accounts of consumption of countries and/or catchments can increase understanding about humanity's appropriation of water resources and give indications for decision makers in water management.

1.3. Research objective

The encompassing objective of this research is to understand pharmaceutical pollution of freshwater systems using an integrated assessment of pharmaceutical emissions, their drivers, their impacts and potential responses.

Three research questions are formulated in support of this objective:

- *How can pharmaceutical pollution from diverse sources and its impacts be quantitatively assessed at different geographical levels?*

- *How can differences in pharmaceutical pollution potential be assessed among different livestock production systems?*

- *What are the alternative societal solutions to pharmaceuticals in the aquatic environment and what are requirements for their implementation?*

The rationale behind these three questions lies in addressing (parts of) the knowledge gaps identified around pharmaceutical pollution and its assessment as outlined in the previous sections. The first research question aims to assess pharmaceutical pollution from human and veterinary use by quantifying emissions and evaluating their impact. Using the grey WF as an indicator of pollution in volumetric terms is novel and allows to set results (per geographical level or assessed entity) in context with water availability and consumptive as well as degradative WFs investigated in other studies. Specific attention is given to the assessment of veterinary pharmaceuticals. Here the shortcomings of existing methods are (partially) addressed by developing an approach to model and assess substance-specific pharmaceutical pollution over it's lifecycle (from administration to water) per livestock type. Pollution resulting from manufacturing is not covered by the assessment in this thesis.

The second research question targets further knowledge gaps related to veterinary pharmaceutical pollution. Specifically, factors influencing pharmaceutical use are assessed and brought into the context of different livestock production systems. A framework to identify pharmaceutical pollution potentials of different production systems is created and a pilot assessment for a set of different substances is conducted.

The third research question focusses on societal responses to pharmaceuticals emissions into freshwater systems. Here, the existing research on solution which largely focusses on individual (mostly technical) measures is expanded by exploring alternative pathways how society can handle pharmaceutical pollution.

1.4. Research approach and structure

To achieve the research objective and answer the research questions, knowledge and methods from various disciplines are integrated, according to the logical framework of Figure 1-2. A series of aspects is combined and integrated to 1) assess pharmaceutical emissions from human as well as veterinary use; 2) map different geographical levels; and 3) use methods and integrate perspectives sourcing in emission modelling, water management and social sciences.

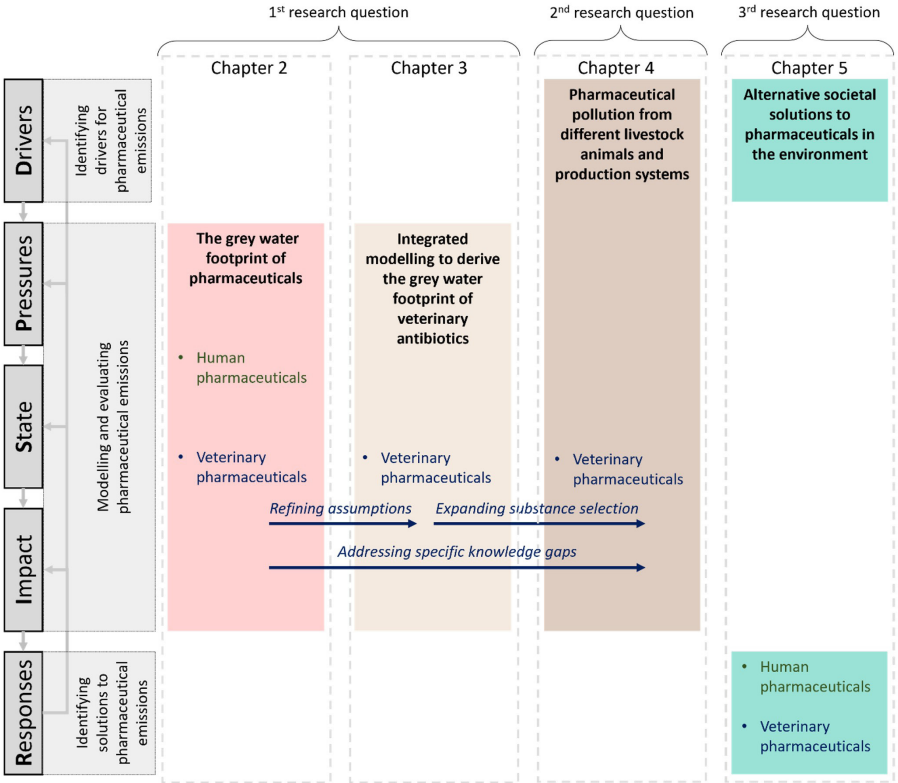

Figure 1-2. Logical framework of the thesis setup.

To address the first research question, a method to assess the grey water footprint of human and veterinary pharmaceuticals is developed. Chapter 2 of this thesis presents methods to estimate pharmaceutical emissions from human and veterinary use, whereby precautionary assumptions are taken for the environmental fate and transport of the veterinary pharmaceuticals. According pollution is expressed as GWFs at different geographical levels – from global to catchment scale. Moreover,

GWFs are displayed for entities such as animal products or consumers to increase understanding about humanity's appropriation of freshwater.

The third chapter builds up on modelling veterinary pharmaceutical emissions (in this case antibiotics) and associated GWFs. Specifically, precautionary assumptions that were taken in the previous chapter are refined by integrating a set of models over the pharmaceuticals' entire lifecycle to estimate their diffuse emissions to surface waters. The particular focus is on pharmaceutical fate and transport after the distribution on agricultural land.

Veterinary pharmaceuticals are as well in the spotlight of Chapter 4, where selected knowledge and information gaps that were outlined in the previous chapters are addressed. The chapter presents an environmental assessment of pharmaceutical pollution for different livestock production systems. While manifold studies assess environmental performance of various livestock production systems, none of these include pharmaceutical pollution. The expanded knowledge about pharmaceutical pollution from different animal types and livestock production systems can serve as a basis for future agricultural and environmental policies.

After increasing understanding about the environmental aspects of pharmaceuticals in water, the fifth chapter explores the system's drivers as well as alternative societal solutions to human and veterinary pharmaceuticals in the aquatic environment. Thus, the current system is investigated and based on transition theory alternative future solutions to pharmaceuticals in the aquatic environment as well as requirements for successful implementation are identified. These different pathways how society can handle the situation are explored based on literature as well as on stakeholder interviews.

1.5. The MEDUWA-Vecht(e) project

This research is conducted as part of the MEDUWA (medicines unwanted in water) project which tackles the reduction and prevention of pharmaceutical emissions as well as multi-resistant bacteria in different environmental media. The 27 MEDUWA partners from research, private companies, governmental and non-governmental organizations aim to develop a variety of approaches to avoid pharmaceutical pollution along the entire medicine chain. While developed solutions should be universally applicable, the project's regional focus lies in the German-Dutch Vecht river catchment. The transboundary catchment served as a study site where the diverse MEDUWA innovations (measuring, visualizing, and communicating about pharmaceutical emissions and multi-resistant bacteria; simulating measures to reduce emissions; mitigating and preventing emissions) were developed and ap-

plied. Comprehensive details about the project's outcomes can be found on www.meduwa.eu. This thesis' objectives associate with the MEDUWA project's concept by investigating the complete pharmaceutical lifecycle from source to sink.

CHAPTER TWO

THE GREY WATER FOOTPRINT OF HUMAN AND VETERINARY PHARMACEUTICALS

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The grey water footprint of human and veterinary pharmaceuticals

Abstract

Water pollution by pharmaceuticals is widespread, causing both environmental and human health risks. We assess pharmaceutical water pollution from human and veterinary pharmaceuticals at three geographical levels: global, national (considering Germany and the Netherlands) and catchment level (with a case study for the Vecht catchment shared by Germany and the Netherlands). The grey water footprint (GWF), a measure of water pollution in volumetric terms, is estimated from pharmaceutical loads entering the aquatic environment, considering different pollutant sources and pathways. We study different substances depending on data availability, which varies across geographical levels. Results show a global per capita GWF of 1,900 m^3 yr^{-1} resulting from human consumption of ciprofloxacin. The largest GWFs in both Germany and the Netherlands were found for ethinylestradiol for human and amoxicillin for veterinary use. The estimated per capita GWF from human use of ethinylestradiol is 2,300 m^3 yr^{-1} for Germany and 11,300 m^3 yr^{-1} for the Netherlands. The per capita GWFs of German and Dutch consumers of animal products are 12,900 and 10,600 m^3 yr^{-1}, respectively. For the Vecht catchment, we estimate the water pollution level per sub-catchment by comparing the GWF to available runoff, which enables us to identify geographic hotspots. In the basin as a whole, GWFs from human and veterinary pharmaceuticals both exceed available runoff. At all levels, pharmaceutical water pollution substantially adds to earlier water footprint studies that excluded this type of pollution, which demonstrates the importance to include pharmaceutics in water footprint studies.

2.1. Introduction

Worldwide, about 600 pharmaceutical compounds and transformation products from pharmaceuticals have been traced in the aquatic environment (Aus der Beek et al., 2015). Exposure to pharmaceuticals has led to ecotoxicological effects on various species, such as vultures, fish, frogs and duckweed (Aus der Beek et al., 2015, Sumpter, 2010), which has resulted in serious concerns, especially regarding

drinking water risks (WHO, 2012) and antimicrobial resistance (WHO, 2014). Urban wastewater discharge is generally regarded the dominant source of pharmaceuticals in water, whereas discharge from manufacturing, hospitals, animal husbandry and aquaculture can be important locally (Aus der Beek et al., 2015). Human and veterinary pharmaceuticals enter the aquatic environment via distinct pathways (Kümmerer, 2008a). Figure 2-1 illustrates sources and pathways of pharmaceutical residues to freshwater resources considered in this study.

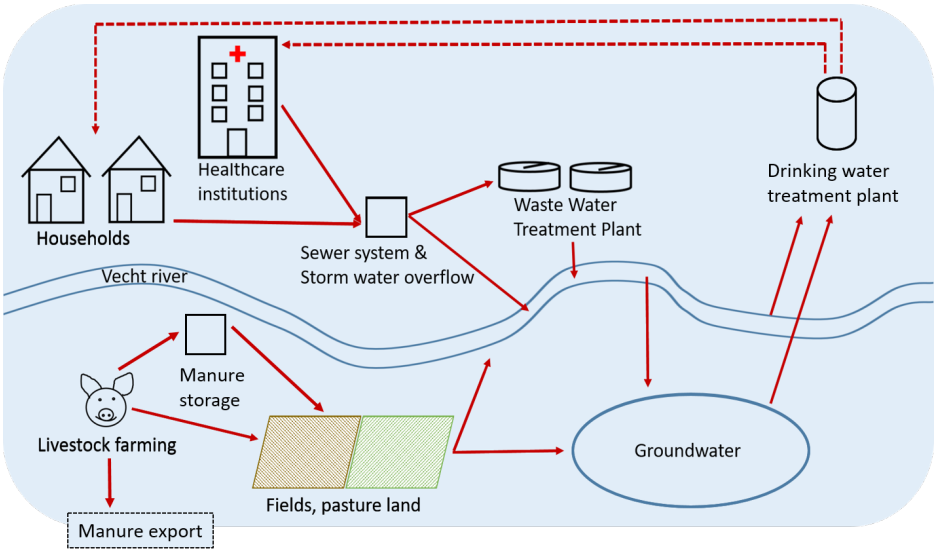

Figure 2-1. Pathways of human and veterinarian pharmaceuticals entering the environment.

Pharmaceuticals are designed to cure people and animals, or diagnose or prevent diseases. They have a precise function within target bodies. The administered dose is rarely entirely decomposed by the body; substantial fractions are generally excreted, mainly via urine (Winker et al., 2008). The excreted fractions of human pharmaceuticals and their metabolites are mostly discharged into the sewer system (Hughes et al., 2013) and enter the receiving water body as point source. In the case of livestock, manure from treated animals, collected in liquid, solid or mixed form (Weinfurtner, 2011), contains pharmaceutical residues and will generally be applied to crop fields or grasslands as fertilizer (Kümmerer, 2008b). A fraction of the pharmaceuticals thus brought onto land will leach to groundwater or reach open water through surface runoff (Boxall, 2008), thus forming a diffuse source of pollution.

This study uses the grey water footprint (GWF) concept to assess water pollution by pharmaceuticals from households, hospitals and animal husbandry considering

different pathways. The GWF indicates the volume of water required to assimilate pollutant loads to acceptable concentrations (Hoekstra et al., 2011). Despite water footprint research since 2002 (Hoekstra, 2017), investigation of the GWF related to pharmaceuticals is in its infancy. There has been extensive research into the GWF related to the use of fertilizers (Liu et al., 2012, Mekonnen and Hoekstra, 2015, Mekonnen and Hoekstra, 2018) and pesticides (Gil et al., 2017, Lamastra et al., 2014, Vale et al., 2019), but only one case study on the GWF of human pharmaceutical use has been published (Martinez-Alcala et al., 2018). There have been various efforts to estimate pharmaceutical loads to freshwater (Alder et al., 2010, Ter Laak et al., 2010, Winker et al., 2008) and to monitor concentrations of pharmaceuticals in wastewater effluents and in streams (Hirsch et al., 1999, Kasprzyk-Hordern et al., 2008, Ternes, 1998). None of the previous studies took a perspective as we undertake in the current study, translating the loads of both human and veterinary pharmaceuticals to water into a GWF and putting this GWF in the context of the limited assimilation capacity of freshwater systems. The objective is to gain insight in the GWF of pharmaceuticals from different sources and explore which of the selected substances and emission pathways are most influential and what parameters are most important. The GWF is quantified and spatially mapped, distinguishing between GWFs related to households and hospitals and different types of livestock farming. GWFs are thereby expressed as polluted water volumes per area, but also per community, per person, and per unit of animal product (meat, milk, egg). The results are compared with the GWF of other pollutants and thus add a useful extension to the assessment of the overall WF of human society.

We consider the GWF of pharmaceuticals at three spatial levels. In a global analysis for two substances we obtain a global picture of the severity of water pollution through pharmaceuticals. At national level we estimate and contrast pharmaceutical pollution in two countries (Germany and the Netherlands) for a range of substances and compare the GWF per person related to direct pharmaceutical use to the GWF per person from the consumption of animal products (in the supply chain of which veterinary pharmaceuticals were used). In a detailed, high-resolution analysis at river basin level (for the Vecht catchment shared by Germany and the Netherlands) we identify local hotspots of water pollution through pharmaceuticals. We estimate the potential effect of the GWF per sub-catchment by calculating the water pollution level (WPL) as the ratio of the GWF to catchment runoff.

2.2. Methods and data

2.2.1. Geographical levels of analysis

At global level, where data on pharmaceutical use are extremely limited, we estimate the pollution from human use of carbamazepine and ciprofloxacin, using data on loads emitted to the aquatic environment from Oldenkamp et al. (2019). At national level, environmental loads and related GWFs are estimated for Germany (GE) and the Netherlands (NL), both for human and veterinary pharmaceuticals. Regarding human pharmaceuticals, substances from several therapeutic groups are included whereas the selection of veterinary pharmaceuticals is limited to antibiotics. Details on the substance selection are included in the Appendix A1.1. The basin level study for the Vecht catchment (VC) considers the same substances as on the national level. A detailed description of the catchment is in the Appendix A1.2.

2.2.2. Grey water footprint and water pollution level

Water footprint (WF) assessment is a method to quantify consumptive as well as degradative freshwater use. The consumptive WF refers to the consumption of rainwater (green WF) and groundwater or surface water (blue WF). The degradative WF, called the grey WF (Hoekstra et al., 2011), refers to the volume of water that is required to assimilate pollutants, which is the volume of water needed to dilute pollutants to the extent that the quality of the ambient water remains above water quality standards (Franke et al., 2013). The GWF [m^3 yr^{-1}] is defined as the load of pollutant L [kg yr^{-1}] divided by the difference between the maximum allowed concentration C_{max} [kg m^{-3}] and the natural background concentration C_{nat} [kg m^{-3}] (Hoekstra et al., 2011). For pharmaceuticals considered here, C_{nat} is zero. The GWF is estimated separately for different substances. The overall resultant GWF is equal to the largest GWF across the examined contaminants (Hoekstra et al., 2011). We estimate GWFs on a temporal scale of one year.

The water pollution level (WPL) in a basin or sub-catchment is defined as the ratio of the GWF [m^3 yr^{-1}] to the catchment's runoff R [m^3 yr^{-1}] (Hoekstra et al., 2011). WPL>1 indicates that ambient water quality standards are violated. WPL is estimated in the Vecht case study on annual basis per sub-catchment. Runoff (precipitation minus evaporation) is estimated from data at a resolution of 1 km^2 for the reference period 1961-1990 (BFG, 2019) and extrapolated to the Dutch part of the catchment as climatic and hydrological conditions are comparable.

2.2.3. Human pharmaceutical loads

Following modelling approaches presented by e.g. Alder et al. (2010) and Ter Laak et al. (2010), pharmaceutical loads entering the aquatic environment as point sources are estimated as:

$$L_h = S \times f_e \times (1 - f_r) \quad (2.1)$$

where L_h [kg yr^{-1}] is the load of a specific human pharmaceutical to water, S [kg yr^{-1}] the sales of the pharmaceutical in a defined geographical area, f_e [-] the excreted fraction, and f_r [-] the fraction removed by wastewater treatment.

Pharmacy sales are obtained on national and VC level for GE and NL. Data on pharmaceutical use in hospitals is collected from hospital pharmacies in the VC. Substance-specific input values for excreted pharmaceutical fractions and removed fractions in wastewater treatment plants are retrieved from scientific literature (Appendix A 1.3).

2.2.4. Veterinary pharmaceutical loads

Veterinary pharmaceutical loads are estimated separately for beef cattle, dairy cattle, pigs, broiler and laying hens, for GE and NL as a whole and for the VC. The main emission pathways via direct (excretion of grazing animals) and indirect (manure collection and application) emissions were considered (Boxall, 2008). Aggregated loads per pharmaceutical and livestock type are defined as:

$$L_t[i] = L_d[i] + \sum_m L_{in}[i,m] \quad (2.2)$$

where $L_t[i]$ [kg yr^{-1}] is the total load of a specific veterinary pharmaceutical from livestock type i, $L_d[i]$ [kg yr^{-1}] the load from manure directly emitted to pasture land, and $L_{in}[i,m]$ [kg yr^{-1}] the indirect load from manure type m (liquid or solid) applied to fields after temporary storage. Following descriptions by Boxall et al. (2004), direct loads are estimated as:

$$L_d[i] = 365 \times a[i] \times f_e \times f_d[i] \quad (2.3)$$

where a [kg day^{-1}] is the administered substance per day, f_e [-] the excreted fraction, and f_d [-] the fraction directly emitted to pasture land.

The pharmaceutical load from manure that has been stored before application to fields is estimated per livestock type i and manure type m (liquid or solid) using a first-order degradation model (Ray et al., 2017, Wang and Yates, 2008), assuming constant production of manure over time (see derivation in Appendix A 1.4):

$$L_{in}[i,m] = \frac{365}{T[i,m]} \times \left(\frac{a[i] \times f_e \times (1 - f_d[i]) \times f_{man}[i,m]}{k[i,m]} \times \left(1 - e^{-k[i,m] \times T[i,m]}\right) \right) \quad (2.4)$$

where (1-f_d) [-] is the fraction of the daily production that is stored, f_{man} the fraction of manure type m, k [day^{-1}] the degradation rate, T [days] the duration of one storage period, and 365/T [-] the number of storage periods per year. By definition, k equals ln(2) divided by the half-life of the substance (which differs per type of manure and livestock type).

Amounts of administered substances (separately for beef cattle, dairy cattle, pigs, broilers and laying hens) are estimated based on veterinary pharmaceutical sales data for GE and NL. By lack of livestock-specific data, we assume the same excretion fractions as in human metabolism. Data on pharmaceutical degradation during manure storage are obtained from literature. Data sources and assumptions are provided in the Appendix A 1.4.

Pharmaceutical transport to water through leaching and runoff has been addressed through experimental trials (Hamscher et al., 2005, Kay et al., 2005, Ostermann et al., 2013, Pan and Chu, 2017, Popova et al., 2013, Spielmeyer et al., 2017, Stoob et al., 2007), modelling attempts (Bailey, 2015, Knäbel et al., 2016, Mackay et al., 2005) and risk assessment methods (CVPM, 2018, Menz et al., 2015), but a comprehensive method applicable for the scope of this study is lacking. Given lack of data on decay in the soil and because pharmaceuticals from agricultural use have been found in freshwater resources under agricultural fields in GE and NL (Karfusehr et al., 2018, Kivits et al., 2018), we follow here the precautionary principle by assuming that all loads applied to the field could potentially end up in freshwater. This may overestimate water quality impacts given potential degradation or accumulation in the soil (Hannappel et al., 2014, Kümmerer, 2008a). There is great variance in mobility among different pharmaceuticals (Boxall, 2008). Plant uptake or photodegradation can occur after pharmaceuticals have been applied to the field (Jechalke et al., 2014). We address this issue of potential overestimation in a sensitivity analysis presented in the Appendix A 2.3.

2.2.5. Limit concentrations of pharmaceuticals

Although the EU included pharmaceuticals in the priority substances and watch list under the water framework directive (European Commission, 2016, European Commission, 2019), there are no legally binding environmental limit concentrations for pharmaceuticals (Barbosa et al., 2016). Here, we take predicted no-effect concentrations (PNEC) as maximum allowed concentrations for the GWF calculations (Bergmann et al., 2011). PNEC values for the substances considered are taken from literature (see Appendix A 1.5) and reach from 0.00001 μg L^{-1} for ethinylestradiol to 60 μg L^{-1} for metformin (Bergmann et al., 2011). For amantadine, for which no PNEC value is available, we have taken 0.1 μg L^{-1}, the threshold value for environmental risk assessment of pharmaceuticals suggested by the European Medicines Agency (CVPM, 2018).

2.3. Results

2.3.1. Global perspective

Based on global loads for carbamazepine and ciprofloxacin to freshwater from Oldenkamp et al. (2019) and PNEC values used in this study, global GWFs of 50 billion m^3 yr^{-1} (carbamazepine) and 14,556 billion m^3 yr^{-1} (ciprofloxacin) were determined, which on a per capita basis is 7 m^3 yr^{-1} (carbamazepine) and 1,900 m^3 yr^{-1} (ciprofloxacin). While the latter in particular is very substantial – compared for instance with a global nitrogen-related GWF of 1,940 m^3 yr^{-1} (Mekonnen and Hoekstra, 2015) – water pollution from pharmaceuticals is likely to increase. The IMS Institute for Healthcare Informatics (2015) predicts a global pharmaceutical consumption increase of 32% from 2015 to 2020. Klein et al. (2018) predict a global increase of human antibiotic use by 15% towards 2030 under unchanged antibiotic use policies and antibiotic consumption rates. Extrapolating the growth of global antibiotic consumption as observed in the past years, they estimate per capita consumption to rise by 161% and total consumption by 202%. This growth largely results from emerging markets, where populations and per capita consumption rise (IMS Institute for Healthcare Informatics, 2015). Growth in per capita consumption of pharmaceuticals appears to correlate to growth in gross domestic product per capita (Klein et al., 2018). For global veterinary antibiotic consumption an increase of 67% from 2010 to 2030 is predicted due to the global rise in animal product consumption and the shift towards more intensive farming practices. This trends would also lead to an increase of global GWF of pharmaceuticals.

2.3.2. National GWFs for Germany and the Netherlands

Human pharmaceuticals: The largest GWFs of human pharmaceuticals in GE and NL, based on pharmacy sales, excretion rates and removal rates in wastewater treatment, are estimated at 190 and 193 billion m^3 yr^{-1}, respectively, resulting from the hormone ethinylestradiol, which is not used in relatively large amounts but has a comparatively low PNEC. Total GWFs for all substances are given in the Appendix A2.1. Although the German population is around five times larger than the Dutch population, the total Dutch GWF is larger for two out of the eleven investigated substances, namely ethinylestradiol and oxazepam.

Figure 2-2 shows the per capita GWFs for selected substances for GE and NL. Differences in GWF are up to four orders of magnitude among compounds, resulting from a combination of different consumption volumes, excreted fractions, removed fractions in WWTPs and given PNECs. For some substances there is a one order-of-magnitude difference in per capita GWF between GE and NL. This results from different per capita consumption in the two countries, i.e. the per capita GWF linearly depends on the per capita consumption. The per capita GWF for ethinylestradiol is about five times higher for NL than for GE. GE has a larger per capita GWF than NL for eight out of the eleven substances, resulting from differing per capita sales. The largest difference in per capita GWF between the two countries is found for the antibiotic erythromycin, with a nine times larger value for GE. The national average per capita GWFs of carbamazepine for GE and NL are within the same order of magnitude as the global average (7 m^3 yr^{-1}), although slightly higher. For ciprofloxacin, the German and Dutch per capita GWFs are approximately half of the global average (1,900 m^3 yr^{-1}).

Veterinary pharmaceuticals: Between 1% and 33% of the pharmaceuticals sold to the livestock sector in Germany and the Netherlands are estimated to reach freshwater resources (Table 2-1), considering country specific input data. Note that the livestock sector in one country mainly contributes to water pollution in the same country, but due to cross-border manure trade, exported fractions can end up in neighbouring countries. The net trade of manure between NL and GE is from the former to the latter (Leenstra et al., 2014), so some of the pharmaceuticals from the Dutch livestock sector end up in water bodies in Germany. On the other hand, a substantial part of the water pollution in Germany flows downstream to the Netherlands. For national GWF estimations of this study, we investigated GWFs related to production of animal products and therefore present the GWF of livestock production per country, even though pollution might take place elsewhere. For the VC we evaluate manure export from the region and present this as part of the results.

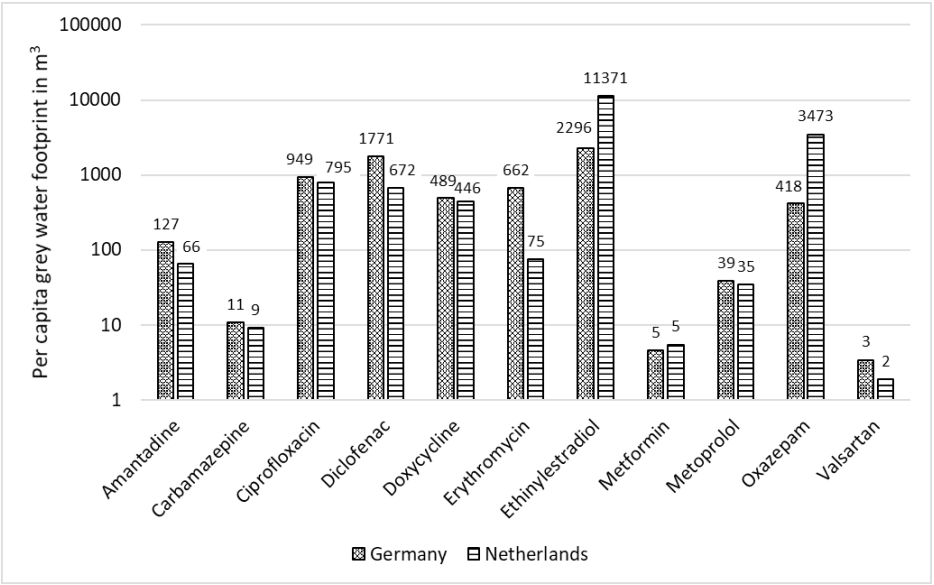

Figure 2-2. German and Dutch per capita GWFs related to human pharmaceutical use for selected substances.

Table 2-1. Estimated fractions of sold veterinary pharmaceuticals in Germany and the Netherlands that enter freshwater resources.

	Amoxicillin	Doxycycline	Oxytetracycline	Sulfamethazine	Tetracycline
Germany	9.7%	14.3%	33.2%	1.3%	24.0%
Netherlands	1.7%	5.1%	11.8%	0.9%	9.2%

The largest GWFs of livestock production are from amoxicillin and amount to 1.5 and 0.3 trillion m^3 yr^{-1} for GE and NL, respectively, exceeding the GWFs of human pharmaceuticals. The Appendix A 2.1 provides GWFs per livestock sector and country for all substances. In GE, beef cattle contribute most (53%) to the overall GWF, whereas in NL dairy cattle contribute most (60%). Note that this distribution is a first approximation, resulting from the assumptions taken in this study regarding the distribution of pharmaceuticals over the different animal types.

Given their weight, a beef or dairy cow has a larger annual GWF than a pig or chicken (see Appendix A 2.1). More informative, Table 2-2 shows the GWF per unit of animal product. Among the three meat types, beef has the largest GWF in GE (654 m^3 kg^{-1}) whereas pork has the largest GWF in NL (212 m^3 kg^{-1}). Chicken meat

Table 2-2. GWFs related to selected substances per unit of animal product produced in Germany (GE) and the Netherlands (NL) compared to the total (global average) water footprint (WF) of the same products estimated earlier when excluding the GWF from veterinary pharmaceutical use.

Animal product	Unit	Grey water footprint related to veterinary pharmaceutical use										Total WF [2]
		Amoxicillin		Doxycycline		Oxytetracycline		Sulfamethazine		Tetracycline		
		GE	NL	GE	NL	GE	NL	GE	NL	GE	NL	
Beef meat	$m^3\ kg^{-1}$	654	148	114	50	0.68	0.29	0.16	0.13	15	8	15
Milk	$m^3\ L^{-1}$	15	11	3	4	0.02	0.02	0.003	0.01	0.35	0.55	1
Pig meat	$m^3\ kg^{-1}$	51	212	8	88	0.07	0.79	0.004	0.06	2	21	6
Chicken meat	$m^3\ kg^{-1}$	15	0.14	4	0.09	0.03	0.0006	0.002	0.0001	1	0.03	4
Egg	$m^3\ kg^{-1}$	2	0.5	0.6	0.3	0.006	0.003	0.0003	0.0003	0.5	0.2	3

has the smallest GWF in both countries. Except for pork, GWFs for all products are larger in GE than in NL. As shown in the table, the pharmaceutical-related GWFs add substantially to the total WFs of the animal products as estimated previously while excluding pharmaceutical-related GWFs (Mekonnen and Hoekstra, 2012) .

The direct and indirect pharmaceutical-related GWF of a consumer: For both Germany and the Netherlands, Figure 2-3 shows the pharmaceutical-related GWF (for the critical substance amoxicillin) per consumer resulting from meat, milk and egg consumption next to the GWF of a consumer because of direct (human) pharmaceutical use (for the critical substance ethinylestradiol). The GWFs related to animal products in each country are based on consumption data per country and estimates on GWF per unit of product from Table 2-2. Pharmaceutical-related GWFs from direct human medicine use as well as through the consumption of animal products exceed earlier estimates of total consumer WFs that did not yet account for pharmaceutical pollution. Mekonnen and Hoekstra (2011) estimated the total German and Dutch WFs to be 1426 and 1466 $m^3\ cap^{-1}\ yr^1$, respectively, which included water consumption related to home water use and consumption of agricultural and industrial products and water pollution through nitrogen from various sources.

2 excluding pharmaceutical-related GWF, source: Mekonnen and Hoekstra (2012)

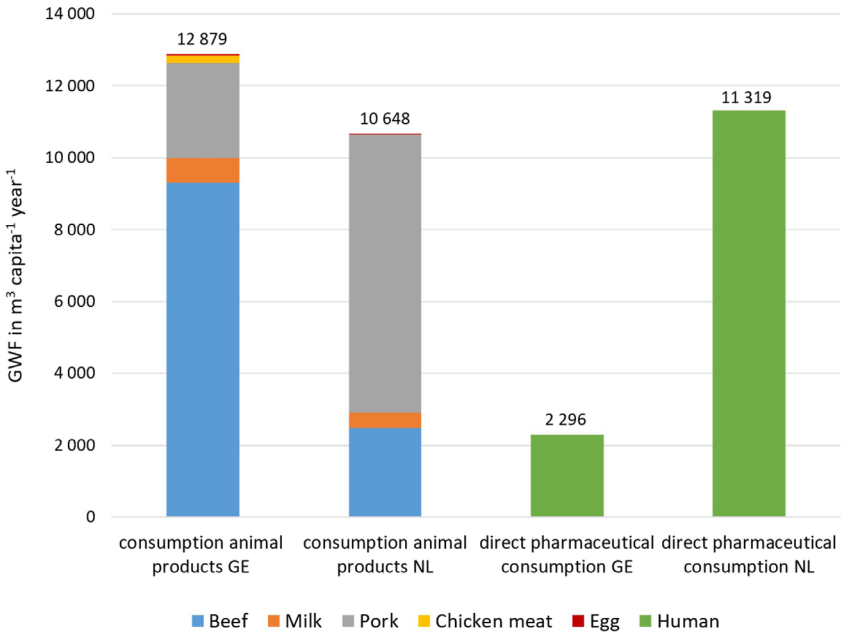

Figure 2-3. Annual GWF per capita resulting from animal product consumption (amoxicillin) and from direct pharmaceutical consumption (ethinylestradiol) in Germany (GE) and the Netherlands (NL).

2.3.3. The Vecht river catchment

Human pharmaceuticals: The VC is mapped and described in detail in the Appendix A 1.2. Table 2-3 presents the GWF per substance in the VC from households and hospitals. For the most critical substance ethinylestradiol, where the GWF exclusively results from households, approximately 95% of the total GWF in the catchment results from the Dutch part. This is due to the combination of more inhabitants in the Dutch area and a higher per capita use of the substance. GWFs for all substances are presented in the Appendix A 2.2.

There are approximately 4400 hospital beds in the region, divided over 15 hospitals (seven in GE, eight in NL). For six out of the 10 substances investigated, the GWF from hospitals adds less than 1% to the GWF from households. For ciprofloxacin, however, the GWF from hospitals amounts to about 10% of the total. The contribution of hospitals to the total GWF in the catchment is thus substance-specific.

Figure 2-4 shows the relative contributions of municipalities to the total GWF in the catchment, for ethinylestradiol (the most critical substance) and erythromycin (with quite

Table 2-3. Grey water footprint of selected substances in the German and Dutch parts of the Vecht catchment.

	Grey water footprint [10^6 m^3 yr^{-1}]		
Substance	Households	Hospitals	Total
Amantadine	130	1.2	131
Carbamazepine	18	0.02	18
Ciprofloxacin	1465	155	1620
Diclofenac	1443	22	1465
Doxycycline	861	7	868
Erythromycin	408	15	423
Ethinylestradiol	16104	n.d.	16104
Metformin	9	0.03	9
Metoprolol	67	0.44	67
Oxazepam	5099	64	5163
Valsartan	4	0.02	4

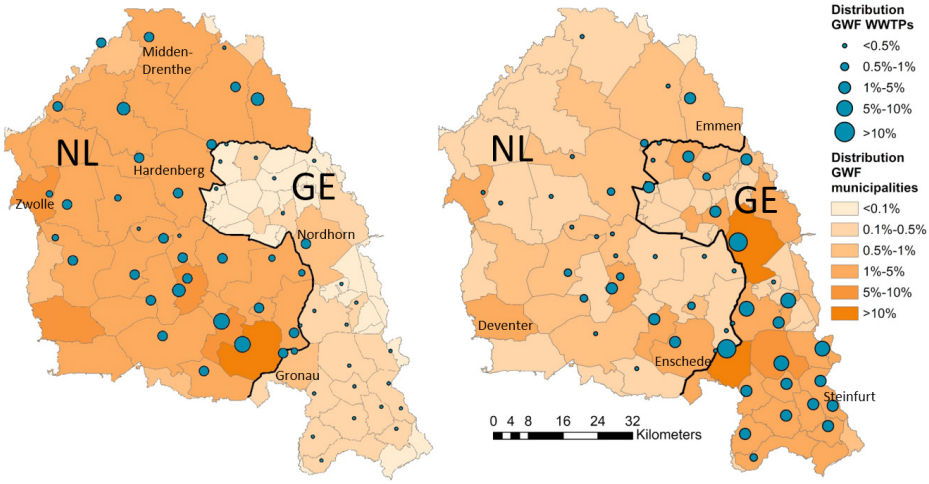

Figure 2-4. Relative contributions of municipalities and wastewater treatment plants (WWTPs) to the total GWF related to ethinylestradiol (left) and erythromycin (right) the Vecht catchment.

a divergent spatial pattern). The actual loads occur through the wastewater treatment plants (WWTPs) in the catchment, the contributions of which to the total are shown as well. Though the municipalities vary in size, it can be observed that GWF hotpots occur in the more densely populated communities such as Enschede and Nordhorn. The WWTPs that contribute most to the overall GWF are obviously located in or near the municipalities that contribute most. The share of different municipalities in the overall GWF in the catchment differs across substances, explained by diverging per capita sales.

Veterinary pharmaceuticals: The largest GWF (93 billion m^3 yr^{-1}) resulting from livestock in the VC is for amoxicillin, with the German part of the catchment contributing 53%. Whereas amoxicillin is the critical substance at catchment level, the maximum GWF on the Dutch side is determined by doxycycline. Substance-specific pharmaceutical loads and GWFs are presented in the Appendix A 2.2.

Substantial amounts of manure produced in the VC are exported from the region, thus externalizing pharmaceutical emissions (Figure 2-5). In the German part of the catchment, 80% is used as agricultural land (arable and grassland); in the

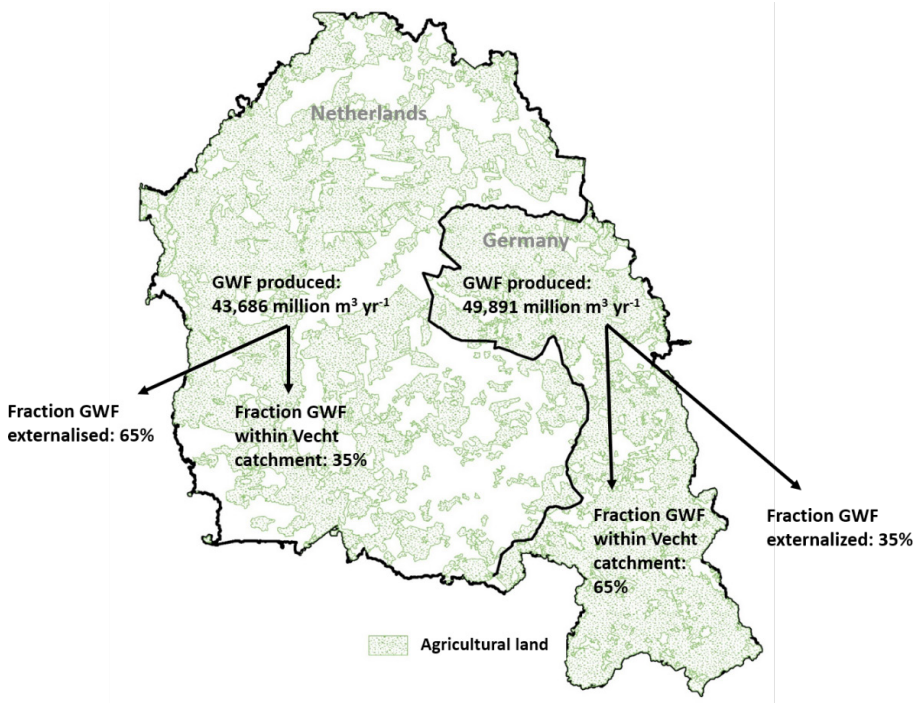

Figure 2-5. GWF related to veterinary use of amoxicillin produced in the Vecht catchment and fractions remaining within and being exported from the catchment.

Dutch part this is 52%. Considering a nitrate limit for manure of 170 kg N ha^{-1} yr^{-1} (European Commission, 2010) and the available agricultural land in the VC, we find a maximum possible application of approximately 25 and 38 million kg N yr^{-1} in the German and Dutch parts of the catchment, respectively. Produced nitrogen from animal excretion was estimated at 38 and 109 million kg yr^{-1} in the German and Dutch parts, respectively, taking into account livestock densities and animal-specific nitrogen excretion factors, implying manure surpluses in both parts of the catchment. The German area thus externalizes 35% of its GWF; the Dutch part even 65%.

Water pollution levels in the Vecht catchment: The total catchment's runoff is about 2 billion m^3 yr^{-1} on average. The runoff per km^2 per sub-catchment ranges from 202,000 to 378,300 m^3 km^{-2} and is 332,500 m^3 km^{-2} for the catchment as a whole. Differences in runoff per sub-catchment (Figure 2-6) follow from differences in hydrology and sub-catchment size.

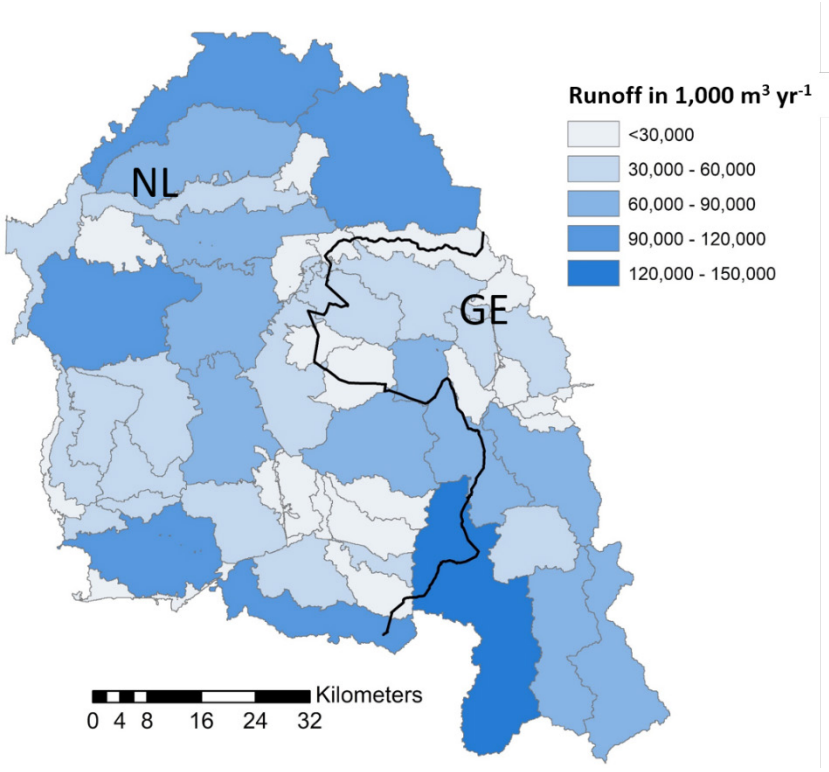

Figure 2-6. Average runoff per sub-catchment of the Vecht river catchment.

Figure 2-7 shows the WPL in the VC resulting from ethinylestradiol, the most critical human pharmaceutical, and from amoxicillin, the most critical veterinary pharmaceutical. The total GWF related to human use of ethinylestradiol is 13 billion m^3 yr^{-1}. The total GWF related to veterinary use of amoxicillin is 48 billion m^3 yr^{-1}. For both, human and veterinary pharmaceuticals, the GWF exceeds the available runoff. WPLs across sub-catchments differ, indicating hotspots. For human pharmaceuticals, WPL is high in sub-catchments with large disposals from WWTPs. In several sub-catchments WPL<1, which means that the GWF can be assimilated by the runoff generated within the area. In NL, per capita GWF for ethinylestradiol is 4.2 times larger than in GE, contributing to higher WPLs in sub-catchments on the Dutch side. In one sub-catchment, WPL exceeds 100, demonstrating a remarkable hotspot. This high value is caused by the presence of WWTPs of two majors cities, namely Enschede and Hengelo (connecting over 274,000 inhabitants), a GWF of 11,123 m^3 yr^{-1} per inhabitant and a relatively low runoff.

The WPL from veterinary pharmaceuticals exceeds 1 for all sub-catchments. It results from amoxicillin and distributes more homogeneously over the catchment than the WPL for ethinylestradiol from human use. While human pharmaceutical emissions enter as point sources at specific locations, veterinary emissions are diffuse and spread out, as manure is applied throughout the basin. The GWF per area related to the veterinary pharmaceutical emissions in the VC is 22 and 7 million m^3 km^{-2} for the German and Dutch side, respectively. We observe that the sub-catchments with the lowest WPLs for veterinary pharmaceuticals, show a high WPL for human pharmaceu-

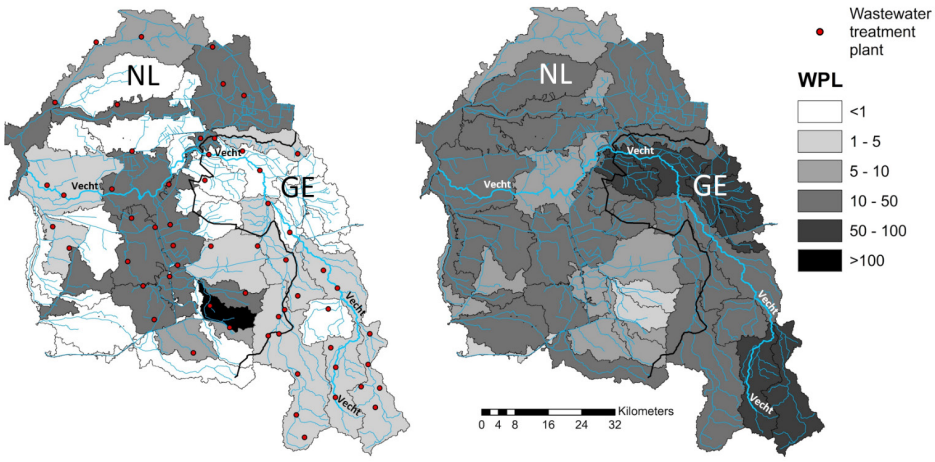

Figure 2-7. Annual average WPL in the Vecht catchment resulting from the maximum GWF of human (left) and veterinary (right) pharmaceutical use, resulting from ethinylestradiol and amoxicillin, respectively.

ticals, because there is little agricultural land in densely populated areas. Note that WPLs presented here refer to locally generated pollution, which excludes incoming water pollution from upstream sub-catchments. We take this approach as we are not considering biogeochemical (decay) processes along the river streams.

2.4. Discussion

2.4.1. General observations

This study shows that per capita GWFs of human pharmaceuticals can hugely vary across substances and among countries. The latter can be explained by differences in consumption patterns (Klein et al., 2018, OECD, 2017) and wastewater treatment coverage (Oldenkamp et al., 2019). Global trends predict an increase in pharmaceutical use for both humans and livestock. If wastewater treatment in countries with increasing consumption does neither increase nor improve, GWFs of human pharmaceuticals will rise. The GWF from veterinary pharmaceuticals will increase with increasing consumption of animal products if there are no changes in application routines. To draw more robust conclusions about GWFs of pharmaceutical pollution on a global level, substance-specific information on consumption patterns as well as influential parameters have to be available and analysed within future research.

2.4.2. GWFs of pharmaceuticals in context

The global average per capita GWF from the human antibiotic ciprofloxacin estimated here is 1,900 $m^3\,yr^{-1}$. This is a lot when compared to the global average WF of 1,385 $m^3\ yr^{-1}$ per person estimated by Hoekstra and Mekonnen (2012), a value including all water consumption and nitrogen-related water pollution from households, industries and agriculture (but excluding water pollution from pharmaceuticals). National per capita GWFs from direct pharmaceutical consumption and from consumption of animal products for GE and NL exceed this WF. The WF of a consumer thus increases substantially when including pharmaceutical pollution.

The results of this study can be compared to estimated GWFs for other pollutants than pharmaceuticals. Mekonnen and Hoekstra (2015) estimate a global nitrogen-related GWF of 13 trillion $m^3\ yr^{-1}$, which is the same order of magnitude as the global GWF of human use of ciprofloxacin found in this study. The global GWF from anthropogenic phosphorus loads was estimated by Mekonnen and Hoekstra (2018)

at 147 trillion m^3 yr^{-1}. The GWFs related to nitrogen in GE and NL were estimated by Mekonnen and Hoekstra (2011) at 14 and 0.85 billion m^3 yr^{-1}, respectively, which in both cases is less than the GWF related to human and veterinary pharmaceuticals found in this research. Martinez-Alcala et al. (2018) estimated the GWF of human pharmaceuticals for a region in southern Spain and found a per capita GWF of 222 m^3 yr^{-1} for carbamazepine resulting from measured concentrations in WWTP effluents, considering a PNEC of 1.2 µg L^{-1}. This is a larger GWF than we found for carbamazepine on global, national and regional level within this study.

A novel part of this research is the link made between pharmaceutical water pollution and specific animal products. Meat and dairy production are major water users, contributing about one third of the global WF of humanity (Hoekstra (2020) while not yet considering pharmaceutical pollution. Mekonnen and Hoekstra (2012) estimate the average WF of beef to be about 15 m^3 kg^{-1} (the sum of water consumption and nitrogen-related water pollution), while here we find the amoxicillin-related GWF of beef with a magnitude higher for NL and GE. This shows that the GWF related to veterinary pharmaceuticals raises an additional issue related to the consumption of animal products.

An interesting aspect of the Vecht study was the investigation of a transboundary catchment with intensive livestock agriculture. Yet, pharmaceutical pollution from households is dominant in the catchment as a whole, mainly because the VC externalizes 50% of the produced GWF resulting from veterinary pharmaceuticals. The contribution of hospitals to the GWF in the VC is minor, although specific substances can locally contribute substantially. We found significant differences in per capita GWF for the same human pharmaceuticals in GE and NL. For instance, the per capita GWF of erythromycin in the VC is 16-fold larger in GE than in NL. As GE is located upstream, it is likely that NL will be affected by German emissions.

2.4.3. Uncertainties and limitations of the study

Several input parameters considered in the GWF estimations come with uncertainty, mainly due to assumptions made to fill data gaps. We evaluate the sensitivity of the outcomes to several input parameters (see Appendix A 2.3). The results show that especially changing several input parameters at the same time can lead to substantially lower or higher GWFs. One other critical input parameter for the GWF assessment is the PNEC used as maximum allowed concentration. PNECs are derived from ecotoxicological data. Depending on data availability, e.g. for different target species, an assessment factor is applied as a precautionary approach. Further, PNECs can be derived considering different endpoints of toxicity. Consequently, different PNECs

exist in literature for individual compounds. The choice of PNEC influences GWF results. Besides that, there are no limit values regarding the toxicity of a mixture of pharmaceuticals in water, which could be a relevant aspect to address in future studies. Despite these uncertainties, the main conclusion that the GWF of certain pharmaceuticals is very large compared to other forms of water pollution remains unaffected.

Further, several aspects that potentially affect the results are not included in this study resulting in limitations. First, the study covers a limited number substances while there are thousands of different compounds on the market (Jorgensen, 2008). Second, we exclusively assessed the GWF related to pharmaceutical consumption, while the manufacturing of pharmaceuticals can come along with aquatic pollution as well (Fick et al., 2009, Larsson, 2014, Sim et al., 2011). Third, this study neglects that unconsumed pharmaceuticals could be disposed directly into the sewage system causing pollution (Barnett-Itzhaki et al., 2016, Persson et al., 2009, Vollmer, 2010). Fourth, pharmaceuticals purchases via additional routes (e.g. from abroad) is not included. Fifth, for the GWF estimation exclusively the excretion of parent compounds is considered while excreted metabolites can be likewise (or even more) ecotoxic and therefore environmentally relevant (Celiz et al., 2009, Kümmerer, 2008b). The exclusion of metabolites may lead to underestimation of GWFs. Sixth, WWTP removal rates are considered assuming all sewage water undergoes treatment. However, pharmaceuticals can enter the aquatic environment via storm water overflows before undergoing treatment during rainfall events (Kay et al., 2017). Seventh, for veterinary pharmaceuticals we estimate consumption per livestock sector, but neglected differences between treated and non-treated animals that correlate with factors such as farming practices and the health status, age and weight of the animals. Eighth, following the precautionary principle, the leaching and runoff fraction of veterinary pharmaceuticals was assumed to be 100%. For the regional analysis, WPL related to veterinary pharmaceuticals exceeded 1 in all sub-catchments, indicating violation of water quality standards. Especially for non-mobile and fast-degrading substances, the precautionary approach might be overestimating, but was considered the most appropriate approach due to insufficient knowledge and data availability.

An issue that deserves follow-up research is temporal variability. The GWF and WPL analysis cover a temporal span of one year and do not account for temporal variability of input parameters. However, several factors fluctuate in time, like pharmaceutical use depending on the season (Christoffels et al., 2016, Van Boeckel et al., 2014, Yu et al., 2013), periodic peaks of manure application in spring and autumn (Boxall, 2008) and climatic variations determining runoff.

Despite the given uncertainties and limitations, this study presents a method

leading to a first estimate of GWFs related to pharmaceuticals for human and veterinary pharmaceuticals at three geographical levels. Given the lack of data, the presented findings give a unique and satisfying indication of water pollution related to pharmaceutical use, which can be improved in the future.

2.5. Conclusion

The severity of water pollution through pharmaceuticals is demonstrated by the estimated GWF related to the global human consumption of ciprofloxacin, amounting to 1,900 m^3 yr^{-1} per capita. This is more than the overall aggregated consumptive WF per person in the world (considering all water consumed at home, and in industries and agriculture), estimated in previous studies. The trend of increasing global human and veterinary pharmaceutical consumption rises the likelihood for growing global water pollution from pharmaceuticals. This study demonstrates that GWFs can vary substantially among compounds (influenced by loads and PNECs) as well as regions (influenced by loads), leading to different hotspots depending on the substance under investigation. Therefore, the inclusion of other pharmaceuticals into a global GWF assessment could potentially increase the GWF found in this study. One substance causing this could be ethinylestradiol, which shows the largest GWF within the national and regional GWF assessment of this study, but is not included in the global assessment. Among the veterinary substances, amoxicillin resulted in the largest GWF. The national veterinary GWF from livestock production exceeded the human GWF for both countries. As a precautionary approach is taken for the transport of veterinary pharmaceuticals in the soil and over land, we may overestimate GWFs. However, amoxicillin is known for its mobile behaviour, which justifies the precautionary approach chosen. Further, the study demonstrates that GWFs from livestock production are partly externalized to other regions due to manure export. From a consumption perspective, an individual's pharmaceutical-related GWF depends on direct pharmaceutical consumption as well as consumption of animal products. An effective way for consumers to reduce pharmaceutical pollution thus includes eating less meat, eggs and dairy, which comes along with a large range of other environmental and health benefits as well (Willett et al., 2019). In the VC, WPLs exceed acceptable levels for both human and veterinary pharmaceutical, illustrating the severity of freshwater pollution on river basin scale. Additionally, it can be assumed that downstream catchments are receivers of runoff as well as human and veterinary pharmaceuticals from upstream through natural flow.

CHAPTER THREE

AN INTEGRATED MODELLING APPROACH TO DERIVE THE GREY WATER FOOTPRINT OF VETERINARY ANTIBIOTICS

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An integrated modelling approach to derive the grey water footprint of veterinary antibiotics

Abstract

Water pollution by veterinary antibiotics (VAs) resulting from livestock production is associated with severe environmental and human health risks. While upward trends in global animal product consumption signal that these risks might exacerbate toward the future, VA related water pollution is currently insufficiently understood. To increase this understanding, the present research assesses processes influencing VA pollution from VA administration to their discharge into freshwater bodies, using an integrated modelling approach (IMA). For the VAs amoxicillin, doxycycline, oxytetracycline, sulfamethazine, and tetracycline we estimate loads administered to livestock, excretion, degradation during manure storage, fate in soil and transport to surface water. Fate and transport are modelled using the VA transport model (VANTOM), which is fed with estimates from the Pan-European Soil Erosion Risk Assessment (PESERA). The grey water footprint (GWF) is used to indicate the severity of water pollution in volumetric terms by combining VA loads and predicted no effect concentrations. We apply our approach to the German-Dutch Vecht river catchment, which is characterized by high livestock densities. Results show a VA mass load decrease larger than 99% for all substances under investigation, from their administration to surface water emission. Due to metabolization in the body, degradation during manure storage and degradation in soil, VA loads are reduced by 45%, 80% and 90% on average, respectively. While amoxicillin and sulfamethazine dissipate quickly after field application, significant fractions of doxycycline, oxytetracycline and tetracycline accumulate in the soil. The overall Vecht catchment's GWF is estimated at 250,000 m^3 yr^1, resulting from doxycycline (81% and 19% contribution from the German and Dutch catchment part respectively). Uncertainty ranges of several orders of magnitude, as well as several remaining limitations to the presented IMA, underscore the importance to further develop and refine the approach.

3.1. Introduction

Water pollution by antibiotics is widespread and poses risks to human and environmental health (Aus der Beek et al., 2015). Already a few decades after their discovery in the early 1900s, concerns arose over potential human health risks posed by the use of antibiotics in farming (Kirchhelle, 2018). Since then, research has confirmed this suspicion: antibiotic residues find their way into drinking water and food products (Li et al., 2017, Pullagurala et al., 2018) and are taken up by the human body where they may influence homeostatic mechanisms due to their pharmacologic activity (Simazaki et al., 2015); they are associated with antibiotic resistances across diverse environmental media (Singh et al., 2019); and severe ecotoxicological effects resulting from their environmental presence have been observed (Aus der Beek et al., 2015).

A major source of antibiotic emission into the environment is livestock agriculture, particularly in regions with high livestock densities (Menz et al., 2015, Wöhler et al., 2020a). In 2010 estimated global annual antibiotic use in food producing animals amounted to 63,000 tons (Van Boeckel et al., 2015). Due to rising global demand for animal products and intensification of livestock agriculture, an increased use of such veterinary antibiotics (VAs) of 67% is projected between 2010 and 2030 (Van Boeckel et al., 2015). VAs are administered for therapeutic use, prophylaxis, growth promotion, and increasing production efficiency (Bloom, 2004). The use of VAs in healthy animals is the main reason why antibiotic quantities administered to animals exceed amounts used in humans in many countries (WHO, 2014). Within the EU, VA use for growth promotion was prohibited in 2006 (European Commission, 2005). Yet, in 2017, VA sales of more than 6,000 tons were reported for non-growth-promoting administration in food producing livestock by the European Medicines Agency (2019).

After administration, fractions of pharmaceuticals are excreted from animals' bodies, and in most cases (after temporary storage) emitted to agricultural lands through manure distribution for fertilization (Berendsen et al., 2018, Xie et al., 2018). On entering the environment, VAs can either find their way to freshwater bodies (via various transport routes), degrade, or accumulate in the soil matrix. Overland transport routes of VAs include surface runoff and erosion (Bailey et al., 2015). Runoff is caused by rain or irrigation and transports dissolved VAs into surface waters. Transport via eroded soil particles refers to the relocation of soil material with VAs adsorbed to it (Davis et al., 2006, Kemper, 2008). VAs that remain in the soil matrix (i.e., dissolved in pore water or adsorbed to soil particles) may either degrade over time, or - if VA input exceeds amounts degraded - accumulate (Kemper, 2008). VA emissions into freshwater further occur through leaching, where dissolved VAs per-

colate through the soil matrix into aquifers and seep to surface water via subsurface flow (Mehrtens et al., 2020, Spielmeyer et al., 2017). The dominant transport processes differ between antibiotics due to their differing physiochemical properties, the soil characteristics, and the climatic conditions (Davis et al., 2006, Thiele-Bruhn, 2003). Various efforts have been made to increase understanding of VAs' environmental fate and transport. These include experimental studies (Hamscher et al., 2005, Knäbel et al., 2016, Spielmeyer et al., 2020), risk assessments (CVPM, 2018, Menz et al., 2015) or modelling setups (Bailey, 2015, Mackay et al., 2005). Moreover, fate and transport models not specifically designed to model VAs, could be used to investigate such (e.g. FOCUS (Pereira et al., 2017), ChemFate (Tao and Keller, 2020) or SimpleBox (Hollander et al., 2016). Despite the mentioned attempts, the extent to which VA emissions cause water pollution is not readily understood.

While abovementioned research assesses VA loads and concentrations, we argue that water pollution needs to be interpreted in the context of overall human water appropriation. Different studies capture this perspective by evaluating water pollution from livestock production using the grey water footprint (GWF) as an indicator (see e.g. Liu et al. (2012), Mekonnen and Hoekstra (2012), Mekonnen and Hoekstra (2015)), with one study including VAs (Wöhler et al., 2020b). In that work the GWF was estimated based on a precautionary principle, assuming all environmental VA loads end up in freshwater.

This paper aims to improve understanding of processes that influence VA emissions to freshwater and their resulting water pollution. The research's novelty is the development of an integrated modelling approach (IMA) that simulates relevant processes and resulting VA induced water pollution. Processes investigated are VA administration, excretion, degradation during manure storage, and – most importantly – processes that drive freshwater pollution after field application (i.e., sorption, degradation and overland transport). Here, we build on and significantly improve the beforementioned VA-related GWF study by Wöhler et al. (2020b), especially by refining assumptions for VA fate and transport after their application to agricultural land. Notably, we incorporate Bailey's (2015) VA transport model VANTOM into the IMA. To our knowledge, this is the only well-described approach designed to model transport of VA loads to freshwater. We demonstrate our approach for the Vecht catchment, a transboundary river basin shared by Germany (GE) and the Netherlands (NL). The catchment is characterized by high livestock densities and has been subject to previous investigations of pharmaceutical emissions (Duarte et al., 2021, Wöhler et al., 2020b). Resulting GWFs are reported for selected geographical entities, animal types and animal products (i.e., meat, milk, and eggs).

3.2. Method and data

This study proposes an IMA that collates different models to estimate VA loads from livestock production to freshwater, and to translate model outputs into various metrics of VA-induced water pollution. The IMA consists of six modelling steps, which estimate: 1) VA administration in the livestock sector; 2) VA excretion; 3) VA degradation during manure storage; 4) VA fate and transport to surface water after manure application; 5) GWFs of VAs, and 6) VA induced water pollution levels (WPLs) in the catchment. Additionally, uncertainty ranges to evaluate the result's robustness are assessed. Each of these modelling steps, their data inputs and the uncertainty analysis are described in detail below. The approach is demonstrated by applying it to the Vecht catchment for the selected VAs amoxicillin, doxycycline, oxytetracycline, sulfamethazine[2] and tetracycline. The VA selection is based on their large market share, abundant environmental detection in regions with high livestock densities, and availability of sales and environmental fate data (Karfusehr et al., 2018, Kivits et al., 2018, Veldman et al., 2018, Wallmann et al., 2018). For details on the Vecht catchment see Appendix B 1.1.

3.2.1. VA administration in the livestock sector

The IMA's first step is to quantitatively estimate VA administration rates in the study area. Data on administered VA amounts are not publicly accessible, neither in GE nor in NL, but sales data are available. Hence, amounts administered are assumed equal to amounts sold. For NL, and reference year 2017, Lahr et al. (2019) provide national sales data on four of five compounds studied (amoxicillin, doxycycline, oxytetracycline and sulfamethazine) for the livestock sectors beef cattle, milk cattle, pigs and broiler. We approximate sales data for the laying hen sector based on total amounts per substance obtained from Lahr et al. (2019) and the relative fractions per according substance-group for the laying hen sector[3] presented by Van Geijlswijk et al. (2018). For tetracycline, Dutch sales data per livestock sector is determined based on animal numbers and average body weight per livestock type following the approach outlined by Wöhler et al. (2020b). Sector-specific antibiotic sales for the Vecht catchment are estimated proportionally to the region's livestock densities provided by CBS (2019). For GE, sales data for four of the five compounds (amoxicillin, doxycycline, oxytetracycline and tetracycline) was obtained at postcode level (first two digits) from

2 Also known under the synonym sulfadimidine.

3 The underlying assumption is that sales for "other poultry farming subsectors" equals sales for the laying hen sector as argued and explained by (Wöhler et al., 2020b)

the Federal Office of Consumer Protection and Food Safety (Wallmann, 2017). Since sales data per livestock sector is lacking, these are estimated by taking distributions across sectors in NL and normalize them with the animal mass in the two regions. Animal mass is estimated using average body weights per animal type and livestock densities, taking data from CVPM (2016), CBS (2019), IT.NRW (2019) and LSN (2019). For sulfamethazine, regional data in GE was not available. Therefore, the outlined approach was followed, but taking instead German national sales data from Wallmann et al. (2018). National sales per livestock sector thus obtained are translated to the Vecht catchment proportionally to livestock numbers. The reference year for German regional sales data is 2016, while national sales data refers to 2017.

3.2.2. VA excretion

After VA administration, VAs are not fully metabolized by the target body and consequently a fraction is excreted unchanged via urine and faeces (Boxall, 2008). These fractions are dependent on the VAs' characteristics, the administration form, and the animal's metabolism (Kemper, 2008). According to the European Medicines Agency (2019), the majority of VAs are administered orally in both, GE (>90%) and NL (>80%). Since animal excretion data for VAs is not comprehensively available, we follow the approach by Wöhler et al. (2020b) and take the more extensively studied excreted fractions of the human metabolism after oral intake as proxy to determine VA amounts in animal manure.

3.2.3. VA degradation during manure storage

VAs in excreta are emitted directly by grazing animals to pastures or temporarily end up in manure storage before being applied to agricultural land as fertilizer (Boxall, 2008). Given VA's organic composition, they degrade during manure storage (Kümmerer, 2008). We adopt the method introduced by Wöhler et al. (2020b) to model VA degradation per livestock type, using a first-order degradation model that considers different manure types (liquid, solid, and mixed) and their respective storage times.

The duration of manure storage depends on the timing and number of fertilizing events. Agricultural policies that regulate fertilizing events differ between GE and NL, as does the manure application agenda. The latter is dependent on several variables, including climatic conditions, soil characteristics, manure and crop type. Exceptions aside, manure applications in both GE and NL are generally permitted from February until August or mid-September in NL (Netherlands Enterprise Agen-

cy, 2020) and from February until the last harvest (on arable lands) or the end of October (on grasslands) in GE (Federal Ministry of Food and Agriculture (BMEL), 2020). As empirical data on manure application periods is lacking, we assume three fertilizing events in both GE and NL: beginning of February, May and August. Manure storage time is deduced from the intervals between the fertilizing events (183, 91 and 91 days respectively). Within these intervals a constant daily manure and corresponding VA input into the storage is assumed. VAs start decaying upon entering the storage. Due to insufficient empirical data on livestock grazing practices (Van den Pol-van Dasselaar et al., 2020), the fact that pigs and chicken are usually kept indoors (Montforts, 1999) and a decreasing trend of grazing cattle (Van den Pol-van Dasselaar et al., 2008), we assume all animals are kept in housing and therefore all manure is being stored before application.

3.2.4. VA fate and transport to surface water after manure application

Once manure is applied to the field, relevant processes for VA fate and transport are soil sorption, degradation, surface runoff and soil erosion, which are assessed using the VANTOM model developed by Bailey (2015). VANTOM estimates VA loads to freshwater by calculating mass budgets of VAs at user-defined spatial and temporal resolution (Bailey, 2015); see Figure 3-1 for a conceptual overview of VANTOM inputs, processes and outputs and Figure B2 in the Appendix for a detailed illustration of each process. We adjusted the original model setup to accommodate for our IMA by using VAs fractions in liquid and solid fertilizer fractions that were already determined in the manure degradation model. The tailored VANTOM estimates VA emissions for 47 sub-catchments of the Vecht catchment with agricultural areas derived from the CORINE land cover map (Copernicus, 2020). Sub-catchments were created based on the catchment's hydrological system and differ in size from 4 km^2 to 405 km^2. We simulate one year (from January to December), with 12 monthly time steps.

VANTOM requires substance-specific input data on VA application, sorption and degradation characteristics, as well as inputs on surface runoff and soil erosion. VANTOM distinguishes between a plough layer and sub-plough layer in the vertical soil profile (Bailey, 2015). In the initial conditions for each time step, both layers are represented by a solid and a liquid soil mass that each contain a VA fraction carried over from the previous time step. Soil masses are determined based on the agricultural area, layer depth, soil porosity, soil solid density, pore water levels and soil liquid density. The layer depth is defined by the fertilizing depth. Mean soil porosities per sub-catchment (varying between 0.46 $m^3\,m^{-3}$ and 0.55 $m^3\,m^{-3}$) were determined

based on Ballabio et al. (2016) . Soil liquid water density is taken as 1000 kg m^{-3} (Bailey, 2015) and the typical particle density of 2650 kg m^{-3} (Schjønning et al., 2017) is used as soil solid density. Monthly pore water levels are calculated as described in the SI and range from 0.36 m^3 m^{-3} to 0.55 m^3 m^{-3} across all sub-catchments.

The Pan-European Soil Erosion Risk Assessment (PESERA) model provides simulated monthly estimates of soil water deficits, surface runoff and soil erosion risk (at a spatial resolution of 1 km^2) required to drive the VANTOM model. PESERA utilises climate, land-use, soil and topography data and has been applied across Europe at a range of scales (Kirkby et al., 2008). PESERA's estimates can be provided on a course spatial and temporal resolution, which makes it suitable for investigations of large areas and longer time periods (Bailey, 2015, Kirkby et al., 2008). A more in-depth description of the model, including inputs and outputs is shown in the Appendix B 1.5.

Fertilizer and VA application: The three fertilizing events are set to take place upon the time step's initiation. Annual manure mass loads are estimated from national manure production data and animal head counts from Foged et al. (2011), while accounting for animal numbers in the Vecht catchment. From the same source, the total mass loads of liquid and solid fertilizer fractions based on country-specific data on manure types was calculated. Based on the maximum EU legal nitrogen application rate of 170 kg N ha^{-1} yr^{-1}, it was estimated that 65% (GE) and 35% (NL) of the total manure produced in the Vecht catchment are distributed on the catchment's agricultural land as fertilizer. By implication equivalent percentages apply to VA loads (Wöhler et al., 2020b). Hereby, we assume an equal distribution of liquid and solid manure load per area. Relative VA loads in each application event depend on the manure storage times.

At the start of each time step, present solid and liquid VA masses in the soil matrix result from the previous time step. We assume VA loads to be zero in January, which represents a long time period since the last fertilizing event and short degradation times (VA's degradation times can range from days to months). During fertilizing events VANTOM simulates manure's vertical distribution (and therefore also the distribution of VAs) homogeneously throughout the plough layer (Bailey, 2015). The plough layer depth in the Vecht catchment is estimated at 0.25 m for arable land based on common ploughing depths (Conijn and Lesschen, 2015, Martínez-Carballo et al., 2007) and at 0.075 m for grassland based on the typical shallow fertilizer injection depth (Saeys et al., 2008). Adding a fertilizer load increases the soil mass which is modelled via an increased soil profile depth. This is determined based on the liquid and solid fertilizer mass load, their densities (1000 kg m^{-3} and 1400 kg m^{-3}, respectively (Bailey, 2015)), and the agricultural area. As the plough layer depth

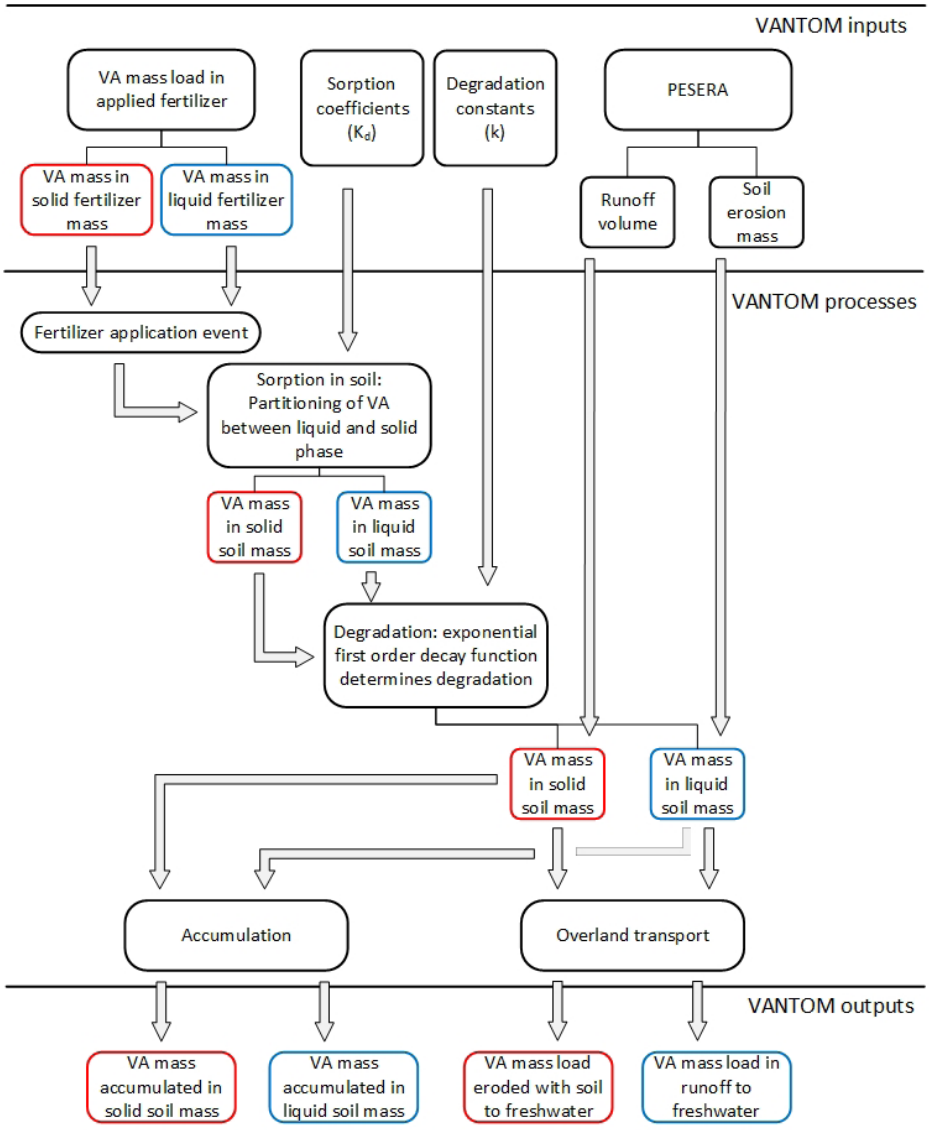


Figure 3-1. Conceptual overview of the VANTOM model, distinguishing between model inputs, processes, and outputs. Veterinary antibiotic (VA) masses in solid form are labelled red, VA masses in liquid form are labelled in blue, adapted from Bailey (2015).

remains constant, the sub-plough layer increases by the depth of added fertilizer. The initial depth of the sub-plough layer - that purely serves the conceptual model setup - is set at 2 cm as suggested by Bailey (2015).

VA sorption: In VANTOM, VA partitioning between the liquid and solid phase in the plough layer is determined by the soil sorption coefficient K_d in the linear sorption equation (Bailey, 2015):

$$\frac{VA_s}{M_s} = K_d \times \frac{VA_l}{M_l} \tag{3.1}$$

Where VA_s and VA_l are the VA masses in the solid and liquid phase respectively, M_s and M_l each represent the solid and liquid soil masses in the plough layer and K_d is the sorption coefficient.

VA sorption depends on several environmental and substance-inherent properties. Several studies investigated the dependence of VA sorption to soil on parameters such as ionic strength, initial VA concentration, soil pH or competitor ions in soil-water matrices (Figueroa-Diva et al., 2010, Figueroa et al., 2004, Kim et al., 2012, Kurwadkar et al., 2007, Teixidó et al., 2012); Wegst-Uhrich et al. (2014) expect environmental parameters to affect VA sorption most. Consequently, we obtained soil properties (by using soil maps for soil texture, pH and organic carbon content) for the study area to select appropriate sorption coefficients out of the wide range of K_d values found in literature (details in the Appendix B 1.3). The median value of sorption coefficients matching the catchment's soil characteristics was used as input for VANTOM. No K_d value could be found within the determined soil's pH range for amoxicillin, hence we selected the value nearest to the range of pH values. Table 3-1 lists the sorption coefficients adopted as input for VANTOM.

Degradation: Once in the soil matrix, continuous dissipation of the VAs starts, whereby biodegradation is the predominant process in aerobic soil conditions of agricultural land (Accinelli et al., 2007). VANTOM accounts for this degradation through an exponential decay function (Bailey, 2015):

$$VA_{rest}[v,c] = VA[v,c] \times e^{-k \times T} \tag{3.2}$$

Where $VA_{rest}[v,c,]$ is the VA mass remaining per soil mass type v (solid or liquid) and soil compartment c (plough layer or sub-plough layer) after degradation, VA is the VA load present as degradation begins, k is the degradation rate (by definition ln(2) divided by the antibiotic's half-life in liquid and solid soil), and T is the time step duration, during which continuous degradation occurs.

Literature reports multiple VA-specific half-lives in soil. Even though a comparison

among studies is difficult as conditions of their derivation are not always consistent (Bailey et al., 2016, Chen et al., 2014), we consider a literature review to obtain degradation parameters for VANTOM inputs as the most suitable option given the current state of knowledge. Hereby we include studies investigating VA dissipation in soil, not only those specifying biodegradation. A comprehensive list of half-lives (in soil for the VAs investigated) found in literature is displayed in the Appendix B 1.4. For this study, we considered the prevailing soil textures in the Vecht catchment (sand, sandy loam and loamy sand) and selected the highest half-life among these found in literature as a worst-case assumption. Identical half-lives were used for VAs in the solid and liquid phase. Due to lack of data, other potentially influential criteria (such as further soil characteristics, initial concentration or experimental setup) were not considered. The selected model inputs for half-lives are shown in Table 3-1.

Overland transport: In VANTOM, VA overland transport is modelled just before the end of a time step. Hereby liquid and solid mass loads that contain VAs, are transported to surface water (Bailey, 2015). VANTOM assumes that all liquid and solid soil mass loads transported over agricultural land in a sub-catchment end up in surface waters. These mass loads are determined from the PESERA estimates of soil erosion and surface runoff. The removal depth of solid soil from the plough layer is estimated based on the monthly erosion across agricultural land in the Vecht catchment (PESERA predicted an annual displacement of 96,000 t soil). The removal depth of liquid soil fractions is assumed constant with 5 mm as maximal erodible layer depth according to PESERA. The liquid soil load depends on the pore water levels at the beginning of each time step, which are based on PESERA's outputs for saturated deficits and the soil's porosity (Appendix B 1.5). VA loads moved through overland transport of liquid and solid soil mass loads are proportional to these and defined as:

$$VA_{rem}[v] = \frac{d_r[v]}{d_p} \times VA_{rest}[v,p] \tag{3.3}$$

Where $VA_{rem}[v]$ is the antibiotic mass load removed from the plough layer to surface water per soil mass type v (solid or liquid), d_r is the removal depth of the upper plough layer, d_p is the constant plough layer depth and VA_{rest} is the VA mass in the plough layer p after degradation.

At the end of a time step, all remaining soil and VA masses are used as inputs for the following time step. The VA loads to surface freshwater are determined every month by the VA overland transport and summed as annual VA loads.

3.2.5. Grey water footprints of veterinary antibiotics

To translate VA emissions into resulting water pollution, we use the GWF as an indicator. The GWF refers to the amount of freshwater required to dilute polluted water volumes to an extent that maximum acceptable concentrations are not exceeded (Hoekstra et al., 2011). In the context of pollution by pharmaceuticals, GWFs are defined as ratio of pollution load entering freshwater bodies L [kg yr^{-1}] to the compound-specific maximum acceptable concentration C_{max} [kg m^{-3}]. L is estimated using the above-described modelling approaches. For C_{max} the predicted no effect concentration (PNEC) is used (Martinez-Alcala et al., 2018, Wöhler et al., 2020b). PNECs were obtained from Bergmann et al. (2011) (Table 3-1). GWFs are determined individually for all investigated substances whereby the resultant GWF equals the largest GWF across the assessed contaminants (Hoekstra et al., 2011). We present GWFs on a temporal scale of one year for the Vecht catchment based on the manure load that is deposited in the area. To estimate GWFs per animal product produced in the catchment, we calculate a GWF based on the total animal products and VA loads produced, assuming identical fate and transport as the average in the Vecht catchment. Using these and following the methodology for water footprint of consumers by Hoekstra et al. (2011), we express GWFs per person, based on the average consumption of animal products produced in the Vecht catchment[4].

Table 3-1. Veterinary antibiotic's sorption coefficients (Kd) and half-lives (DT50) representative for soil conditions of the study area and used as VANTOM inputs (for more information see Appendices B 1.3 and B 1.4), predicted no effect concentrations (PNEC) used as maximum allowed concentration to derive grey water footprints.

Substance	K_d [L kg^{-1}]	DT_{50} [d]	PNEC [µg/L]<?>
Amoxicillin	5.0	1.0	0.0156
Doxycycline	1433.5	76.3	0.054
Oxytetracycline	1445.0	103.0	1.1
Sulfamethazine	4.6	21.2	1
Tetracycline	759.0	82.0	0.251

4 Average per capita consumption for Germany was obtained from Federal Ministry of Food and Agriculture (BMEL) (2019) and Federal Office for Agriculture and Food (BLE) (2019), for reference year 2017. Equivalent data for the Netherlands was obtained from Dagevos et al. (2020), Van Gelder (2021) and Jukema et al. (2020), reference year 2017 and 2013 for eggs.

3.2.6. Water pollution level in the Vecht catchment

The pressure on the Vecht (sub-)catchment's assimilation capacity brought about by GWFs are expressed as the water pollution level (WPL). The WPL represents the ratio of the GWF to the available runoff (both in $m^3\ yr^{-1}$) (Hoekstra et al., 2011). Runoff in this context is defined as the precipitation minus evaporation. Runoff data per sub-catchment was obtained as described by Wöhler et al. (2020b). WPLs>1 indicate violation of water quality standards.

3.2.7. Uncertainty analysis

Wöhler et al. (2020b) have already partly assessed model sensitivity by changing a number of inputs (i.e., VA amounts administered, excreted fractions, manure storage) and evaluated the effect on resulting GWFs. To additionally explore uncertainties related to the newly added VA fate and transport modelling steps in this study, we simulated two extreme scenarios that either reduce or increase VA emissions to freshwater bodies by changing selected VANTOM input parameters (number of fertilizing events, plough layer depth, sorption coefficients and degradation rates). Appendix B 1.6 presents further details of the uncertainty analysis.

3.3. Results

3.3.1. Total VA loads to freshwater

Within the Vecht catchment, the fraction of total administered VA mass load that reaches surface water is below 10^{-5} for all substances investigated. Figure 3-2 disaggregates this number by showing VA mass flows and load reductions for each of the processes and VA substances considered. We find that the average VA mass loss across VA substances due to metabolization is 45% (ranging from 15% to 93%). Degradation during manure storage leads to an average VA dissipation of around 80%, while an averaged 90% of VA loads applied to agricultural land degrade in the soil. The relatively long half-lives of doxycycline, tetracycline and oxytetracycline (in the order of months) result in soil accumulation of applied mass loads between 13% and 21%. Amoxicillin (DT_{50}=1 d) and sulfamethazine (DT_{50}=21.2 d), in contrast, degrade comparatively fast and thus hardly accumulate. Even though the total VA mass load administered in the German part of the catchment is more than double of that in the Dutch part, the aggregated VA

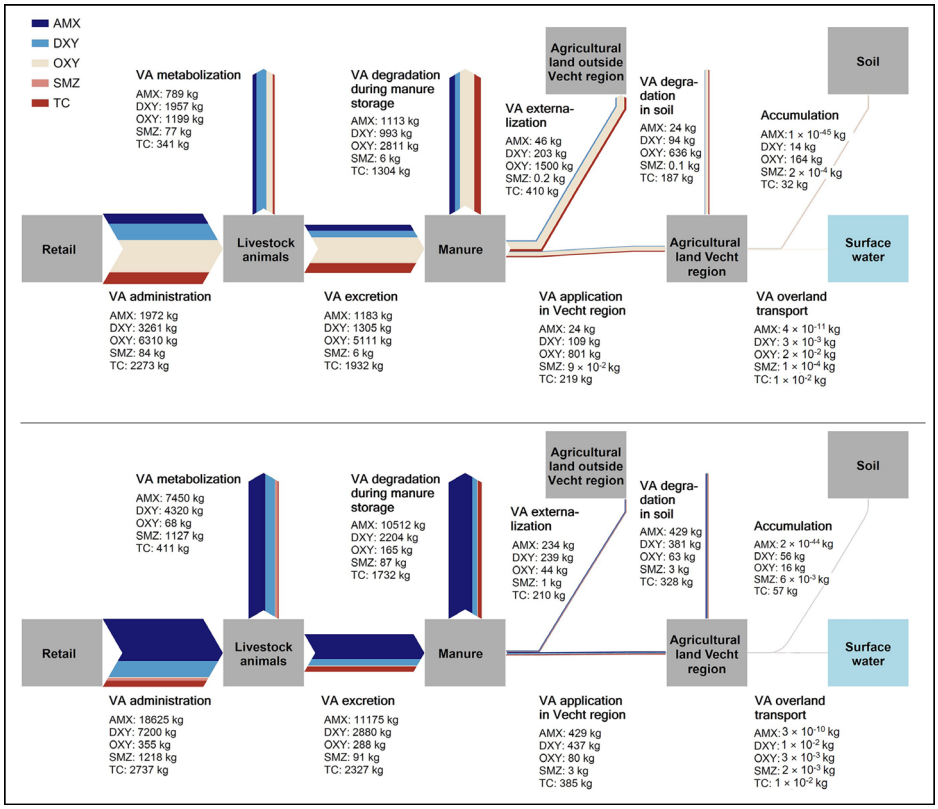


Figure 3-2. Annual veterinary antibiotic (VA) mass flows from administration to surface water emission in the Dutch (top) and German (bottom) part of the Vecht river catchment for the substances amoxicillin (AMX), doxycycline (DXY), oxytetracycline (OXY), sulfamethazine (SMZ) and tetracycline (TC).

mass load to freshwater is comparable (annually 38 g and 30 g in GE and NL respectively). The accumulated VA mass load in GE is 130 kg, in NL 210 kg. This is a result of comparatively high administration of fast-degrading substances in GE, whereas major fractions of VAs administered in NL are degrading slowly.

3.3.2. Grey water footprints

For both, the German and Dutch part of the Vecht catchment, doxycycline is the most critical substance, resulting in an estimated total GWF of 251,000 m^3 yr^{-1}, with the German part contributing 81%. Despite a larger agricultural area in the Dutch part of the catchment, contributions from GE to the GWF are dominant for all VAs except oxytetracycline. The main reason for this is significantly larger VA mass loads per ton of applied manure leading to a larger total applied VA mass load (in NL for oxytetracycline, in GE for all other VAs).

Comparing across livestock sectors, we find that the largest GWFs emerge from beef cattle, followed by pigs, dairy cattle, broilers, and laying hens. The Appendix B 2.1 provides GWFs per VA and livestock sector for the entire catchment, as well as for the German and Dutch parts.

GWFs related to animal products are presented in Table 3-2. Besides the local pollution in the catchment, product-related GWFs also include externalized VA emissions – assuming GWFs per unit emission to be as in the Vecht catchment. Beef meat produced in the German part of the catchment has the largest GWF (9.2 L kg^{-1}) whereas in the Dutch part, pig meat has the largest GWF (1.5 L kg^{-1}). Except for pig meat (where the produced meat to number of pigs ratio is significantly smaller in NL compared to GE), all products show larger GWFs in GE than in NL.

Translating our results to a consumption perspective, we find that the average VA-related GWF of German and Dutch consumers of animal products produced in the Vecht catchment is 159 L yr^{-1} and 75 L yr^{-1}, respectively. These GWFs are only 1% of those found in a previous study by Wöhler et al. (2020b), which can be explained by their precautionary assumption that all emissions to agricultural land end up in freshwater.

Table 3-2. GWFs of the veterinary antibiotics substances amoxicillin (AMX), doxycycline (DXY), oxytetracycline (OXY), sulfamethazine (SMZ) and tetracycline (TC) per unit of animal product, assuming Vecht catchment specific emissions, differentiating between the German (GE) and Dutch (NL) part of the catchment.

Animal product	Unit	AMX		DXY		OXY		SMZ		TC		GWF[a]		Total WF[b]
		GE	NL	GE	NL	GE	NL	GE	NL	GE	NL	GE	NL	
Beef meat	L kg^{-1}	3.5×10^{-9}	2.3×10^{-10}	9.17	9.7×10^{-1}	1.5×10^{-1}	6.6×10^{-1}	4.8×10^{-3}	5.3×10^{-4}	1.6	3.4×10^{-1}	654000	148000	15000
Milk	L kg^{-1}	2.2×10^{-10}	5.6×10^{-11}	1.4×10^{-3}	5.5×10^{-4}	9.0×10^{-5}	1.5×10^{-3}	0	0	3×10^{-2}	2.5×10^{-2}	15000	11000	1000
Pig meat	L kg^{-1}	9.3×10^{-8}	1.8×10^{-7}	4.6×10^{-1}	1.46	3×10^{-3}	3.7×10^{-1}	0	0	1.3×10^{-1}	8.4×10^{-1}	51000	212000	6000
Chicken meat	L kg^{-1}	1.0×10^{-7}	1.3×10^{-8}	1.7×10^{-1}	1.4×10^{-1}	0	0	2.9×10^{-2}	1.8×10^{-3}	6×10^{-2}	2.5×10^{-2}	15000	140	4000
Egg	L kg^{-1}	1.4×10^{-8}	5.4×10^{-9}	1.1×10^{-1}	5.9×10^{-2}	0	0	6.8×10^{-3}	1.3×10^{-3}	6.8×10^{-2}	8.4×10^{-2}	2000	500	3000

[a] *VA-related GWFs resulting from previous, precautionary estimates, source: Wöhler et al. (2020b)*
[b] *Water footprint (WF) excluding VA-related GWF, source: Mekonnen and Hoekstra (2012)*

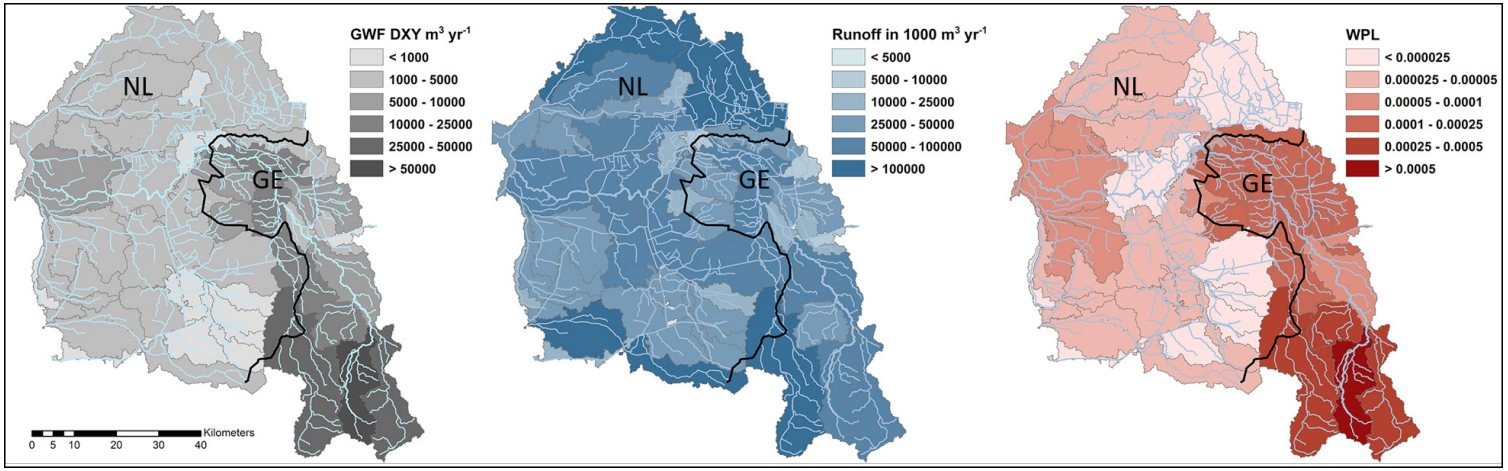


Figure 3-3. GWFs of the most critical substance doxycycline (DXY) (left), available runoff (middle) and water pollutant level (right) per sub-catchment in the Vecht catchment.

3.3.3. Water pollution level in the Vecht catchment

With an average of approximately 2 billion m^3 yr^{-1}, the catchment's available runoff exceeds the total VA-related GWF of 251,000 m^3 yr^{-1} by a factor 8,000. This implies that for the catchment as a whole, water quality standards are not violated due to VA emissions. Also at the level of the sub-catchments, this result holds: no sub-catchment's WPL exceeds 1. For the most critical substance doxycycline, Figure 3-3 shows the GWF, available runoff, and resulting WPLs at sub-catchment level. Both, underlying data and sub-catchment specific GWFs for the other VAs are provided in the Appendix B 2.2.

3.3.4. Uncertainty analysis

The IMA contains several uncertainties that may affect results. For the most critical substance doxycycline we find that the GWF-related uncertainty ranges across three orders of magnitude: from the lowest extreme GWF of 3,600 m^3 yr^{-1} to the highest of 6,491,000 m^3 yr^{-1} on catchment level. Also this maximum GWF would not exceed the catchment's available runoff. The uncertainty range is largest for amoxicillin, spanning 14 orders of magnitude between the least and most conservative estimate. Uncertainty ranges this wide indicate that input data and assumptions have significant effects on the results. All substances' uncertainty ranges (for GE and NL) are illustrated in Figure B5. We attribute the wide uncertainty ranges largely to the weak or absent empirical data base, emphasizing the need to increase monitoring and data collection efforts.

This observation corresponds with conclusions by Wöhler et al. (2020b), who carried out a sensitivity analysis for processes and inputs that were also used in the presented IMA. The authors concluded that GWFs can especially differ when changing multiple input parameters at the same time. Their assessment further showed that GWF results are particularly sensitive to the chosen PNEC (Wöhler et al., 2020b). This also applies for the present research. When diagnosing individual parameters' contributions to the extreme ranges of this study's uncertainty analysis, we found the overall largest influence for the lower uncertainty range from the minimum half-lives, changing the outcome by 12 orders of magnitude at maximum. The influence of other parameters is substance dependent. For the most critical substance doxycycline the parameters' effects on the lower uncertainty range are ranked as follows: maximum sorption coefficient > plough layer increase > decrease of fertilizer events. When assessing the upper uncertainty range, all parameters' influences is substance dependent. For doxycycline the maximum half-life is dominant, followed by the minimum sorption coefficient, the plough layer decrease and the increase of fertilizing events.

3.4. Discussion

3.4.1. Limitations

We developed an IMA to estimate VA loads to the aquatic environment and their associated GWFs and WPLs for the Vecht catchment. Since the IMA relies on a series of models that simplify reality, we did not capture all processes and facets that are relevant in estimating loads, GWFs, and WPLs. For VA administration, the first step of our IMA, limitations emerge from data availability. This study investigated five VAs that were selected based on their use at large quantities and data availability. There are however around 900 different active pharmaceutical ingredients registered for veterinary use (Lahr et al., 2019). Except for a selection of VAs, sales data for livestock administration is not available. Also the data's differences in reference year or spatial resolution might lead to inaccuracies. Moreover, information on farm type specific pharmaceutical use is lacking (Wöhler et al., 2020a), which makes it impossible to account for different farming systems when modelling pharmaceutical administration. Thus, we were not able to present GWFs of animal products distinguishing between production conditions.

To model VA excretions, information on the substances' excreted fractions that can depend on e.g. administration form or different livestocks' metabolisms (Kemper, 2008) are required. Also in this second step of the IMA, limitations were found in data availability. Due to lacking comprehensive VA excretion data for livestock, such of the human metabolism were used. Besides, VA's metabolites are not considered in this study - and consequently also not their potential re-transformation into the parent compound (Lamshöft et al., 2010). This might lead to an underestimation of GWFs.

The IMA's third step models VA degradation in manure, whereby only biodegradation is assumed. However, other processes such as photodegradation or hydrolysis are able to influence VA dissipation as well (Kümmerer, 2008, Wolters and Steffens, 2005). For biodegradation a first-order decay of VAs is assumed, which is commonly done to model pharmaceutical degradation (see e.g. Boxall et al. (2014) or Lämmchen et al. (2021)). Different experimental studies however found that, depending on the substance and experimental conditions, decay kinetics better fitted adjusted degradation models (cf. Blackwell et al. (2007), Wang and Yates (2008)). This indicates that the assumption of a simple first order decay could warrant further scrutiny in the future.

In step four of the IMA (the VANTOM model) we encountered several limitations - some of methodological nature, others result from choices made to demonstrate the IMA for the Vecht catchment.

- First, the model setup with a monthly time step at the spatial resolution of sub-catchments is relatively coarse. We were therefore not able to capture temporal emission peaks (that can result from rainfall-driven transport instantly after fertilizing events (Stoob et al., 2007)) nor spatial components (such as distances to surface waters).

- Second, we selected a modelling period of one year and assumed no VAs presence in its start. However, as results showed that three of the five VAs accumulated in the soil by the end of the modelling period, this assumption might lead to an underestimation of GWFs. If, for instance, all accumulated doxycycline would end up in water, its GWF would increase by a factor 5.

- Third, direct VA excretion by grazing animals to pastures is not considered. Since these VAs do not degrade during manure storage, our approach possibly underrates VA emissions to agricultural land.

- Fourth, lacking empirical data on manure application led to simplifying assumptions when modelling fertilizing events, such as our assumptions that manure from different animal types is equally distributed over the agricultural land or that ploughing and injecting are the only manure application practices available. Neglected techniques such as broadcasting potentially lead to more VA overland transport than modelled for the Vecht catchment. Their use is highly restricted, however, in both, GE and NL (Backus, 2017, Federal Ministry of Food and Agriculture (BMEL), 2017).

- Fifth, choices were made when selecting sorption coefficients and half-lives in soil. For both, selected catchment's soil characteristics were considered, other potentially influential aspects such as temperature or level of microbial activity (Mehrtens et al., 2020, Wang and Yates, 2008) were neglected. While a median for sorption coefficients matching the catchment's characteristics was selected, a sparser data basis on half-lives led to a precautionary choice, assuming the highest value matching the catchment's prevailing soil texture. Latter might underestimate degradation. Further, abovementioned limitations for VA degradation in manure also apply to the modelled degradation in soil.

- Sixth, VANTOM does not model VA losses from plant uptake, which can differ substantially among substances and crops (Boxall et al., 2006).

- Seventh, VA loads transported to freshwater via subsurface flow and leaching are not included in VANTOM. Although Spielmeyer et al. (2020) concluded from their monitoring study that VAs are mostly fixed in the plough layer, VA leaching to groundwater was found possible. Kay et al. (2004) confirm the importance of leaching when they report about VA transport to subsoils through cracks and worm channels. The fact that multiple studies have found VAs in leachate (Blackwell et al., 2009, Kivits et al., 2018, Spielmeyer et al., 2020) indicates that ignoring leaching in the IMA may lead to underestimations of GWFs. The mentioned studies indicate diverse leaching potentials for different VAs based on their mobility. VAs with high sorption potential are less prone to leaching.

- Eighth, it should be noted that VANTOM has not been validated due to insufficient monitoring data. Bailey (2015) recommends a model validation for a study area where VA application and fate is precisely surveyed to compare modelled and monitored VA mass balances.

All described limitations potentially influence the GWF and WPL. As mentioned, the neglection of processes might result in an underestimation of VA loads to freshwater, whereas precautionary choices potentially lead to overestimation. For limitations concerning data availability, effects on the results remain largely unknown. There is currently no data available that allows to validate an integrated modelling approaches that covers the entire pharmaceutical lifecycle. We recommend such analysis to be conducted in the future.

3.4.2. Results in perspective

When applying VANTOM across Germany, Bailey (2015) found VA fractions to freshwater at 0.15% of the applied mass loads for sulfamethazine and tetracycline. For the Vecht catchment, we find values in the same order of magnitude for sulfamethazine. For all other VAs, fractions are yet smaller. These small fractions are consistent with model predictions by Hanamoto et al. (2021) and experimental results by Stoob et al. (2007) or Kay et al. (2005), who respectively estimated less than 1% and maxima of 0.5% and 0.4% of the applied VAs reaching surface waters.

For three of the investigated VAs substantial fractions were found to accumulate in soil (13% to 21% of the applied mass load). Bailey's (2015) fractions for VA accumulation are notably larger, resulting from the assumption of no degradation in solid soil. Here we assumed a degradation of adsorbed VAs as well (even though

under real life conditions degradation only occurs in the liquid phase) to account for degradation of desorbing VAs due to sorption equilibria during one time step. Even though the IMA does not evaluate VA-related soil pollution, accumulating VAs (even at very small concentrations) might pose environmental and human health risks in the Vecht catchment due to associated environmental antibiotic resistances. In their review Williams-Nguyen et al. (2016) discuss the observed increase of antibiotic-resistant bacteria in soil when applying VA-containing manure.

The Vecht catchment's total VA-related GWF in this study was found to be 5 orders of magnitude smaller than the precautionary estimate as well as the GWF of human pharmaceuticals by Wöhler et al. (2020b). Examples showing the minor importance of surface water pollution from applied livestock manure when comparing human and veterinary pharmaceuticals exist from around the globe (Hong et al., 2018, Ramírez-Morales et al., 2021, Reis-Santos et al., 2018). When including our VA-related GWF to the total WF of different animal products, these would increase by 0.02% on average. However, the present study assessed GWFs only for surface waters resulting from VA overland transport. Including groundwater pollution would likely increase VA-related GWFs, especially in regions with intensive livestock farming (Kivits et al., 2018) and for mobile substances such as sulfamethazine (Kim et al., 2010) - one VA that has been found in the Vecht catchment's aquifer (Karfusehr et al., 2018). The detection of VAs in groundwater, which had been applied years or decades ago (Kivits et al., 2018, Spielmeyer et al., 2017) highlights the relevance of this transport process.

3.5. Conclusion

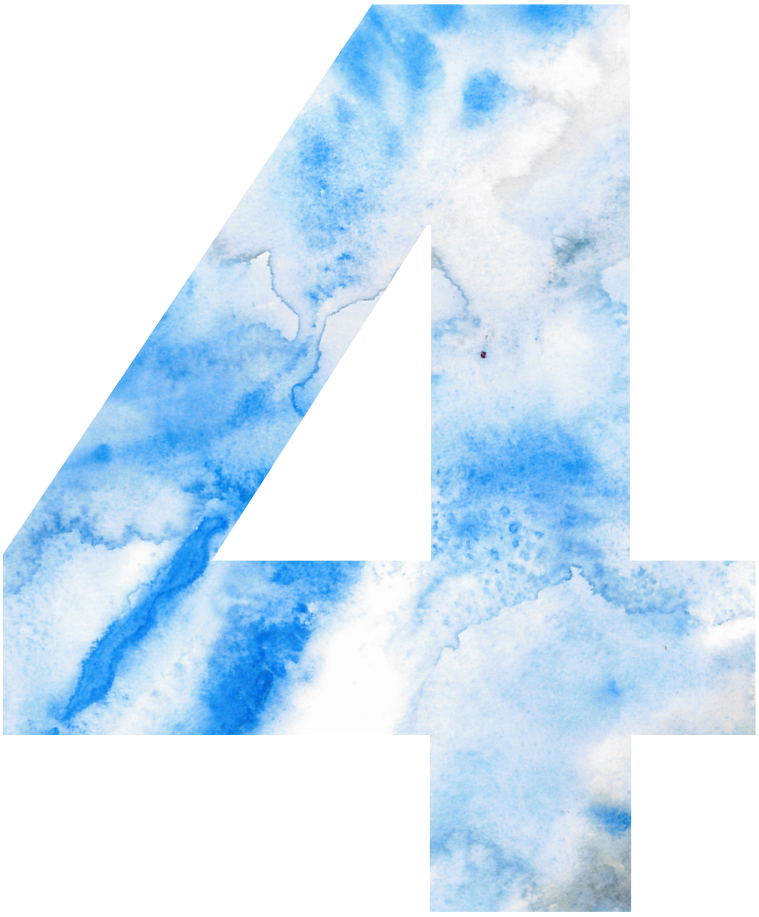
The IMA presented is the first approach to integrate modelling of VA administration, excretion, degradation in manure, fate and transport after field application, and translating obtained loads to GWFs and WPLs. The demonstration of the IMA to the transboundary Vecht catchment refines previous precautionary estimates of VAs' GWFs by including a VA fate and transport model, resulting in significantly smaller VA freshwater loads and GWFs. The present study shows that VA mass loads reduce by over 99% from administration to surface water emission. Doxycycline showed the largest GWF, amounting to 251,000 m^3 yr^{-1} within the Vecht catchment. Since this GWF does not exceed the catchment's available annual runoff, WPLs remain within acceptable water quality standards. However, WPLs >1 might still occur locally and/or temporarily, but are not captured in this study due to the chosen temporal and spatial resolution. 50% of the VA load – and subsequent

GWFs - produced in the Vecht catchment are externalized due to manure exports. GWFs per animal product (including externalized VA emissions) resulted highest for beef meat (9.2 L kg^{-1}) and pork (1.5 L kg^{-1}) in GE and NL respectively.

The uncertainty assessment reveals that GWFs can range over several orders of magnitude, but it remains unclear to what extend assumptions for and neglections of different processes can be influential. The evidence of VAs in groundwater leads to the suspicion that including VA leaching is likely to increase GWFs, especially those of mobile substances. The pollution resulting from VA accumulation in soil (up to 21% of the applied mass load) is not captured in the GWF assessment. Besides ecotoxicological effects in soil, the VA-associated risk of emerging antibiotic resistances stresses the need to include this process in future assessments.

The findings of this study indicate that VAs transported overland cause minor GWFs compared to those of human pharmaceuticals reaching surface waters. Yet, the severity of VA pollution in other environmental media (e.g. soil and groundwater) remains uncertain. This along with the increasing trend of global livestock production and resulting predicted increase in VA use, illustrates the importance to further investigate VA fate and transport to gather a robust basis for decisions on environmental sustainability and protection of freshwater resources in the future.

CHAPTER FOUR



WATER POLLUTION FROM PHARMACEUTICAL USE IN LIVESTOCK FARMING: ASSESSING DIFFERENCES BETWEEN LIVESTOCK TYPES AND PRODUCTION SYSTEMS

Water pollution from pharmaceutical use in livestock farming: Assessing differences between livestock types and production systems

Abstract

Livestock production is considered as major source of pharmaceutical emissions to the environment, causing pollution of different environmental media. The current scientific discourse is focusing on measuring and modelling these emissions as well as assessing their risks. While several of these studies evidence pollution resulting from livestock farming, differences in pollution between livestock types and production systems are largely unknown. In fact, there is no comprehensive analysis of factors that influence pharmaceutical use in the diverse production systems. To address this knowledge gap, this research develops a framework to investigate pharmaceutical pollution from different livestock production systems based on a systematic identification and compilation of factors that influence pharmaceutical pollution in its different lifecycle stages (from administration to the environment). Using the developed framework, a first pilot assessment is conducted for selected indicator substances, covering antibiotics, antiparasitics, hormones and NSAIDs. Both the framework development and the pilot assessment base on interviews (conducted in Germany and the Netherlands) and on literature. The analysis shows that factors across a pharmaceutical's entire lifecycle influence pollution. However, not all of them are livestock type or production system dependent. The pilot assessment reveals that differences in pollution potential between conventional and organic production exist, but for antibiotics, NSAIDs (and partially antiparasitics) some factors lead to higher pollution potential in conventional, others to higher pollution potential in organic systems. For hormones we identified a comparatively higher pollution potential from conventional systems. Among the investigated indicator substance, the assessment over the entire pharmaceutical lifecycle illustrated that flubendazole in broiler production has the highest per unit impact. The framework (and first insights from the pilot assessment) are useful to identify which substances, livestock types, production systems, or the combination thereof has high or low pollution potential. This knowledge can lead to best practice policy recommendations for agriculture and sustainability.

4.1. Introduction

Pharmaceuticals in the environment have gained increasing attention over the past decades as they pose ecotoxicological risks, appear in drinking water as well as in food products and are associated with antimicrobial resistance development (Aus der Beek et al., 2015, Boxall et al., 2006, Hoelzer et al., 2017, Leung et al., 2013, Singh et al., 2019). Global antibiotic use in livestock agriculture is estimated with thousands of tons per year, showing an increasing trend (Van Boeckel et al., 2015). Even though the EU prohibited the use of veterinary antibiotics as growth promoters in 2006 and overall sales in Europe decline, purchases of over 6,000 tons were reported in 2018 (European Commission, 2005, European Medicines Agency, 2020). In Germany and the Netherlands (the geographical setting of this study), antibiotic use has been decreasing due to different policies (Mevius and Heederik, 2014, Wallmann et al., 2018). Yet, antibiotic use in livestock remains substantial, amounting to hundreds of tons per year (SWAB, 2021, Wallmann et al., 2018). The application of other pharmaceuticals (e.g. antiparasitics or hormones) in livestock remains largely unknown as there are no comprehensive datasets available (Di Guardo and Finizio, 2017). Additionally, comprehensive information on veterinary pharmaceutical use differentiated between livestock types or farm characteristics is lacking (Wöhler et al., 2020).

Several attempts to assess pharmaceutical (mostly antibiotic) environmental pollution from livestock animals have been made. These cover risk assessment methods, modeling approaches or experimental studies, e.g. Bailey (2015), Jaffrézic et al. (2017), Kay et al. (2005), Kivits et al. (2018), Menz et al. (2015) or Wöhler et al. (2021), and mostly aim to evaluate the environmental status and impact of pharmaceutical emissions. Despite the evidence of pharmaceutical pollution from livestock production which is shown by these studies, none differentiates pharmaceutical pollution between alternative livestock production systems. Gaining insights about the influence of production systems' characteristics on pharmaceutical pollution is however crucial to evaluate if and how pollution from the various livestock types and production systems differ. Identifying such differences is important to provide policy makers with recommendations for less polluting agricultural systems.

In the EU all agricultural activities are regulated by the Common Agricultural Policy (CAP) - independent of production system or livestock type. Launched in 1962, the CAP had the primary goals of securing food provision to EU citizens and fair living standards for farmers (European Comission, 2020). This policy focus along with the development of artificial fertilizers has led to an intensification of Europe's agricultural systems (van Zanten et al., 2014). Agricultural intensification and farm

expansion has developed further due to CAP reforms and a competitive global market for agricultural goods (van Zanten et al., 2014). However, several environmental impacts such as greenhouse gas emissions, land use degradation or water pollution have been associated with intensive (livestock) farming over the past decades (Ilea, 2009). To tackle these, recent policy reforms aim at the sustainable development of the agricultural sector. This includes a "greening" of the CAP and the adoption of the farm to fork strategy as part of EU's green deal (European Commission, 2019, Nazzaro and Marotta, 2016). The farm to fork strategy specifically mentions the aim to reduce antibiotic use to combat antimicrobial resistance; other pharmaceutical substance groups are not mentioned. The "greening" development of agricultural policies goes in hand with a growing societal demand for sustainable animal products (Lebacq et al., 2013) and increasing organic production (European Commission, 2020a). Organic farming is classified by EU's Council Regulation No 834/2007/EC on organic production and labelling of organic products[2] (European Commission, 2020b) and aims at combining food supply with environmental preservation, whereby pollution prevention of freshwaters is particularly addressed. Veterinary pharmaceutical use is not prohibited, but restricted in organic agriculture.

Policies regulating veterinary pharmaceutical use and pollution are the EU strategic approach to pharmaceuticals in the environment, the EU regulation 2019/06 on veterinary medicinal products and EU regulation 2019/04 on the manufacture, placing on the market and use of medicated feed. While former recognizes livestock as a source of pharmaceutical pollution, proposing different areas of action, the two latter focus mostly on the veterinary pharmaceutical market and supply chain. Environmental relevance of pharmaceuticals is only mentioned as side aspect, e.g. the required environmental risk assessment for authorization of medicinal products. None of the policies relate pharmaceutical pollution to different livestock production systems.

While several researches aim to elucidate on what terms livestock production systems differ in their sustainability performance and what causes these differences (e.g. Boggia et al. (2010), Clark and Tilman (2017), de Vries et al. (2015), Pirlo and Lolli (2019), van der Linden et al. (2020)), these assessments all together neglect pharmaceutical pollution. Consequently, we diagnose that research on pharmaceuticals in the environment overlook the interrelation with production systems, while studies presenting sustainability assessments of production systems do not include pharmaceutical pollution. Therefore, we aim to investigate pharmaceutical pollution from different livestock systems. We do that by developing a framework, based on a systematic identification and compilation of factors that influence pharmaceutical pollution

2 A new regulation is planned to come into force in 2021, but might be postponed to 2022.

in its different lifecycle stages and by applying that framework in a pilot assessment.

To accomplish these objectives, we first select different livestock types and production systems. Next, we develop a framework to assess pharmaceutical pollution from different livestock production systems along the consumption-related pharmaceutical lifecycle (excluding pollution occurring before pharmaceutical administration, i.e. from manufacturing). We assume that major differences exist in the administration, where at the same time the largest knowledge gaps exist. We therefore specifically target at this lifecycle stage. We apply the framework in a pilot assessment to gain first insights on differences in pharmaceutical pollution among livestock production systems, which can serve as policy recommendations relating to agriculture and sustainability. Both, the framework development and the pilot assessment, base on expert interviews conducted in Germany and the Netherlands and on a literature review.

4.2. Methods and data

4.2.1. Selection of livestock types and production system categories

To arrive at a categorization of livestock types and production systems that is useful for the application of our framework, we define a set of desirable categorization properties. First, they need to differentiate livestock types and production systems on their usage of and practices concerning veterinary pharmaceuticals. Second, the categories ideally would be sufficiently homogeneous in aspects relevant for veterinary pharmaceuticals to characterize with modest ambiguity. Third, the categories need to be sufficiently traceable in statistics to allow an operationalization of the assessment. For the selection of categories we conducted a literature review.

For livestock types, Eurostat (2021) describes beef cattle, dairy cattle, pigs, broiler chicken and laying hens as the most dominant livestock types for the German and Dutch context (Eurostat, 2021). These categories are (largely) overlapping with those published in the context of antibiotic use in Germany the Netherlands (Van Geijlswijk et al., 2018, Wallmann et al., 2018). We therefore consider this livestock type categorization suitable for our assessment. A description of livestock sectors in the EU, Germany and the Netherlands that gives background information is given in Appendix C 1.1.

For selecting livestock production systems manifold categorizations exist in literature. For example, intensive (Ilea, 2009) and extensive (Delattre et al., 2020) livestock farming, precision livestock farming (Hartung et al., 2017), multi-species livestock farming (Martin et al., 2020) or integrated crop-livestock farming (Moraine

et al., 2014)). These categories do however not base on any regulatory indicators and are mostly defined in the context of individual studies, fitting the according research purpose and setup. A categorization scheme that is frequently used for statistical analysis of farming structures in the EU are farm typologies. The approach roots in pure economic reasoning as it originates from the time where EU's agricultural policies targeted profitable production (Andersen et al., 2007). Andersen et al. (2007) argue that an environmentally based extension to farm typologies is essential for environmental assessments that should give grounds for today's and future policies. One legally certified difference in production systems exists in the EU, which is between organic and conventional (non-organic).Organic farming is regulated by the EU's Council Regulation No 834/2007/EC on organic production and labelling of organic products[3] (European Commission, 2020b). Various standards for livestock production are set out in the regulation. These cover the origin of the animal, husbandry practices and housing conditions, breeding, feed, disease prevention and veterinary treatment as well as cleaning and disinfection. The overall focus of best environmental practices, protecting natural resources and high animal welfare standards is reflected in these standards. Pharmaceutical use is touched upon in the criteria for breeding and disease prevention and veterinary treatment. Former prohibits the use of hormones and other substances to control reproduction. Latter regulates the use of allopathic medicinal products, which is only permitted for disease treatment. Restrictions and accompanying measures such as an extended withdrawal time apply in this case and are defined in EU regulation 889/2008 on rules governing organic production, labelling and control (European Commission, 2020b). To assure consistency among member states, national legislation defining organic farming is not permitted (Früh et al., 2014). Every farming type that is not covered by this regulation is considered conventional.

Summarizing, in this research we differentiate between the five different livestock types beef cattle, dairy cattle, pigs, broilers and laying hens as dominating livestock types in the countries of investigation. Given that a proper categorization between production systems which is meeting abovementioned requirements is lacking, we select the distinction between organic and conventional production systems as existing, legally defined classification to be used in our environmental assessment focusing on pharmaceutical pollution. For each combination of livestock type and production system we investigate factors of influence to pharmaceutical pollution.

3 A new regulation is planned to come into force in 2021, but might be postponed to 2022.

4.2.2. Framework development

To develop a framework for assessing pharmaceutical pollution from different production systems, we followed the logic of the consumption-related pharmaceutical lifecycle (see e.g. Slana and Dolenc (2013). This means that we distinguish pollution phases along the pharmaceutical lifecycle from administration in livestock to the environmental impact, as illustrated in Figure 4-1.

For each of the lifecycle stages administration, metabolization and consequent excretion, pharmaceuticals in manure, pharmaceutical application to agricultural land, pharmaceutical's environmental behavior and pharmaceutical's environmental impact, we sketch what factors influence the pharmaceutical load and pollution, and if these factors differ among livestock types and production systems. By definition, some of the lifecycle stages are purely substance-dependent and therefore independent of their source.

The framework is developed based on the rationale of cause-effect, investigating for each stage of the lifecycle, what factors cause (or inversely avoid) pharmaceutical loads and consequently pollution. Cause-effect relationships are a common rationale to ground frameworks for environmental assessments (see e.g. Cormier and Suter (2008), Niemeijer and de Groot (2008), Mourhir et al. (2016), Rugani et al. (2019)). Understanding the dynamics between social and environmental systems is pivotal for environmental assessments that often aim to serve (environmental) policies (Binder et al., 2013, Bodde et al., 2018, Kelly et al., 2013). One of the most prominent frameworks including cause-effect relationships is the Driver-Pressure-State-Impact-Response (DPSIR) framework established by the European environmental agency (Kristensen, 2004). We used these existing frameworks and their rationale as an inspiration to create the first framework to assess pharmaceutical pollution from different livestock types and production systems.

While the identification of factors relating to the pharmaceutical administration are retrieved from expert interviews, factors concerning the other lifecycle stages are obtained from literature. Compiling this information leads to a framework that can be used to crosscheck which causes apply in different livestock types and production systems. If possible (i.e. if available data allows), the individual elements of the framework can be filled with quantitative data as well.

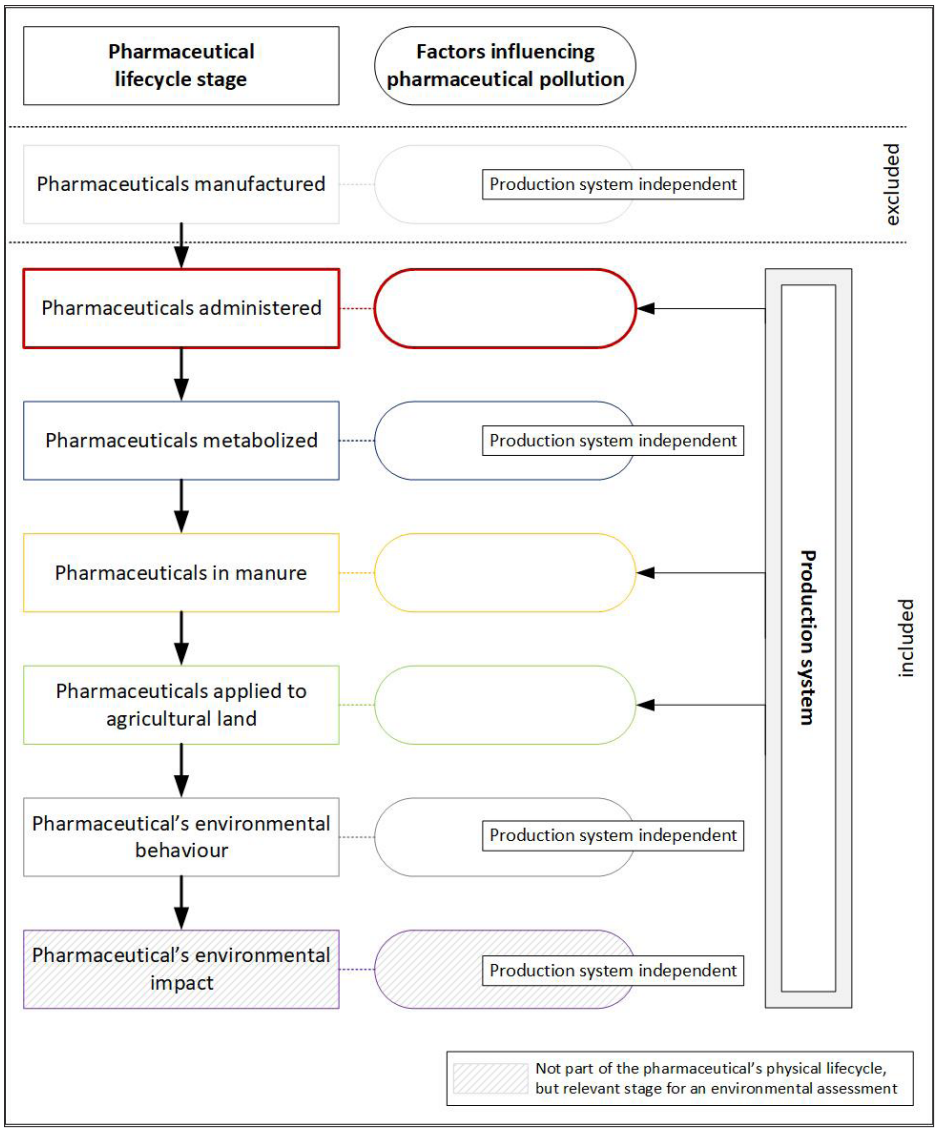


Figure 4-1. Conceptual setup for the framework development following the consumption-related pharmaceutical lifecycle.

4.2.3. Pilot assessment

For contextualization of the German-Dutch case adopted in the pilot study, we first give an overview of pharmaceutical use in German and Dutch livestock production systems – focusing on purposes and common practices of pharmaceutical appli-

cation. Following this overview, the pilot assessment is conducted. Hereto we fill the framework with information using data that is retrieved from both, interviews and literature. First, we present a qualitative comparison of pollution potential from pharmaceutical administration between conventional and organic production per substance group. Second, we conduct substance-specific pilot assessments for a set of indicator substances assessing all lifecycle stages of the framework. Indicator substances (most relevant in terms of quantity and/or frequency used) per substance group and livestock type are retrieved from the interviews. For the lifecycle stages administration, pharmaceuticals in manure and pharmaceuticals in manure applied to agricultural land the pollution potential resulting from each of the identified factors is (qualitatively) indicated per production system. The substance-specific rates for excretion, degradation in manure, the environmental behavior expressed as degradation in soil and the environmental impact threshold in terms of predicted-no-effect-concentration (PNEC) are indicated in quantitative terms (Appendix C 1.2). Note that (due to non-availability of data) a quantitative assessment of administered amounts per production system is lacking, even though considered relevant for a complete evaluation of the pollution potential.

4.2.4. Data collection

Data for both, the framework development and the pilot assessment, was collected in two ways: 1) reviewing pertinent literature, 2) conducting expert interviews. For the literature review peer-reviewed publications, grey literature and policy documents were thematically scanned for each of the lifecycle stages as well as for the description of livestock sectors and the overview of pharmaceutical use in Germany and the Netherlands. Expert interviews were conducted in a semi-structured format with German and Dutch livestock veterinarians. This choice was made because they have expertise about what influences pharmaceutical use and are having a representative overview of different farms and production systems. Through German and Dutch agricultural and veterinarian organizations/associations we identified relevant interviewees, namely veterinarians who specialized on different livestock types. Following the procedure of snowball sampling we consolidated the iterative process of interviewee identification and received further contacts. Snowball sampling is an established method to identify stakeholders in qualitative environmental research (Bendtsen et al., 2021). In total 31 veterinarians were contacted of which 14 ultimately gave an interview. Half of the interviewed veterinarians are based in Germany, the other half in the Netherlands. Six interviewees had a specialization in cattle (beef and/or dairy), four in pigs and four in poultry

(layers, broilers and turkeys). Three of them were (also) working as policy advisors. All interviews were conducted through video-calls in June and July 2021.

The semi-structured interview setup followed a pre-designed questionnaire, provided in the Appendix C 1.2. The questionnaire consists of five content-related sections that align with the research aims and method stated above: 1) general aspects about pharmaceutical use in livestock production systems; 2) factors and drivers influencing pharmaceutical use in livestock production; 3) differences in pharmaceutical use among livestock types and production systems; 4) indicator pharmaceuticals; 5) assessing the pharmaceutical lifecycle.

Based on audio-recordings all interviews were transcribed non-verbatim. The transcripts were coded using the atlas.ti software. Codes were created for a thematic analysis, following the questionnaire's setup. For instance, individual codes were created for factors influencing pharmaceutical use per livestock type. To compile the coded text passages, code reports were retrieved. From these reports information was extracted and analyzed. Following up on the example to thematically analyze influential factors, we for instance listed all factors named, and clustered them systematically. From veterinarians' judgement about how influential the named factors are in different production systems, the differences in pharmaceutical administration in diverse production systems was qualitatively assessed (in general and specifically for a set of indicator substances listed by the interviewees).

4.3. Results

4.3.1. A novel framework to assess pharmaceutical pollution from different production systems

Figure 4-2 illustrates the framework to assess pharmaceutical pollution from different livestock types and production systems for the pharmaceutical lifecycle stages: administration, metabolization, pharmaceuticals in manure, application to agricultural land, environmental behavior and environmental impact. While the factors that fill the framework for the stage of pharmaceutical administration result from the conducted interviews, factors for the other stages were obtained from literature. We differentiate between factors that potentially differ among livestock types and production systems and factors that are purely substance dependent and thus independent of their source. For the administration the framework shows collated factors mentioned for any livestock type. Not all factors are however relevant for all livestock types, see Appendix Table C2.

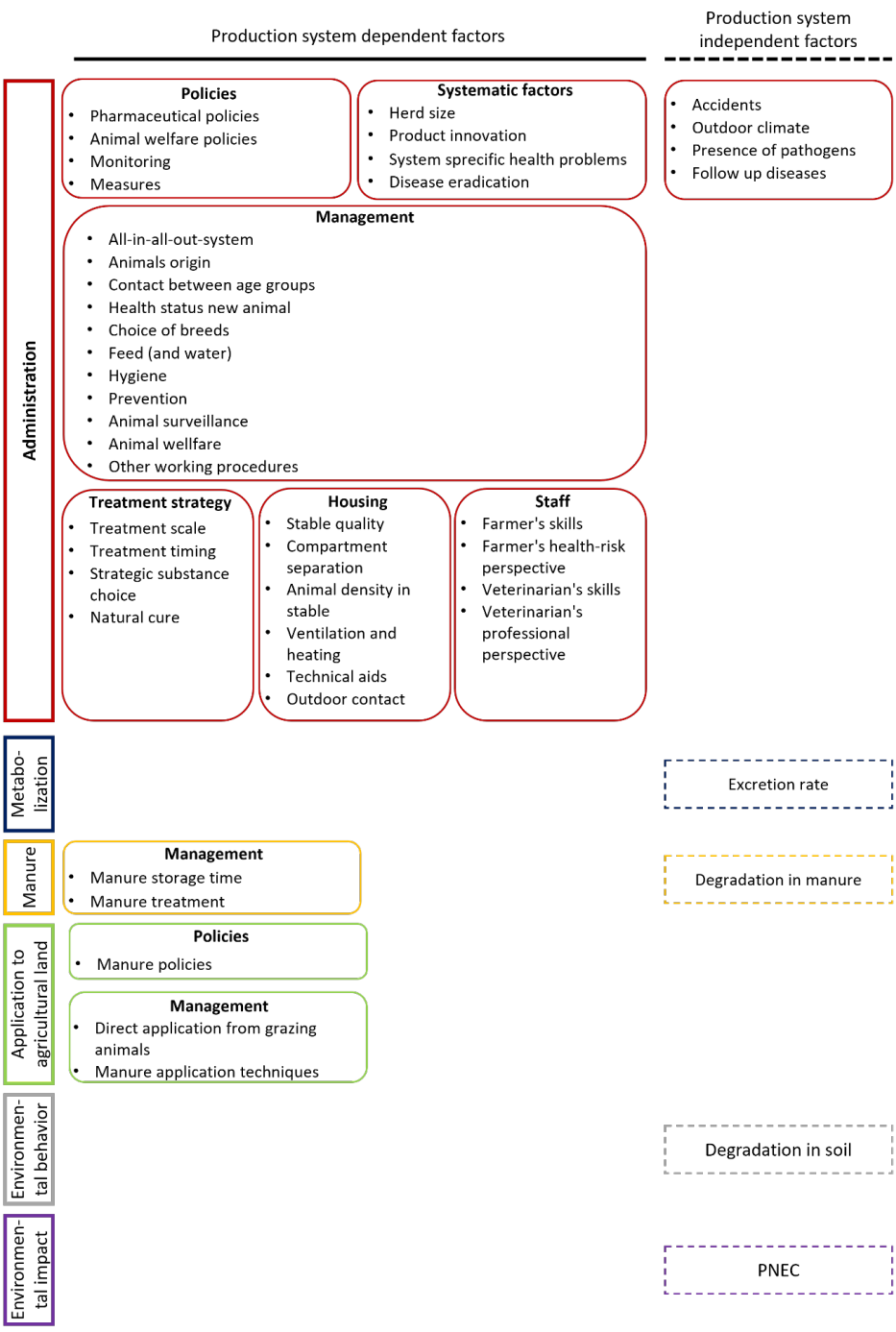


Figure 4-2. Framework illustrating identified factors that influence pharmaceutical pollution.

4.3.2. Pilot assessment

4.3.2.1. Purposes and common practices of pharmaceutical use in Germany and the Netherlands

In the EU veterinary pharmaceuticals are defined as veterinary medicinal products under directive 2001/82/EC and describe substances or a mixture of substances that diagnose, prevent or treat diseases, or that restore, correct or modify physiological functions in animals. The interviews revealed that for different livestock types pharmaceuticals with various functions are applied for diverse purposes. For prevention (especially in the context of viral infections) vaccines were considered of exceptional importance. Preventive treatment with antibiotics is restricted in both, Germany and the Netherlands (Köper et al., 2020, Speksnijder et al., 2015). The majority of interviewed veterinarians highlighted this, but explained that a metaphylactic use is possible. Especially in beef cattle (veal), pigs and poultry metaphylactic treatment is common practice due to typical housing situations of large herds. For veal and pigs veterinarians described the aim of treating the smallest unit possible, whereas this is hardly possible for poultry where herds typically consist of ten thousands of animals (in the case of non-transmittable sicknesses, affected poultry are generally selected for killing). To restrain disease entry and spreading, a synchronized all-in-all-out system per stable, farm or even region has been established in the pig and poultry fattening sectors. For all animal types (including dairy cattle), herd treatment exists for antiparasitic therapy.

Despite these practices, the interviewees described that most pharmaceutical use is to treat diseases once they have occurred. They outlined that veterinary stock controls are conducted for early disease detection. While in the Netherlands a veterinary-herd contract is mandatory (Bondt and Kortstee, 2016), it is common to have frequent veterinary stock controls in Germany as well. Yet, some farmers prefer to call veterinarians on demand only. According to the interviewed veterinarians, pertinent health issues occur across livestock's diverging life stages and body functions. In the dairy sector most pharmaceuticals are used in the context of calving and udder health. Here, generally individual cows are treated. Veals are specifically receptive for infections in the first weeks of their life. For pigs the breeding and piglet sectors are the most challenging for health management. Depending on the livestock type, the occurring diseases differ, and consequently also the applied substances. Table 4-1 presents an overview of commonly treated diseases per livestock type. A pharmaceutical substance group that is only minorly used to treat diseases, but mostly to modify physiological functions, namely the reproductive cycle, is hormones. To understand the relevance of different substance groups for the diverse livestock types, we also included an overview of such (based on the information from interviewees) in Table 4-1.

Table 4-1. Commonly treated diseases and applied substance groups for different livestock types (data based on interviews with veterinarians).

Livestock type	Cattle	Pig	Chicken
Commonly treated diseases	• Respiratory diseases (especially in calves) (e.g. bovine respiratory disease, pneumonia) • diarrhoeal diseases (especially in calves) • Parasites (e.g. worms, lice, cryptosporidium) • Metabolic diseases (e.g. Ketosis in dairy cows) • Lameness and claw problems • Udder infections, especially mastitis (in dairy cows) • Fertility problems (e.g. ovary-related diseases) (in dairy cows) • Milk fever (in dairy cows) • Abomasum displacement (in dairy cows) • Uterus infections (e.g. caused by trueperella pyogenes or E. coli) • Diverse disease-causing pathogens that occurred as secondary infection after a primary viral infection	• Respiratory diseases (e.g. pneumonia, bronchitis) • diarrhoeal diseases (especially in piglets) • Diseases of the central nervous system (e.g. meningitis caused by streptococcus suis) • Wound infections (especially in piglets) • Glässer's disease • Parasites (e.g. ascaris suum, coccidia, sarcoptes) • Fertility problems • Urinary tract infections • Diverse disease-causing pathogens that occurred as secondary infection after a primary viral infection (e.g. influenza, cicovirus)	• Bacterial infections of especially the respiratory tract or intestines (by e.g. pasteurella, E. Coli, enterococcus, staphylococcus, ornithobacterium rhinotracheale) • Parasites (e.g worms, coccidia) • Clostridiosis • Lameness • Footpad dermatitis • Erysipelas • Polyserositis • Diverse disease-causing pathogens that occurred as secondary infection after a primary viral infection (e.g. avian rhinotracheitis, marek's disease, infectious bursal disease)
Applied substance groups	• Antibiotics • Antiparasitics • Nonsteroidal anti-inflammatory drugs (NSAIDs) • Hormones (in dairy cows)	• Antibiotics • Antiparasitics • Nonsteroidal anti-inflammatory drugs (NSAIDs) • hormones	• Antibiotics • Antiparasitics

Over the past years, limiting the use of antibiotics has been in the focus of EU as well as German and Dutch national policies. Besides the EU-wide prohibition of antibiotics as growth promoters in 2006 (European Commission, 2005), a harmonized monitoring of veterinary antibiotic sales in European countries was requested by the European Commission in 2010 (European Medicines Agency, 2021). Köper et al. (2020) indicate that the implementation of a monitoring scheme alone has led to the reduction of antibiotic use in Germany. In 2014, a benchmarking system with consequent actions was the first mandatory measures to reduce antibiotic use in fattening farms (noting that the dairy livestock is excluded from this system). Between 2011 and 2018 antibiotic sales reduced by 58% in Germany (Köper et al., 2020). The Netherlands implemented step-wise antibiotic reduction targets from 2008 onwards; the latest goal is to reduce antibiotic use by 70% with reference to 2009 (Mevius and Heederik, 2014). This target was first reached in 2019, whereby reductions differ per livestock type (Groot et al., 2021). Antibiotics are not only regulated as substance group, but also per substance which interviewees mentioned potentially relevant for environmental pollution. One example are the categories of antibiotic use in livestock in the Netherlands (1st, 2nd, 3rd choice and prohibited substances) (Werkgroep Veterinair Antibiotica Beleid, 2021). The interviewed veterinarians mentioned that the preference to apply certain substances differs in the two countries as well.

4.3.2.2. Pharmaceutical pollution from different livestock types and production systems

Comparing administration of different substance groups: For the pilot assessment we first analyzed the conducted interviews to retrieve information about where the pollution potential for the various pharmaceutical substance groups differs between conventional and organic production per livestock type. We did this for each of the factors identified for the lifecycle stage of pharmaceutical administration and present these qualitative outcomes in Appendix Tables C5 to C9. The presented results are described as tendencies for pharmaceutical pollution and result from interviewee's precise statements or from combining logics of different interviews and assuming that some general statements about production systems apply to all livestock types. Yet, we were not able to fill in information for all factors. For interpretation of the results it is necessary to emphasize that several interviewees pointed out that even if there is a tendency, exceptions exists in all production systems with respect to most of the factors.

Comparing pollution potential for different livestock types shows that major differences exist in applied substance groups, i.e. no administration of hormones and NSAIDs in chicken. Also hormones are not considered relevant in the beef cattle

sector since all interviewees described that beef cattle originate from dairy farms. However, the sector description (Appendix C 1.1) shows that bovine meat is also produced in primary production and therefore also in these systems hormone use might exist. Furthermore, differences between livestock types exist for specific factors that relate to livestock type-specific production characteristic. One example for this is the feed quality and composition (that is influential to the animal health and thus pharmaceutical use) where interviewees specifically mentioned a difference between conventional and organic in pig and chicken production, but not in cattle.

When comparing the conventional to the organic production system we can summarize that – depending on the factor - both production systems can have more or less pollution potential. While for example hygiene practices lead to less pollution potential in conventional systems, disease prevention measures have the same tendency in organic systems. For several factors we did not identify differences. Here the production system is not primarily influential, e.g. accidents can happen in all production systems with similar consequences for pollution. For some factors no difference between production systems result from the fact that there was no difference mentioned in the interviews, e.g. for the factor "animal origin" stating that more animal origins on one farm lead to higher likelihood of disease outbreaks.

Another observation is that for each livestock type and each substance group (or the combination thereof) a number of influential factors do not apply. This is specifically the case for the substance group hormones. Hormones are given for reproduction purposes or to cure diseases that relate to fertility and reproduction. Consequently, all factors that are influential to infectious diseases, are not influencing the use of hormones. When comparing production systems, we see a clear tendency that pollution potential for hormones is larger in conventional production systems compared to organic. This roots in the fact that the use of hormones in organic production is limited to disease treatment, meaning that hormone administration for fertility management is only practiced in conventional systems.

The pollution potential of antiparasitics is influenced by a variety of factors, but in beef and dairy cattle we only identified one factor where it differs between production systems: Outdoor contact. Due to the regulation that all organically raised animals (independent of the livestock type) are required to have outdoor contact, the tendency for pollution resulting from antiparasitic use is higher in organic farming compared to conventional.

The pollution potentials for antibiotics and NSAIDs are mostly analogous for the various factors. Interviewees described that often these substance groups are administered for the same diseases either in parallel, or enforcing treatment with NSAIDs first, before falling back to antibiotic use. For these substance groups the

most differences among production systems were identified.

It should be noted that some of the factors condition each other. An example for this is the abovementioned restriction of hormone use in organic production systems that is reflected by conventional system's higher pollution potential for several factors other than pharmaceutical policy.

Pilot assessment for indicator substances: All indicator substances are listed the Appendix Table C10. For the pilot assessment we selected one substance per group and livestock type, prioritizing those named by German and Dutch interviewees and those mentioned most often. The results indicate where most pollution potential is expected. Besides the qualitative comparison among production systems, the excretion rate, degradation in manure and soil as well as the PNEC evaluate pollution potential quantitatively. Figure 4-3 exemplary presents the pilot assessment for oxytetracycline in dairy cattle production. The pollution potentials from the excreted fraction and the degradation (in manure and soil) are high and medium, respectively. The PNEC is comparatively high, indicating a low pollution potential for the lifecycle stage environmental impact. The Figures C1 to C13 in the Appendix illustrate results for all other indicator substances and livestock types assessed. Comparing these, we identify flubendazole in broiler production to have the highest per unit impact as result of a comparatively high excretion rate, slow degradation and low PNEC. Here also qualitative differences among production systems exist – for some factors conventional systems have the tendency for higher pollution, for others the organic systems. For several substances we diagnose the lack of data to conduct a complete pilot assessment. Specifically for the hormone prostaglandine F2alpha we were not able to retrieve any information about the excretion, degradation or environmental impact. Despite these gaps, the assessment gives a starting point to understand differences in pollution from different livestock types and production systems. Moreover, it helps to identify which substances, livestock types, production systems or the combination thereof is likely to have the highest pollution potential.

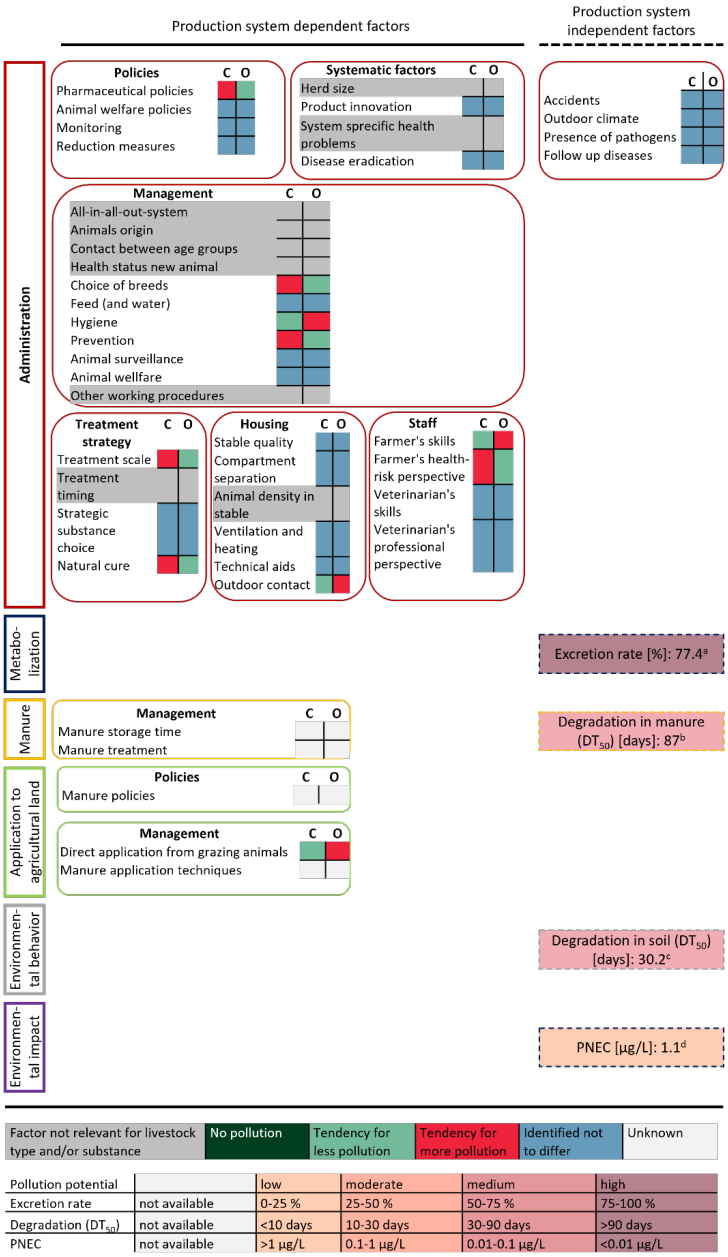


Figure 4-3. Pilot assessment for oxytetracycline pollution from dairy cattle production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] average excretion rate (Nouws et al., 1985); [b] median DT50 (Berendsen et al., 2018); [c] median DT50 (Aga et al., 2005, Blackwell et al., 2007, Boxall et al., 2006, Chen et al., 2014, Li et al., 2010, Li et al., 2016, Wang and Yates, 2008, Yang et al., 2009); [d] predicted no effect concentration (PNEC) (Bergmann et al., 2011).

4.4. Discussion

4.4.1. Results in perspective

No comprehensive analysis that compares pharmaceutical pollution from different livestock types and production systems exists (Sanders et al., 2019). There are however studies that compare individual aspects between organic and conventional farming (or production system characteristics thereof) that can affect pharmaceutical pollution. In this section we reflect on our findings from the pilot assessment (with focus on factors of pharmaceutical administration that showed differences between conventional and organic systems) in perspective to a few existing studies.

Herd size was identified as a systematic factor during our assessment. While hormone treatment to synchronize herds and influence littering is prohibited in organic farming, interviewees observed this practice in conventional (cattle and pig) farms with large herds. For dairy farming Crowe et al. (2018) see the EU's milk quota removal as major reason for herd size increase and consequent need of fertility management, where hormone administration is one alternative method. Thus, it is unclear which methods farms with large herds tend to use and how much hormone pollution is resulting from this.

The breeds of livestock were identified to relate to health status and pharmaceutical use. Interviewees described that breeds designed to maximize production - commonly used in conventional systems - are potentially more disease-sensitive. Louton et al. (2019) conclude that slow growing broiler breeds generally have better health status. Thus, also pharmaceutical use in slow-growing broilers will be less compared to conventional races, supporting the finding of the present study.

Our results indicate that hygiene standards are less strict in organic systems – especially compared to highly industrialized farms. Hence, health problems and pharmaceutical use tend to increase with decreasing hygiene. This tendency is reflected by other studies as well. Delsart et al. (2020) describe hygiene difficulties for alternative pig farms due to for instance organic materials used as floor coverage. Also in organic dairy farming udder hygiene is less frequently done compared to conventional farms (Orjales et al., 2016).

Animal densities are lower in organic compared to conventional production systems. The results of this study indicate that lower animal densities lead to less pharmaceutical use and are supported by Rayner et al. (2020) who conclude that broiler health decreases with higher stocking densities. Tuyttens et al. (2008) on the other hand could not assign health and welfare differences in organic and conventional broiler to individual factors such as stocking density. Yet, the authors found that overall welfare was better in organic than conventional farms (Tuyttens et al., 2008).

Outdoor contact – according to the presented results - makes animals more vulnerable for infections and parasites. The fact that outdoor contact is a prerequisite in organic livestock production leads to the conclusion that this factor is causing more pharmaceutical use and pollution in organic farming compared to conventional. This phenomenon is described by several studies. A review of alternative pig farming systems (including organic) highlights the risks of disease entry (through various pathways such as wild boars, rats or ticks) and parasites to those production systems that provide outdoor contact (Delsart et al., 2020). Van Wagenberg et al. (2016) conclude that contact with manure and outdoor access are reasons for parasite infections.

For several factors we identified ambiguities. One example is the natural cure, which we identified to happen more in organic farming compared to conventional. This comes with the risk that for failure of natural curing, the disease can become more severe and spread out in other animals. Orjales et al. (2016) observed equivalent occurrences in a comparative study of conventional and organic dairy cows. Here the non-administration of antibiotics in a group of organic cows led to chronic infections.

Besides the comparison of individual factors, we identified one review study that compiles and compares aspects of sustainability between organic and conventional livestock production (van Wagenberg et al., 2017). Though the study lacks direct statements about pharmaceutical use, it does conclude about animal welfare and public health as indicators of social sustainability. Findings illustrate that sometimes conventional systems (e.g. in cow's udder health) and sometimes organic systems (e.g. less antimicrobial resistances) perform better. This lack of structural bias between conventional and organic production was mirrored in the assessed pharmaceutical pollution potential in this study: For some factors the conventional system shows higher pollution potential (e.g. prevention) and for other factors the organic (e.g. hygiene). Palczynski et al. (2021) diagnose knowledge exchange about good practice in livestock management as small effort with large potential for animal health. For the findings of the present study this could indicate that knowledge transfer about practices causing less pollution can lead to overall less pollution (at least when high pollution is not inherent to the production system).

4.4.2. Limitations and reflections

We identified several limitations for our study that relate to the research method. The first set of limitations concerns the conducted interviews. The number of interviews is limited. While we aim for comprehensiveness at the various steps where data from the interviews is used, we do not claim that the assessment is complete

as veterinarians' insights, experiences and viewpoints might differ. Even though the interviewee selection followed an established and transparent method, there is potential bias with regard to only interviewing veterinarians that were willing to participate. Furthermore, the interviews were conducted in Germany and the Netherlands, consequently outcomes might not be directly transferable to other regions as production systems' characteristics such as housing can differ among countries (Früh et al., 2014). Livestock types were classified in a way that falls short in capturing differences in production steps of animals, e.g. for pigs differences in pharmaceutical administration exist between sows, piglets and the fattening stages. Also the categorization of production systems comes with limitations. Wallenbeck et al. (2019) show that characteristics of organic farms with the same livestock type can differ and so can medicine use. The cause for this was, however, not discussed in detail (Wallenbeck et al., 2019). Moreover, interviewees stressed that for both the conventional and the organic production systems labels that guarantee certain production characteristics (e.g. the prohibition of specific substances) exist. Considering these sub-categories would potentially result in different outcomes.

We further identified limitations that may have impacted on the research outcomes. The identified factors are exclusively those directly linked to the pharmaceutical lifecycle. For instance, manure application is considered, but interlinked aspects such as soil treatment practices potentially affecting pollution are not accounted for. In the pilot assessment we do not assess pharmaceutical quantities administered which would be important for a comprehensive risk assessment comparing different substances. We also do not consider metabolites in the assessment, despite their pollution potential (Celiz et al., 2009). Substance-specific indicators come with limitations as well, e.g. the excretion rate is not accounting for topical administration of antiparasitics. Furthermore, qualitative results are displayed as tendencies because quantitative data is lacking. Several interviewees emphasized the ambiguity in their qualitative descriptions due to the heterogeneity of farms within one production system category. Moreover, it is to be noted that not all interviewees had experience with organic production systems because of the comparatively small share of organic production. This was specifically the case for the Dutch beef cattle sector.

Reflecting on the results of the pollution potential we judge that the qualitative comparison between production systems is rather robust due to the high degree of agreement between interviewees' responses. The quantitative comparison of the pollution potential between the indicators excretion rate, degradation and PNEC is rather sensitive.

4.5. Conclusion

The research presents a novel framework to assess pharmaceutical pollution from different livestock production systems, covering the entire pharmaceutical lifecycle from administration to environmental impact. Along each lifecycle stage we were able to identify factors that influence pharmaceutical pollution. Manifold of these factors – especially those for the lifecycle stage of pharmaceutical administration – can differ among livestock types and productions systems. Other factors, such as the degradability in manure or soil, are purely determined by the substance and thus are independent of their source.

One objective of this paper was to develop a framework to assess pharmaceutical pollution of different livestock production systems. A remaining challenge identified is the lack of production system categories that is useful to environmental assessments, specifically including pharmaceutical pollution. Furthermore, we emphasize the lacking usefulness of current public databases such as Eurostat to proceed to even a quantitative assessment using our framework in the future.

In the pilot assessment we took an in-depth look at differences in pollution potential between production systems for the stage of pharmaceutical administration in the German-Dutch context. This analysis revealed that for numerous factors a difference between production systems is not expected. Yet, for other factors we were able to identify tendencies for pollution potential to differ between conventional and organic production. For the substance groups antibiotics and NSAIDs for some factors the conventional system has higher tendency for pollution, for other factors it is the other way around. This is the same for antiparasitic substances except for cattle where tendencies for more pollution was only observed in organic farming. Pollution with hormones is overall more likely to result from conventional livestock.

Comparing the pollution potential among indicator substances and livestock types assessed revealed that flubendazole used in broiler production has the highest per unit substance impact. This is a result of a high excretion rate of flubendazole in broilers combined with slow degradation in manure and soil and a low PNEC.

Using the presented framework, the pollution potential can be identified across substances, livestock types and production systems. Hence, the framework is a useful tool to identify where most pollution is expected. Based on these insights, policy recommendations can be formulated, potentially leading to overall less pollution. Results of the pilot assessment can support scrutinizing assumptions that are currently taken for modelling and risk assessment approaches to evaluate pharmaceutical pollution due to scattered and incomplete data available.

CHAPTER FIVE

ALTERNATIVE SOCIETAL SOLUTIONS TO PHARMACEUTICALS IN THE AQUATIC ENVIRONMENT

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Alternative societal solutions to pharmaceuticals in the aquatic environment

Abstract

Environmental contamination with pharmaceuticals is widespread, inducing risks to both human health and the environment. This paper explores potential societal solutions to human and veterinary pharmaceuticals in the aquatic environment. To this end, we adopt transition research's multi-level perspective framework, which allows us to understand the dynamics underlying pharmaceutical emissions and to recognize social and technical factors triggering change. Our qualitative analysis is based on data collected through literature research and interviews with actors from pharmaceutical industry, the health and agricultural sector. The research aims at identifying potential future solutions including requirements for as well as barriers to pathways leading to these solutions and describing the role of key actors involved. The three alternative societal solutions identified are: 1) accepting pharmaceuticals in the environment - substantial changes to the system are not required; 2) reconfiguring the current system by implementing various innovations that reduce pharmaceutical emissions; 3) fundamentally changing the current system to (largely) avoid pharmaceutical emissions. The paper further elicits societal, financial, organizational, regulatory and technological requirements that can facilitate implementation of these solutions. This work is novel as it constitutes a systemic view on all stages of the pharmaceutical lifecycle, comprehensively synthesizing options and measures along the entire lifecycle into societal solutions that are framed as transition pathways. Deriving societal solutions from key actor's perspectives is innovative and provides insights to reflect on choices societies are going to have to make regarding pharmaceuticals in the environment.

5.1. Introduction

Around the globe, pharmaceuticals along with their metabolites and transformation products are frequently found in the aquatic environment (Aus der Beek et al., 2015). Besides ecotoxicological effects on different plant, fish and bird species emerging from pharmaceutical exposure (Aus der Beek et al., 2015), pharmaceuti-

cal residues are found in drinking water (Leung et al., 2013) and food products (Boxall et al., 2006). Furthermore, antimicrobial resistance associated with the presence of antibiotics in the environment is a global threat (Singh et al., 2019). Since both, human and veterinary pharmaceutical use continue to increase globally (due to population growth, rising per capita consumption and growing livestock) the issues are likely to exacerbate (Klein et al., 2018, Van Boeckel et al., 2015).

Pharmaceuticals are potentially emitted into aquatic environments along each step of their lifecycle - from manufacturing via application to disposal. At manufacturing sites, pharmaceutical discharges can be emitted directly to water bodies (Larsson, 2014). After consumption, fractions of administered pharmaceuticals are excreted (Winker et al., 2008). Pharmaceuticals excreted by humans are typically discharged into sewers first, before entering receiving waters as point sources (Hughes et al., 2013). Fractions excreted by animals reside in manure that can be spread on agricultural land as fertilizer (Kümmerer, 2008a). From there they can enter the aquatic environment through runoff or leaching (Sarmah et al., 2006). Finally in the disposal stage, inaccurate discarding practices can lead to pharmaceutical pollution of freshwaters (Vollmer, 2010).

Aus der Beek et al. (2015) compile data from numerous studies that proof pharmaceutical presence in different aquatic media. Depending on the compound, geographical location and emission source, hotspots for pharmaceutical concentrations have been identified at e.g. manufacturing sites (Larsson, 2014), wastewater discharges from households or hospitals (Aus der Beek et al., 2015) and areas with intensive livestock industry (Menz et al., 2015).

Pharmaceutical's individual physicochemical, pharmacological and biological properties – and therefore their environmental behaviours – vary widely (Kümmerer, 2008a). With several thousand pharmaceutical substances authorized to the European market (European Medicines Agency, 2020, Kümmerer, 2008a), environmental impact of the manifold substances is extremely diverse.

Previous research focussed on environmental, chemical and technological aspects of pharmaceuticals in the environment (PIE), rather than societal ones (Daughton, 2016). Frequently discussed solutions to PIE focus on removing pharmaceuticals from wastewater through improved treatment technologies. These have proven to effectively remove a variety of pharmaceuticals, where often the degree of removal depends on the intensity or reaction time of the method (e.g. for ozonation or activated carbon) (Mansour et al., 2018, Paucar et al., 2019, Szabová et al., 2020). Nevertheless, this focus is criticized in the scientific discourse, as until now no individual end-of-pipe technology has proven to sufficiently eliminate all substances (Kümmerer, 2008b, Voigt et al., 2020), there is no adequate knowledge about (long term)

ecotoxicological risks for remaining effluent concentrations even if removal rates are high (Angeles et al., 2020), and doubts are raised over it's added costs, feasibility and reasonability (Eggen et al., 2014, Kosek et al., 2020, Voigt et al., 2020). Moreover it is unclear if current technologies can remove prospectively developed substances or compounds that are created during treatment processes (Kosek et al., 2020, Kümmerer, 2008b). Besides, technological end-of-pipe solutions do not address the issue of PIE over the entire lifecycle and neglect approaches that relate to societal aspects of how pharmaceuticals are prescribed, used, and disposed.

We argue that including the societal dimension into the discussion is essential, as the way society utilizes pharmaceuticals drives environmental emissions along the entire pharmaceutical lifecycle. Society must find a way to deal with trade-offs between improving human and animal health through pharmaceutical use and environmental sustainability.

To date, comprehensive studies that include societal embedding of proposed solutions are lacking. In particular, there is a clear knowledge gap in addressing appropriate institutional settings, economic, cultural and behavioural incentives and actors' collaborations towards successful strategies.

In this paper we explore alternative societal solutions to deal with PIE by using the multi-level perspective (MLP), a framework that conceptualizes patterns for system change at different analytical levels (Geels, 2011). A societal function (in this case pharmaceutical supply and use) is performed by a socio-technical system, an established configuration. Changes of the existing system occur due to developments and interplay at the different levels. We perform actor interviews and enrich as well as cross-check these with comprehensive literature to delineate different future solutions, following MLP theory. The core of the paper is to inspect actors' perceptions of the situation regarding PIE and identify their understanding and visions on solutions, their ideas regarding actor roles, and their opinion on requirements to implement solutions. Further, we explore what barriers actors foresee for each solution. Interviews were conducted in Germany and the Netherlands. While the research's scope is on the aquatic environment, the topic was framed towards interviewees as PIE in general.

5.2. Theoretical framework, methods and data

5.2.1. Multi level perspective framework

This study uses the MLP to describe and analyse alternative societal solutions to PIE. The framework originates from transition research, which investigates system changes over time. MLP considers the setting in which transitions occur as a socio-technical system (Geels and Kemp, 2012), which is framed as the pharmaceutical lifecycle from development to environmental emission in this study.

Embedded in the socio-technical system, the MLP differentiates between three analytical levels landscape, regime and niche (Geels, 2011). A conceptual overview of the MLP, including the contextualization of the pharmaceutical lifecycle, is illustrated in Figure 5-1.

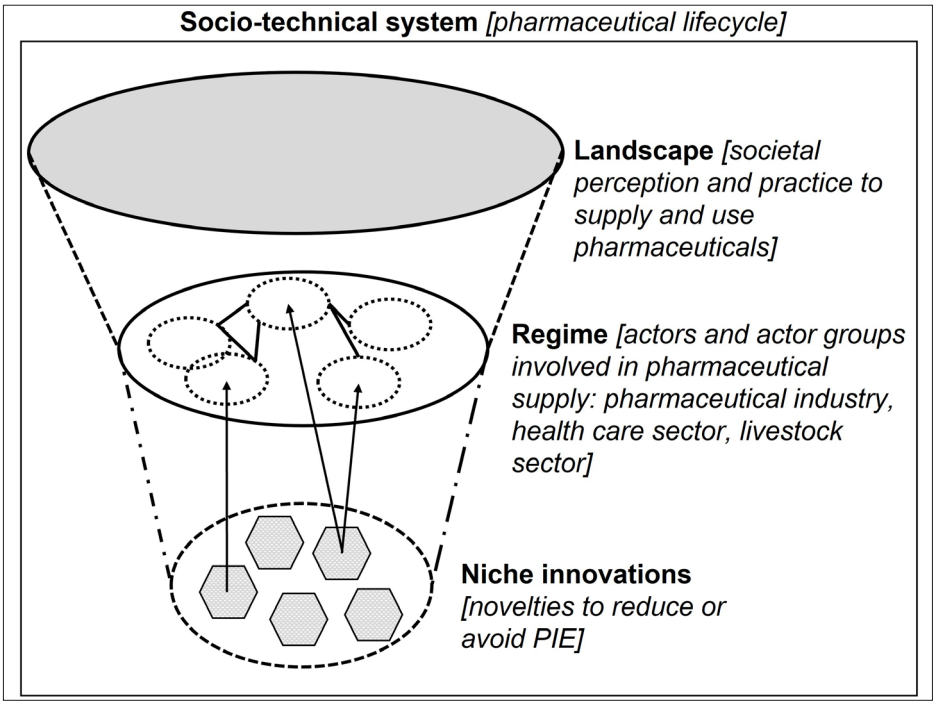

Figure 5-1. Conceptual overview of the Multi-Level Perspective illustrating the three analytical levels landscape, regime and niches of the socio-technical system in context of the pharmaceutical lifecycle, adapted from Geels (2002).

The regime level is assigned to the space where actors interact, maintaining the setting of the socio-technical system according to anchored rules that determine the

functioning of the system. It represents a complex arrangement of social groups and actors related to the system's societal function (Holtz et al., 2008). In this research we specifically focus on actor groups related to the societal function of pharmaceutical supply. Niches refer to emerging innovations that might prevail (Geels and Kemp, 2012). In the context of pharmaceutical lifecycle, both technical and non-technical innovations reducing PIE are considered. The landscape is the exogenous context within the socio-technical system including the natural environment, material components like infrastructure and societal components such as legal structures, cultural believes and political trends (Geels, 2002). With the core of this research being on alternative societal solutions to PIE, we focus on the societal components of the landscape level by describing and interpreting policy developments in the EU along with Germany and the Netherlands as cases where regime actors were interviewed. In addition, we outline landscape changes mentioned by the interviewed regime actors.

Geels (2011) and Geels and Schot (2007) describe transitions as shifts from one regime to another whereby the landscape and niche levels are derived concepts in relation to the regime. Landscape dynamics creating pressure on the regime and occurring innovations at niche level can create momentum for a transition (Geels and Schot, 2007). This research uses the MLP to structure what alignments of changes at the different levels can lead to distinct futures regarding PIE. A detailed description of these pathways is presented in the Appendix D 1.1.

5.2.2. Data collection

Data from regime actors was collected through 15 semi-structured interviews. Even though this research investigates the system of the pharmaceutical lifecycle as a whole, interviewees were specifically selected from pharmaceutical industry, the healthcare and agricultural sector as these are considered to play a pivotal role in the pharmaceutical supply as well as in a potential transition process. The participants were selected after the principles focus group and snow-ball sampling as outlined by Reed et al. (2009); this is described in the Appendix D 1.2. The interview was clustered into six sections: (i) participant background; (ii) today's situation and problem description regarding PIE; (iii) future and potential solutions regarding PIE; (iv) requirements on landscape and niche level for potential solutions; (v) responsibilities for potential solutions; (vi) critical reflection on solutions. The interview manuscript can be found in Table D1 in the Appendix.

Pertinent literature was studied to gain insight on developments at niche, regime and landscape level, complementing and cross-checking interview data. This

resulted in an inventory of existing niche innovations, an outline of current regime dynamics and a description of ongoing societal landscape changes.

5.2.3. Interview analysis

All interviews were transcribed non-verbatim and coded for qualitative analysis with assistance of atlas.ti software. Codes were created upon the different sections outlined under 2.2. We extracted code reports to thematically analyse today's situation as well as alternative societal solutions to PIE. To delineate these, the theory of transition pathways by Geels and Schot (2007) was followed (see Appendix D 1.1). Each interview contributed to sketch alternative future regimes, whereby each future regime is based on input from multiple interviewees and from literature. As the study is qualitative, we do not weigh alternative solutions, but rather elicit actors' perspectives on different options and pathways.

5.3. Results

5.3.1. The current socio-technical system of the pharmaceutical lifecycle

5.3.1.1. Landscape changes affecting pharmaceuticals in the environment

First legal steps concerning PIE were introduced by the EU in 1995 when requesting environmentally relevant information for market authorization of new pharmaceutical products. Nonetheless, only in 2005 information requirements were specified, avoiding the previously insufficient environmental risk assessments (ERA) (Wennmalm and Gunnarsson, 2010). In case of expected high environmental impacts, legislation differentiates between human and veterinarian pharmaceuticals. Authorization of the former is not affected by high environmental risk as EU guideline 2001/83/EG states this cannot impact the risk-benefit consideration (Koschorreck and Hickmann, 2008, Parliament and Comission, 2001). Still, measures to minimize environmental risks should be taken, if possible. A high environmental risk from veterinary pharmaceuticals can obstruct market release in two cases: environmental risks cannot be minimized and a comparable compound is available (Koschorreck and Hickmann, 2008). These landscape developments show that human health is prioritized over environmental health. However, animal health is not generally prioritized over environmental health.

The first grounds for European water legislation emerged in the 1970s with e.g. water quality standards for drinking water abstraction. An important transformation took

place decades later by implementing the Directive 2000/60/EC, commonly known as Water Framework Directive (WFD). Implemented in 2000, the WFD represents a fundamental guideline for European water management, specifically considering pollution prevention (European Commission, 2016b). However, pharmaceutical pollution is not explicitly mentioned. To complement EU water management, a watch-list for emerging water pollutants was implemented under the WFD in 2015, intended to provide targeted, high-quality information on substances of concern (European Commission, 2016a). The list is iteratively evaluated, whereby substances are added and removed. The watch-list comprised the first link of pharmaceutical pollution to EU water legislation. Barbosa et al. (2016) conclude that despite legislative developments under the WFD, legal discharge limits for pharmaceuticals are lacking.

Whereas the WFD targets freshwaters' quality status independent of the emission sources, water pollution through pharmaceutical production is additionally addressed in Directive 2010/75/EU known as industrial emissions directive. It demands the inclusion of environmental limit values when giving industrial permits (European Commission, 2019b). Given the non-existence of EU limit concentrations for pharmaceuticals, these must be established by the permitting authority in coherence with experts' best available technique reference document. Environmental inspections are implemented as a control mechanism (European Commission, 2019b). Additionally, in 2013 the EU enforced that all imported pharmaceutical ingredients have to be produced with respect to good manufacturing practices by EU standards (European Commission, 2012).

Addressing PIE for the first time from a lifecycle perspective in policy, the European Commission published a strategic approach to PIE in 2019. The approach provides different areas of action along the pharmaceutical lifecycle, to be followed by the EU and

Table 5-1. Landscape changes determined through regime actor interviews.

Landscape element	Influential changes
Policy	Regulative developments regarding PIE
Demographics	Aging population in Europe increases medicine use
Migration	Increasing medicine use due to re-introduction of previously controlled diseases
Societal trend	Societal pressure to decrease animal numbers (specifically mentioned for the Netherlands)
Societal trend	Society demands animal production under high animal welfare standards, increasing use of certain pharmaceuticals

it's member states (European Commission, 2019a). Nevertheless, the approach neither presents discharge limits nor quantifiable targets for proposed actions. On national level, the Dutch government developed a chain approach to address PIE from a lifecycle perspective, releasing an implementation program in 2018. The program outlines different actions to reduce human pharmaceutical emissions. Veterinary pharmaceutical emissions are not (yet) part of the approach (Government of the Netherlands, 2019). In Germany, no governmental policy exclusively tackles PIE. However, governmental bodies initiated a stakeholder dialog that developed a strategy to implement measures reducing trace pollutants in waters (BMU and UBA, 2019). Policy developments along with other landscape changes mentioned by regime actors are displayed in Table 5-1.

5.3.1.2. Regime dynamics affecting pharmaceuticals in the environment

Pharmaceutical development and manufacturing: The required ERA for market authorization (section 3.1.1) forces regime actors to consider environmental aspects in pharmaceutical development. Nevertheless, interviewees described potential neglection of the total environmental loads through the product-based approach and the lack of follow-up after authorization as shortfalls of the existing ERA. The pharmaceutical developing sector was mentioned to give priority to human over environmental wellbeing. Likewise, in ERA legislation environmental risks cannot lead to exemption from authorisation. Regime actors explained that drivers for pharmaceutical development are the discovery of substances resulting in first-ever treatment of diseases, and of products preferable over existing pharmaceuticals, e.g. fewer side effects. Economic interest significantly drives the development of new pharmaceuticals, as mentioned for antibiotics by various interviewees. Little research is conducted to develop new antibiotics, which would likely be classified as reserve medication in case of patients' resistance towards common antibiotics. This classification potentially results in prescription restrictions, limiting profit margins irrespective of development costs. The latest AMR industry alliance report describes a challenging overall economic environment for researching companies and proposes financial incentives from governments as a solution (AMR Industry Alliance, 2020).

Environmentally beneficial dynamics of the pharmaceutical developing sector cover vaccine developments or the recent focus on biopharmaceuticals. Alongside, Taylor (2016) describes synergies between drug design criteria and positive environmental significance, e.g. full oral adsorption leading to less excreted fractions. Further, regime actors agreed that the sector respects the environmental relevance of pharmaceuticals, also because the topic was recognized as highly media-effective and therefore politically relevant.

The relevance of image was as well mentioned for the manufacturing industry. One

interviewee described that scoring well in environmental rankings is positively received by shareholders. Further, participants portrayed the industry's increasing awareness of their responsibility after several reports were doubting responsible manufacturing. However, pharmaceutical manufacturing happens along global production chains, complicating implementation and control of ubiquitous sustainability criteria. On global level, industrial discharge limits are rare (Larsson, 2014). Regulations exist within the EU (section 3.1), but most pharmaceutical manufacturing takes place outside Europe (Larsson, 2014). Interviewees from the health and agricultural sector were strongly concerned about pollution from manufacturing, especially outside the EU. Nevertheless, technological developments for industrial wastewater treatment exist along with self-regulation by the industry (AMR Industry Alliance, 2020, Larsson, 2014).

Human health sector: The sector's core priority is curing humans, commonly using allopathic medicine. According to regime actors, medicine use is promoted by pharmaceutical industry, governments, doctors' and pharmacists' organization, denoting non-transparent dynamics. One interviewee explained that critical considerations exist on the functioning of certain pharmaceuticals (where effects are statistically significant, but not clinically relevant), but is generally not shared by doctors. Another identified mechanism supporting medicine use is the patients' amenity to prefer medical prescriptions over behavioural change to improve well-being. This is similar to humans endorsing environmental cautiousness, but not acting accordingly themselves - a value-action gap well-known in environmental research (see e.g. Kollmuss and Agyeman (2002)). Moreover, medical staff is not intrinsically aware of PIE, misperceptions towards wastewater treatments' effectiveness exist and dealing with PIE is perceived to surpass their responsibility. Nevertheless, regime actors also observed emission limiting dynamics within the health sector. They described increasing media-reporting about PIE, raising awareness among staff and patients. Specifically for the Netherlands, a trend towards less surgeries and de-prescribe medicines was observed.

Pharmaceutical leftovers potentially leading to environmental emissions exist in healthcare institutions and private households (Daughton and Ruhoy, 2011). Interviewees mentioned prescription routines leading to leftovers and criticised the absence of unified, safe disposal systems.

Agricultural sector: Pharmaceutical use in livestock is practiced to avoid and treat diseases in animals used for animal production. Besides therapeutic use, there is use for prophylaxis, growth promotion and increased production efficiency (Bloom, 2004). In the EU, growth promotion with pharmaceuticals was prohibited in 2006

(European Commission, 2005). Where economic competitiveness is a main driver for the agricultural sector (Sarmah et al., 2006), a more efficient production leads to more financial profit and stability. Limiting disease spread and having healthy animals is a key to this strategy (Sarmah et al., 2006). Regime actors described different dynamics analogous to efficiency, driving environmental emissions of pharmaceuticals. One of these is the economic trade-off between treating diseases once they occur and prevention through vaccines or management practices. Another is the economic decision to preventively treat the entire herd to avoid disease spreading once an individual is infected. Sarmah et al. (2006) closely link big animal numbers on farms to medicine use controlling disease spread. However, interviewees indicated that conditions and treatment practices differ among animal types and farming systems, causing differences among farms. Yet, there is no information available on pharmaceutical use intensity differentiated between farming systems, farm sizes or animal types, impeding comparisons. One participant explained that antibiotic use on organic farms is highly restrictive, as it is also regulated by the EU (Ivemeyer et al., 2012), but organic farm animals spend more time outside, making them more vulnerable to certain health issues. Another trend described is increasing farm productivity as farm size and degree of specialization grows. Interviewees observed the phenomenon that regional hotspots of large, highly specialized farms cause high animal densities and pollution potential where the animal products are exported from that region. Regime actors were also critical on the fact that veterinarians prescribe and sell pharmaceuticals providing them a financial prescription incentive.

Discussions of veterinary pharmaceuticals in the environment strongly focus on antibiotics. Several regulations, e.g. reporting of medicine application, is only required for antibiotics, possibly causing overlooking the relevance of other substance groups.

5.3.1.3. Niche innovations

Niches where innovations reducing PIE occur developed along the entire pharmaceutical lifecycle. Figure 5-2 illustrates existing niche innovations with overall descriptions per innovation identified. For some niche innovations multiple approaches have been discovered (e.g. different pharmaceutical removal technologies are summarized as "advanced wastewater treatment"). An overview of niche innovations, including alternative approaches is presented in Appendix D 2.1.

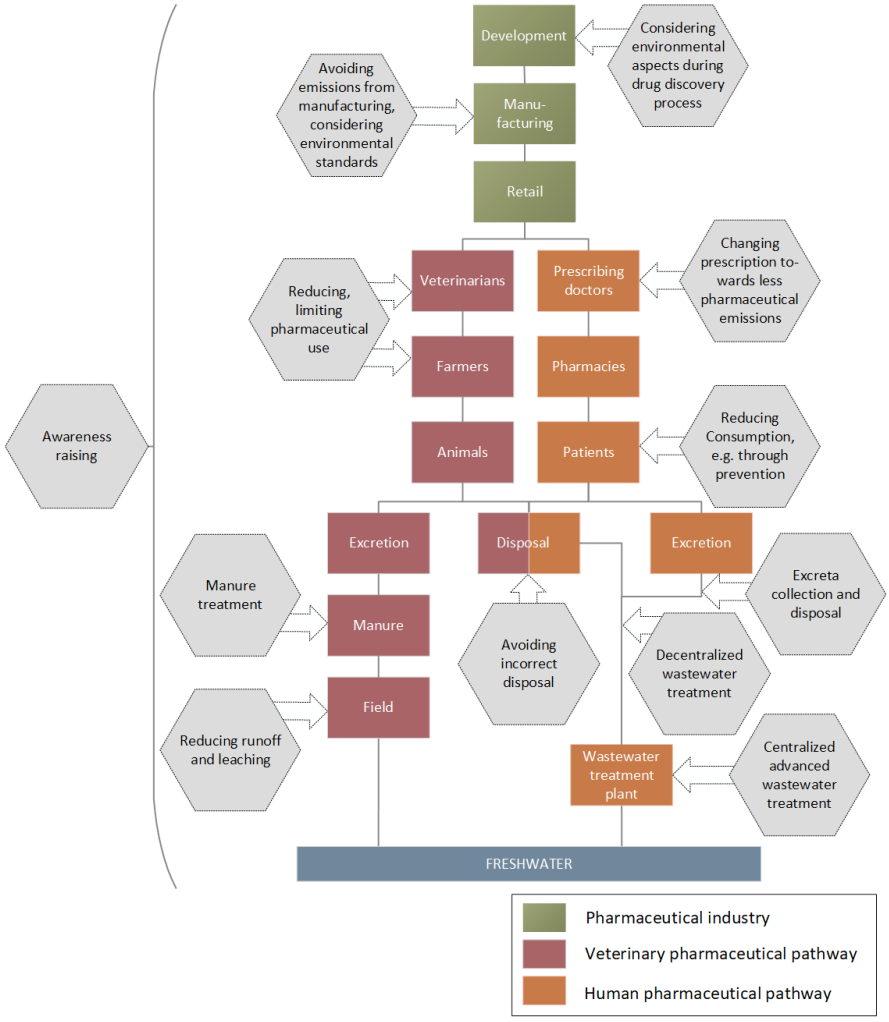

Figure 5-2. Pharmaceutical lifecycle from the development to disposal, and niche innovations (in hexagons) illustrating where they have an effect.

5.3.2. Potential societal solutions

Three alternative societal solutions were identified: 1) Accepting pharmaceuticals in the environment as a reproduction process without regime shift; 2) Implementing niche innovations in different sectors as a reconfiguration pathway where a new regime emerges from the existing regime, hereby regime actors remain; 3) A system change as a de-alignment of the current regime, potentially with re-alignment of an entirely new regime. Figure 5-3 gives an overview of the three identified solutions, embedding case-specific items into the concepts of different transition pathways.

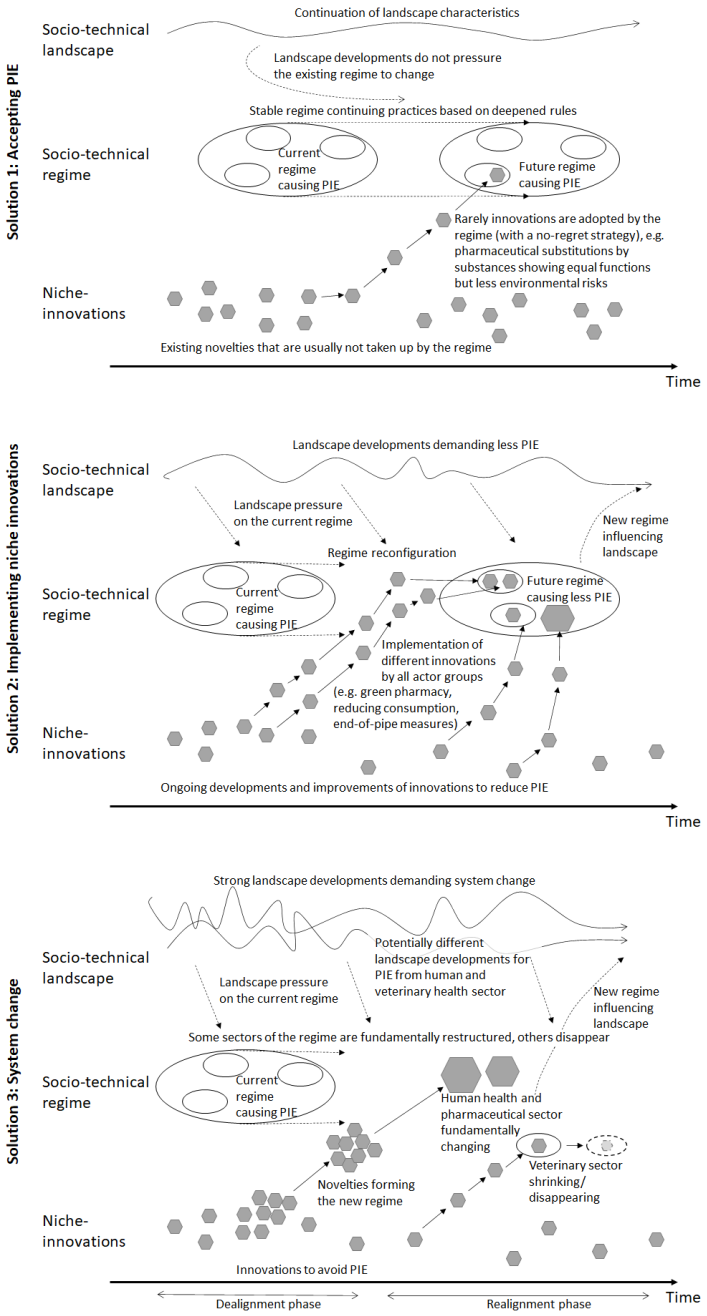

Figure 5-3. Transition pathways for different societal solutions to pharmaceuticals in the environment (PIE), from top to down: 1) accepting PIE, 2) implementing niche innovations, 3) system change. Adapted from Geels and Schot (2007).

Accepting pharmaceuticals in the (aquatic) environment: From an environmental risk perspective, pharmaceutical substances bear identical risk as any other chemical. From an environmental management viewpoint however, health benefits distinguish pharmaceuticals from other chemicals (Taylor, 2016). Regime actors reflect this opinion by describing that pharmaceutical emissions are inevitably in guaranteeing human and animal wellbeing. We therefore identified the first future solution as "accepting pharmaceuticals in the environment", a reproduction of the current regime. Especially regime actors of the pharmaceutical industry and the human pharmaceutical sector pointed out that society would always prioritise pharmaceutical use over their environmental relevance. Consequently, they believe that the societal perception of pharmaceutical's importance (section 3.2) will not change, preserving existing regime dynamics. Other interviewees were convinced that options to reduce pharmaceutical use exist, but are not entirely avoidable due to serious diseases such as cancer. Hereby, they suggested to follow a no-regret strategy, where avoidable emissions are reduced without trade-offs. Requirements mentioned for this approach are evidence on environmental risk and knowledge about emission sources of pharmaceuticals.

Implementing niche innovations: Interviewee statements for this solution varied from individual innovations to broad sets of measures for complementary or parallel implementation. An overarching innovation mentioned by most participants is awareness raising, involving education and knowledge transfer. Awareness raising is perceived as relevant to increase public understanding of the topic, but also to equip actor groups with knowledge to implement other innovations. A comprehensive list of awareness-raising elements and their requirements is given in the Appendix D 2.2.

The so-called green pharmacy is a frequently discussed approach to PIE, which interviewees considered relevant as well. Firstly, they referred to the design of new substances while considering environmental biodegradability. Where pharmaceuticals are stable within the target body fulfilling their function, they degrade during wastewater treatment or in the environment (Straub, 2016). Kümmerer (2019) describes different methods resulting in more environmentally friendly ß-blockers, antibiotics and one cytostatic. Secondly, multiple regime actors suggested the enhanced development of nature-based pharmaceuticals and phytotherapeutics. Literature introduces these concepts as "benign by nature" (Straub, 2016), where synthetically developed pharmaceuticals are substituted by natural compounds not showing environmental toxicity. One example is alkaline phosphatase, a naturally-occurring enzyme preventing inflammations (Seinen and Feil, 2019). Thirdly, participants mentioned new dosage forms where the same effect is achieved

with smaller substance amounts. Pharmaceuticals with low bioavailability require high administered doses to reach pharmaceutically active concentrations, leading to large excreted fractions (Straub, 2016). So-called prodrugs are inactive in their original form. After administration, prodrugs metabolize and become pharmacologically active. This leads to reduced doses, increased bioavailability and smaller excreted fractions (Straub, 2016). Lastly, regime actors explained that vaccine development can reduce pharmaceutical use and emissions.

Regarding drug authorization, one interviewee argued for improving the existing ERA. Another participant pleaded to exclusively authorize pharmaceuticals that proof to have more clinically relevant effects than placebos and remove non-complying substances from the market.

Interviewees named a series of requirements to realize development-related innovations:

- *societal and sectoral demand*
- *research unbiased as to the result*
- *willingness by pharmaceutical industry*
- *new orientation of pharmaceutical industry*
- *financial and legislative governmental research support to incentivise*
- *governmental enforcement*
- *enforcement by health insurance companies*
- *taxation to incentive sustainable pharmacy*

Coherently with literature (Larsson, 2014), participants considered the reduction of emissions from manufacturing alongside with the implementation of environmental standards as essential for the industry. This requires research-based standards and technologies to safely dispose industrial pharmaceutical wastes or treat wastewaters. To guarantee that manufacturers meet standards, one participant suggested a "carrot and stick approach": Incentivizing and rewarding well-performing manufacturers on the one hand, enforcing and sanctioning poorly-performing companies on the other hand. Additionally, one interviewee suggested to move all pharmaceutical production to Europe, where supposedly environmental requirements are stricter.

Another set of niche innovations targets the supply and use of human pharmaceuticals. Participants agreed that pharmaceutical use, thus emissions, can be reduced through lifestyle interventions such as reducing weight, eating healthy, physical activity. Deffner and Götz (2008) likewise describe health-supporting measures to reduce PIE arguing for prescribing and financially supporting these through the

health care system. Requirements for lifestyle interventions found are:

- *public education*
- *motivation among people*
- *promoting lifestyle interventions instead of pharmaceutical use*
- *rewarding system for good performance*
- *regulatory measures on unhealthy products (taxing, restricting accessibility)*

Moreover, regime actors argued for the implementation of niche innovations related to prescription and use of pharmaceuticals: Changing prescription routines, using pharmaceuticals appropriately, alternative treatments. A list describing detailed elements and their requirements is presented in the Appendix D 2.3. In Sweden, these niches were adopted by the regime through environmental classification of pharmaceuticals, supporting practitioners to choose alternative pharmaceuticals posing less environmental risk (Ågerstrand et al., 2009).

Estimates on incorrectly disposed leftover pharmaceuticals differ strongly (from 0% in Sweden to 92% in the U.S.) and continuous monitoring about pharmaceutical discarding is lacking (Vollmer, 2010). Numerous participants of this study see incorrect disposal as an ongoing issue. They named smaller package sizes and pharmaceutical recycling as innovations to reduce pharmaceutical leftovers. For remaining leftovers, they stressed the need for safe and ubiquitous disposal systems, advertised through public media and pharmacies.

Moreover, regime actors mentioned that end-of pipe innovations can contribute to this solution, whereby they differentiated between decentral and central pollution control technologies. Decentral innovations covered installations in household toilets, wastewater treatment at healthcare institutions or urine collection systems. Several such ideas are elaborated in literature, e.g. contrast agent collection with urine bags (Niederste-Hollenberg et al., 2018). Interviewees listed following requirements:

- *technological developments for household installations*
- *focus on specific pharmaceuticals for urine collection*
- *urine collection must be feasible for patients*
- *case by case decisions about most suitable system*
- *innovation funding; decision on who covers costs*

Centralized installations removing pharmaceuticals at municipal wastewater treatment plants are perceived as useful complements to source-oriented inno-

vations. This approach has been intensively researched – considering numerous technologies including ozonation, activated carbon or membrane filtration (Fröhlich et al., 2019, Homem and Santos, 2011) - and regionally implemented, for instance in Switzerland (Eggen et al., 2014). Furthermore, these technologies can be effective against metabolites as well (Rúa-Gómez et al., 2012). Given high costs for these technologies, regime actors suggested to focus on hotspots where additional treatment is economically and ecologically useful. They see necessity for funding schemes and propose ascertainment of society's willingness to pay.

Disease prevention was described relevant for the livestock sector as well. Besides vaccines, health-supporting management plays a significant role. Participants stressed the importance of well-managed housing, food and hygiene. These measures are likewise discussed in literature (Klatte et al., 2017). However, understanding the effectiveness of adjusted livestock management on environmental pollution requires further investigation and costs may hamper implementation (Evans et al., 2019). Requirements mentioned by interviewees to overcome these aspects include:

- *Knowledge by farmers*
- *Quality system for farmers*
- *Broad, coherent animal health data collection for better knowledge on health management (e.g. animal health index)*
- *Novelties improving health management (e.g. housing)*
- *Investments on farms*
- *Higher prices for animal products*

Other innovations proposed target the application of pharmaceuticals in livestock. We clustered these as illustrated in Table 5-2.

Table 5-2: Niche innovations targeting pharmaceutical use in livestock plus requirements

Niche innovation	Detailed elements	Requirement
Restricting pharmaceutical use	Restricting substances proven to cause human or environmental health issues	
	Precautionary prohibition of substances not proven to have no environmental or human health risk	

Reducing pharmaceutical use	Using reduction potential	Farmers' and veterinarians' willingness to change routines Not paying veterinarians for selling medicine, but for keeping animals healthy and for their know-how
	Extend benchmarks and measures from antibiotics to all pharmaceuticals	enforcement
	Breed more robust animals to decrease use	
Changing application form		legal permission where necessary
Alternative treatments	Phytotherapy	innovations knowledge and willingness by veterinarians
	Homeopathic therapy	
	Natural feed supplements reducing pharmaceutical use	

Manure treatment and improved soil management were named as end-of-pipe innovations. Besides manure incineration (Derksen et al., 2015), different treatment options such as heating, drying, pasteurisation exist (Vidaurre et al., 2016). Despite these options proposed in literature, interviewees named the development of treatment methods along with loosening legal regulation on manure processing as requirements for this innovation. Soil properties influence pharmaceuticals' leaching and runoff potential significantly (Sarmah et al., 2006), which is why optimized soil management practices (soil cover, optimized organic content, high root density) were described as beneficial. Knowledge about these practices was named as a key requirement.

To avoid incorrect disposal of veterinary pharmaceutical leftovers, one participant proposed that veterinarians collect leftovers from farms and safely dispose them.

System change: De-alignment of the current system can occur independently for the human and veterinary sector. For the agricultural sector, different directions of system changes were brought up by the interviewees (Figure 5-4, including requirements). Rethinking farming systems and reducing animal numbers are transitions, where the current agricultural sector changes fundamentally. Similarly, Lamine (2011) investigates transition pathways towards ecologization of agriculture. The disappearance of livestock and the ban of pharmaceuticals are transitions where most likely entire sectors disappear.

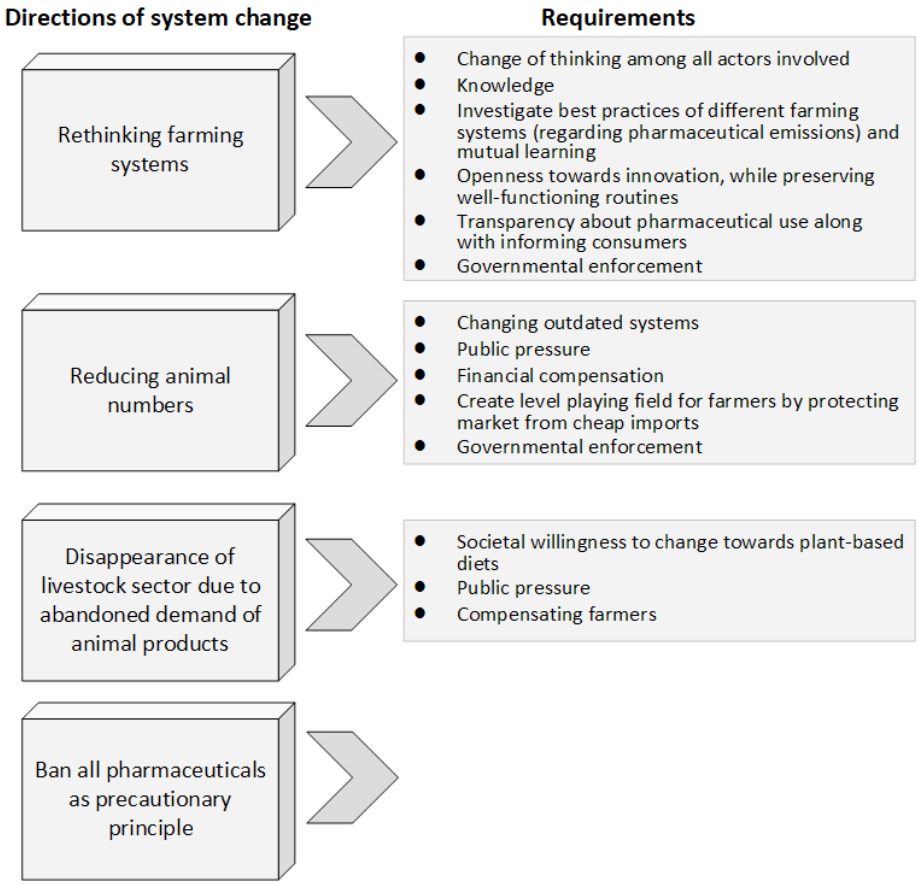

Figure 5-4. Directions of system changes and their requirements as societal solutions to veterinary pharmaceuticals in the environment, resulting of stakeholder interviews.

System change concerning human pharmaceutical emissions was also discussed among regime stakeholders. One participant mentioned the ban of pharmaceuticals as a solution in case society values environmental quality over individuals' human health. This is a rationale where environment as a common good is exploited by pharmaceutical use and correlated pollution of individuals. Giubilini (2019) follows a similar idea describing antibiotic resistance as a tragedy of commons where consequences of individual's antibiotic use affect the entire society. Another interviewee proposed a system change towards categorizing the necessity of treatments distinguishing between life-endangering and lifestyle-influencing situations. Consequently, a variety of currently common treatments would disappear in the future.

5.3.3. Responsibilities and barriers to potential solutions

Interview results indicate that a wide range of actors are responsible for proposed solutions. Individual actors or sectors are seen in charge of implementing innovations within their competence. Governmental institutions were given responsibility to enforce regulations and control mechanisms. Society was described as a driver that can demand and induce change This is a typical landscape change potentially triggering a transition. Several participants pointed out that simultaneous actions by different actors are required to reach proposed solutions. A detailed list of actor groups that regime actors see responsible for the implementation of solutions is presented in the Appendix D 2.4.

For the solutions 'implementing niche innovations' and 'system change' regime actors described numerous barriers. Some are specific barriers to individual innovations or requirements; others are overarching hurdles that hinder proposed change. In our analysis, we retrieved financial, knowledge, societal, cultural, responsibility, regulatory, organizational and technological barriers to proposed solutions. A comprehensive overview of barriers is given in the Appendix D 2.4.

5.4. Discussion

5.4.1. Reflection on identified solutions

As checking of results from actor interviews against the existing literature was conducted in the results section, this chapter critically reflects on the pathways of the identified solutions in addition to the results presented.

An established regime of pharmaceutical provision, supply and use is in place. Whilst the human pharmaceutical sector shows lock-ins due to focus on human health over environmental health, the veterinary pharmaceutical sector appears locked in because of rooted (economic) structures. Despite the existence of an established regime, pressuring landscape changes to address PIE alongside with various niche developments were identified. Still, niche innovations are not yet adopted at large scale due to multiple barriers.

Accepting PIE is one identified solution, prospectively not or insignificantly reducing emissions. Expectably, the regime in place is stable, established routines maintain due to lack of societal landscape changes and non-adaptation of innovations. A transition of the socio-technical system is not anticipated. Considering global predictions of rising pharmaceutical use, this solution poses continuous, potentially increas-

ing risk for environmental and human health. This is a contradiction to international agreements such as UN's sustainable development goals (United Nations, 2021) or the strategic approach to pharmaceuticals in the environment by the EU (European Commission, 2019a). Furthermore, it interferes with intergenerational equity. Natural resources are exploited by the current society at the cost of future generations.

Implementing innovations as a solution to PIE covers numerous individual aspects which need simultaneous development to capture the diverse substances and emission pathways. Given their extensive spectrum, emissions are probably reduced, but not avoided as literature indicates the lack of widespread impact of measures (e.g. Straub (2016)). While regime dynamics transform for this solution, the regime of pharmaceutical life cycle and associated actor groups prevail. To achieve this reconfiguration of the existing regime, several barriers, typical lock-in mechanisms (Geels, 2011), have to be overcome (see Appendix D 1.1).

A system change can lead to the avoidance of PIE. We identified several types of system change for the human and veterinary pharmaceutical sectors. While some will change or abandon certain regime groups, likely to result in a reduction of PIE, others are more fundamental, resulting in disappearance of entire sectors and emission avoidance. Both constitute a transition where the societal importance of human pharmaceutical use and the consumption of animal products change fundamentally.

Following transition pathway theory, we identified three independent solutions. However, elements of different solutions may be combined, e.g. accepting PIE for specific cases, developing green pharmaceuticals for human treatment and abandoning the livestock sector.

Setting the three solutions in context of ongoing landscape changes, regime dynamics and niche developments (as outlined in sections 3.1.1 to 3.1.3), trends clearly push towards implementing niche innovations. Landscape changes on policy level aim at accelerating innovation adoption, plus niche innovations are increasingly researched. Regime actors indicated their willingness to adopt various niche innovations, if feasible in terms of availabilities, costs, regulations and other requirements (see 3.3). Furthermore, several innovations reducing PIE have been implemented already, according to the regime actors.

Several elements investigated in this research, were discussed and evaluated in previous studies. However, none of these studies consider different options society has as we do in this research. It is novel to analyse the current system with ongoing changes and explore potential future solutions from there.

5.4.2. Limitations of the study

Conducting this study in a European context generated results potentially not universally applicable. Pharmaceutical use patterns vary widely, leading to globally diverging situations (Klein et al., 2018). Additionally, socio-technical systems differ among regions (Coenen et al., 2012). Distinct niche, regime and landscape levels – e.g. different legal frameworks (Maron et al., 2013), wastewater systems (Malik et al., 2015), socio-cultural values of livestock production (Thornton, 2010) - restrict global implementation of proposed solutions. Consequently, requirements for solutions might differ as well. Yet, the research describes a set of solutions providing universal directions even if not all aspects are directly transferable to all world regions.

The research considers the pharmaceutical lifecycle for human and livestock use, excluding pharmaceutical emissions from e.g. aquaculture or orcharding industry (Gaw et al., 2014, McKenna, 2019). Moreover, interviews were limited to regime actors from sectors related to pharmaceutical supply. By defining this scope, we neglect other actor groups being part of the regime in a broader sense, such as patients or water authorities. We recommend that future research enlarges this pool of actor groups. Further, a bias might exist through participant selection and interviewee viewpoints. Participants were mostly contacted through sector-representing organizations. Even though we stressed special interest by interviewees is not required, (unintentional) selection of actors interested in PIE might have occurred. Consequently, this research bases on interviewees' perceptions, which are valid, but not exclusive. More or other dynamics than those captured through the interviews, might exist.

Regime actors described solutions from their viewpoint of today's situation. Some considered future predictions such as demographics. The future is uncertain, however, if conditions, thus landscape, change fundamentally, so may perspectives on solutions. Thornton (2010) described an emerging global pandemic as such incident.

This qualitative study presents alternatives without quantitatively assessing their consequences in terms of economic, societal or environmental effects, which should become subject of further research.

5.5. Conclusion

Different societal solutions to deal with PIE were identified by investigating the pharmaceutical lifecycle through actor interviews and literature, using the MLP framework and it's theory on transition pathways: 1) accepting pharmaceuticals in

the environment, 2) implementing niche innovations, 3) system change. They illustrate a wide spectrum of futures in terms of pharmaceutical emissions, regime dynamics and societal changes. Accepting PIE does not require changing the current regime, but pharmaceutical pollution will at best remain, but likely worsen, considering global trends. However, we found it is more likely that a range of innovations is going to be implemented as innovation development occurs in various niches, current regime actors describe dynamics towards implementation of niche developments and societal landscape dynamics such as policy changes push towards this direction. Nevertheless, it is not fully clear (yet) how this will affect PIE. On the other hand, a transition to a new regime, with highly restricted human pharmaceutical use and decimated livestock sector, is expected to result in a substantial effect on PIE. The major system and sectoral changes needed however, will require societal pressure, governmental enforcement and financial incentives.

This study illustrates how, in the Dutch-German context, society unequivocally prioritises human wellbeing over environmental risks. A fundamental system change for human pharmaceuticals is therefore not to be expected until this deeply rooted perception changes. For the veterinary sector this hierarchy is less pronounced, as landscape developments show. If these developments result in the societal decision to reduce or renounce livestock production as well as the consumption of animal products, this is (in time) expected to reduce animal related PIE.

Exploring alternative societal solutions to PIE while considering the entire pharmaceutical lifecycle and emphasizing the societal dimension is novel in the largely technology dominated discourse on PIE. Requirements for and barriers to changes thus provide a valuable contribution to society at large and decision makers in particular when dealing with PIE.

CHAPTER SIX

DISCUSSION AND CONCLUSION

Discussion and conclusion

This thesis presents a unique integration of environmental and societal aspects regarding pharmaceutical-related water pollution. Using the DPSIR framework as structure, it presents insights for all DPSIR stages, adopting and combining methods of multiple disciplines. This includes a quantification of pharmaceutical emissions and an evaluation of their environmental impact, using the GWF as an indicator of degradative water consumption (chapters 2 and 3). Chapter 4 is set out at the interface between systematic drivers and pollution potential of veterinary pharmaceuticals whereby differences among livestock production systems are analysed and discussed. In Chapter 5 an analysis of the current system causing pharmaceutical emissions is presented. Taking this as a starting point, alternative societal solutions are delineated. While each of these chapters provides novel scientific insights, the thesis as a whole is the first integrative assessment on pharmaceutical pollution. This integration (which should be considered as a first attempt where various aspects such as the pharmaceutical manufacturing are still lacking) adds a novel, interdisciplinary scope to the scientific discourse about pharmaceuticals in the environment. On the one hand it highlights the relevance of the existing and still expanding research on emission measuring, modelling and risk assessments. On the other hand, it demonstrates what dynamics are causing these emissions and how societies can handle the situation in the future.

To communicate about the integrative aspects around pharmaceutical pollution, results of this work were presented in scientific papers and conferences, but also to a wider societal audience through a watershed information systems or webinars and stakeholder dialogs as part of the MEDUWA-Vecht(e) project and the Water Footprint Network. I consider giving the topic a more societal audience essential considering the interlinkages between the topic's societal and environmental dimension.

An integrating understanding about the severity of pharmaceutical pollution, where it majorly originates from and what potential futures exists provides knowledge for decision making in different policy fields as well. Current policy developments targeting at sustainable development have a strong focus on integrating environmental and societal objectives. Global examples are the UN's Sustainable Development Goals. Different goals specifically target at human health (SDG 3 – good health and wellbeing) and environmental health (SDG 6 – clean water and sanitation, SDG 14 – life below water and, SDG 15 – life on land) (United Nations, 2021). Another example is the one health approach, which considers human, animal and environmental health as interlinked. In this context, the EU has implemented the European one health

action plan against antimicrobial resistance in 2017 (European Commission, 2021a). Also in agricultural policies the interlinkages between sustainability topics become more visible. The recently adopted CAP reform states diverse objectives relating to environmental, economic, social and health aspects (European Commission, 2021b). These policy developments emphasize the need to integrate perspectives in order to make cautious policy decisions. In the context of pharmaceutical pollution integrated assessments have however not received sufficient attention given the current policy developments. Moreover, pharmaceutical pollution is often a forgotten dimension in policies targeting at sustainable development.

6.1. Assessing pharmaceutical emissions from diverse sources and their impacts

Water pollution by pharmaceuticals is widespread, causing both environmental and human health risks. By estimating the GWF as an indicator of water pollution for different entities and geographical levels, this study enriches the scientific discourse in a dual way as described in the following paragraphs: 1) the WF research is augmented by a GWF assessment of pharmaceuticals, a set of pollutants rarely investigated in this context; 2) a contribution to the research field of pharmaceuticals in the environment by increasing understanding of the current state of pharmaceutical pollution.

Over the past two decades the WF has become an established tool to account for consumptive and degradative water use related to the provision of goods and services (Hoekstra, 2019). Research has expanded around both, the consumptive (e.g. Mekonnen and Gerbens-Leenes (2020), Mekonnen and Hoekstra (2020), Vanham et al. (2019)), and degradative (e.g. Aldaya et al. (2020), Feng et al. (2021), Mekonnen and Hoekstra (2018)) elements of the WF, but including pharmaceuticals into WF assessments is new. This describes a methodological innovation of this thesis, which presents GWFs of human and veterinary pharmaceuticals at different geographical levels.

The scientific literature on pharmaceuticals in the environment has been increasing over the past decades and (at least for a series of substances) knowledge about their environmental occurrence, behaviour and associated risks is substantive. Recent reviews show that pharmaceutical substances in waters have been detected globally and (at least partially) at concentrations where effects on aquatic organisms can be expected (Adeleye et al., 2022, Aus der Beek et al., 2016, Richardson and Ternes, 2018, Świacka et al., 2022). Despite their finding that in the majority of studies does not specify the emission source, Aus der Beek et al. (2016) conclude (from the studies pro-

viding information on the pharmaceutical origin) that globally most pharmaceuticals enter the aquatic environment from domestic waste water discharges. Other emission sources, such as agriculture, show importance locally (Aus der Beek et al., 2016). In this thesis the GWF was first estimated for human as well as veterinary pharmaceuticals at different geographical levels (chapter 2). The results show that this type of pollution contributes substantially to WFs estimated in previous studies, which did not include pharmaceutical pollution. Per capita GWFs resulting from average Dutch human pharmaceutical consumption is for instance one magnitude higher than the total per capita WF estimated by Mekonnen and Hoekstra (2011). Moreover, the assessment on catchment level, where GWFs were compared to the available runoff, indicated hotspots for which critical pharmaceutical loads were exceeded and thus ecotoxic effects cannot be excluded. Considering that water resources are finite in terms of quantity and quality (van Vliet et al., 2017), this study's outcomes highlight the relevance of including pharmaceutical pollution in the assessment of freshwater availability.

Due to the precautionary assumption of all environmental veterinary pharmaceutical emissions being emissions to freshwater in the 2nd chapter as well as identified knowledge gaps about veterinary pharmaceutical emission modelling, an integrated modelling approach for veterinary pharmaceuticals was developed in Chapter 3. This approach covers emission modelling over the pharmaceutical's lifecycle from livestock administration - via excretion, degradation during manure storage, fate in soil – to the transport into surface water. A specific focus was set on the fate and transport after field application which was estimated using the veterinary antibiotic transport model (VANTOM, (Bailey, 2015)). The approach was applied to the German-Dutch Vecht river catchment, a region with high livestock densities compared to the EU's average (Eurostat, 2019). Menz et al. (2015) have shown that there is increased environmental risks resulting from veterinary pharmaceuticals in regions with above-average livestock densities. The results of Chapter 3 demonstrate that for the case of the Vecht catchment, less than 1% of the administered antibiotics are expected to reach surface waters. Major fractions of the substance loads dissipate during metabolization in the body, storage in the manure and in the soil. Despite these results, I warrant awareness to the topic due to three aspects. First, the study's uncertainty analysis revealed uncertainty ranges of several orders of magnitude, which was largely attributed to weak or absent empirical data. Second, the outcomes show that substances can accumulate in soil and resulting effects are not captured in the assessment. In a recent review about pharmaceuticals in soil, the authors call attention to the topic as soils can become a source of pharmaceuticals emissions to groundwater and cultivated plants and thus enter the food chain

(Gworek et al., 2021). Third, the pollution of groundwater is not assessed. This pollution however exists as studies conducted in German and Dutch regions with high livestock densities have shown (Karfusehr et al., 2018, Kivits et al., 2018).

6.2. Pharmaceutical pollution from different livestock production systems

Pharmaceutical pollution resulting from livestock production is evidential. Still, no previous study has investigated if differences in pollution exist among different livestock production systems. Such investigation can however be insightful for an understanding of how sustainable the different production systems are performing with regard to the diverse sustainability themes (van der Linden et al., 2020). Considering current policy developments such as the CAP reform under the European Green Deal, which specifically aim for sustainable development, stress the importance of including the so far forgotten pharmaceutical pollution in sustainability assessments.

In Chapter 4 of this thesis a framework to assess pharmaceutical pollution from different livestock production systems is developed. Using the framework, a pilot assessment is conducted for a set of indicator substances in the German-Dutch context. The study differentiates between the livestock types beef cattle, dairy cattle, pigs, broilers and laying hens as well as between the production systems organic and conventional. The framework presents an inventory of factors that are influential to pharmaceutical pollution along the entire pharmaceutical chain. In the pilot assessment it is shown that the pollution potential for some of these factors differ among conventional and organic production systems, for others no difference was observed. While the differences among production systems are displayed in qualitative terms, the assessment contains quantitative information on substance-specific excretion rate, degradation in manure and soil and PNEC. This allowed to indicate which substances, livestock types, production systems or the combination thereof has the highest or lowest pollution potential. While decision makers can use the information on former to address substances and production systems with high pollution potential with priority, information about latter can be used as best practice examples. Considering the large amount of pharmaceutical substances on the market and ongoing policy developments such as the strategic approach to pharmaceuticals in the environment, prioritizing is a necessary first step, which is an ongoing challenge in the scientific field (Kim et al., 2008, Li et al., 2020, Zhou et al., 2019). For the German-Dutch context Chapter 4 provides data that can be used as a first step for such

prioritization as well as to communicate which substances and livestock types show less pollution potential. Despite this advance, the study revealed several data gaps which should be filled in order to give pronounced advice towards a more sustainable agriculture. As global livestock production and thus veterinary pharmaceutical use is predicted to increase towards the future (Van Boeckel et al., 2015), knowledge on which production systems have the least pollution potential is essential.

6.3. Alternative societal solutions

It is undisputable that humanity has benefited from pharmaceutical use. Nevertheless, manifold evidence about pharmaceutical pollution and related environmental and human health risks exists. Therefore, this thesis gives answers to what options society has to handle the situation. Taking transition research's multi-level perspective framework as a theoretical basis, Chapter 5 presents a novel analysis of the current system leading to today's pharmaceuticals emissions as well as alternative future systems. Exploiting literature and interviews with actors from pharmaceutical industry, the health and agricultural sector, the qualitative analysis increases understanding of current dynamics and gives decision makers indications for potential future pathways. The systematic view on the current system shows that (in the Dutch-German context), society's perception deeply roots in prioritising human wellbeing over environmental risks. For the veterinary sector this viewpoint is less pronounced. Analysing collected data regarding potential future pathways carved three alternative societal solutions: 1) accepting pharmaceuticals in the environment where changes to the current system are not required; 2) modifying the current system by implementing (technical and non-technical) innovations to decrease pharmaceutical emissions; 3) fundamentally changing the current system to minimize pharmaceutical emissions, giving priority to environmental health.

While many studies propose individual (mostly) technical measures to reduce pharmaceutical emissions (e.g. green pharmacy (Leder et al., 2015), waste water treatment plant upgrades (Fröhlich et al., 2019), manure composting techniques (Ramaswamy et al., 2010)), this is the first research taking a societal viewpoint and identifying different future options. This viewpoint adds crucial information to the discourse on (more) sustainable futures that is intended by current policy developments such as the abovementioned SDGs, the One Health Approach or CAP reform.

6.4. Reflection and future outlook

Pharmaceuticals in the environment is a complex research field due to its many facets: 1) pharmaceuticals being life savers and environmental pollutants at once; 2) the large number of substances, metabolites and transformation products; 3) the diversity of emission sources and pathways to the environment. Using the DPSIR framework this thesis integrates several of these facets while at the same time focussing on those where immense research gaps were identified. This thesis' research results contribute to completing the picture on pharmaceutical environmental pollution. Considering that water resources are limited, competing demands and scarcity already exists in many regions around the globe, this study emphasizes the relevance to consider degradative water use specifically for pharmaceuticals in humanity's appropriation of water resources. An aspect not included in this thesis, is the pollution from pharmaceutical manufacturing. To account for the pollution along the pharmaceuticals' entire supply chains, this should be included in future GWF assessments.

One essential question arising from the increasingly comprehensive knowledge about pharmaceutical pollution is how to handle the situation in the future – a topic addressed in this thesis for the first time from a societal perspective. For human pharmaceutical pollution the argument of pharmaceuticals being life savers weights strongly (as also reflected by the UN's SDGs). Here current policies (in the EU) are developing towards implementation of reduction measures along the pharmaceutical lifecycle. Yet, comparisons of measures (including effects, trade-offs and feasibility) are not comprehensively available. Such analysis is, however, essential for policy makers to decide and prioritize on what measures to implement. For veterinary pharmaceutical pollution the assessment of different livestock production systems suggests that certain practices can lead to less pollution. Enforcing such best practices in policies could be a first step to reduce pharmaceutical water pollution. To entirely avoid veterinary pharmaceutical pollution from livestock production would only be possible by putting an end to animal product consumption entirely. This is one of the delineated solutions from this research and furthermore a future option beneficial for other sustainability challenges, such as nitrogen and phosphorus pollution, land degradation or greenhouse gas emissions (Leip et al., 2015).

This thesis has demonstrated the relevance of pharmaceutical pollution for freshwater systems. Considering desired sustainable development as reflected by current policy developments, it can be concluded that pharmaceutical pollution should be lifted from a niche topic that is specifically addressed in pharmaceutical pollution-oriented studies to a mature research theme in sustainability assessments.

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Appendix A: An appendix to Chapter 2

A 1. Methods and data

A 1.1. Substance selection

Table A1 presents the substances considered in the national studies for Germany (GE) and the Netherlands (NL) and in the study for the Vecht catchment. Regarding human pharmaceuticals, we consider a large variety of substances from different therapeutic classes for the grey water footprint (GWF) assessment on national and regional level. The substance selection was based on data availability. The selection of veterinary pharmaceuticals was limited to the therapeutic class of antibiotics. The substances under investigation represent compounds that are sold in large amounts in comparison to other veterinary antibiotics and/or have been detected in the environment within the case study regions (Karfusehr et al., 2018, Kivits et al., 2018, Veldman et al., 2018, Wallmann et al., 2018).

Table A1: Selected substances including therapeutic class and type of application.

Substance	Therapeutic class	Sector of application		GWF assessment	
		Human	Veterinary	Human	Veterinary
Amantadine	Antiviral	✓	×	✓	×
Amoxicillin	Antibiotic	✓	✓	×	✓
Carbamazepine	Antiepilepticum	✓	×	✓	×
Ciprofloxacin	Antibiotic	✓	×	✓	×
Diclofenac	NSAID[1]	✓	×	✓	×
Doxycycline	Antibiotic	✓	✓	✓	✓
Erythromycin	Antibiotic	✓	✓	✓	×
Ethinylestradiol	Hormone	✓	×	✓	×
Metformin	Antidiabetic	✓	×	✓	×
Metoprolol	Beta blocker	✓	×	✓	×
Oxazepam	Psycholeptic	✓	×	✓	×
Oxytetracycline	Antibiotic	✓	✓	×	✓
Sulfamethazine	Antibiotic	✓	✓	×	✓
Tetracycline	Antibiotic	✓	✓	×	✓
Valsartan	Hypertensive	✓	×	✓	×

1 Nonsteroidal anti-inflammatory drug

A 1.2. Characteristics of the Vecht river catchment

The Vecht river catchment (Figure S1) is a transboundary catchment shared by Germany (GE) and the Netherlands (NL). It is part of the larger Rhine river basin, also under the European Water Framework Directive (ICPR, 2015). In GE, the catchment stretches out over the states North Rhine-Westphalia and Lower Saxony, in NL over the provinces Overijssel and Drenthe. The catchment's size is about 6,000 km^2 of which 3,600 km^2 are arable and grassland used for agriculture. The region has approximately 1.5 million inhabitants of which around 20% live in GE and 80% in NL. There are several larger sized cities in the area such as Nordhorn (53,000 inhabitants), Enschede (158,000 inhabitants), Hengelo (81,000 inhabitants), Almelo (72,000 inhabitants) and Zwolle (125,000 inhabitants). The Vecht catchment has relatively high livestock densities, with over 1.4 livestock units per hectare of utilized agricultural area (Eurostat, 2019). The Vecht river has its source near Laer (GE) and flows into the Zwarte Water which leads to the lake Ijssel (NL). Larger tributaries of the Vecht river include the Steinfurter Aa, Dinkel and Regge. There has been intensive human interference into the catchment's hydrological system.

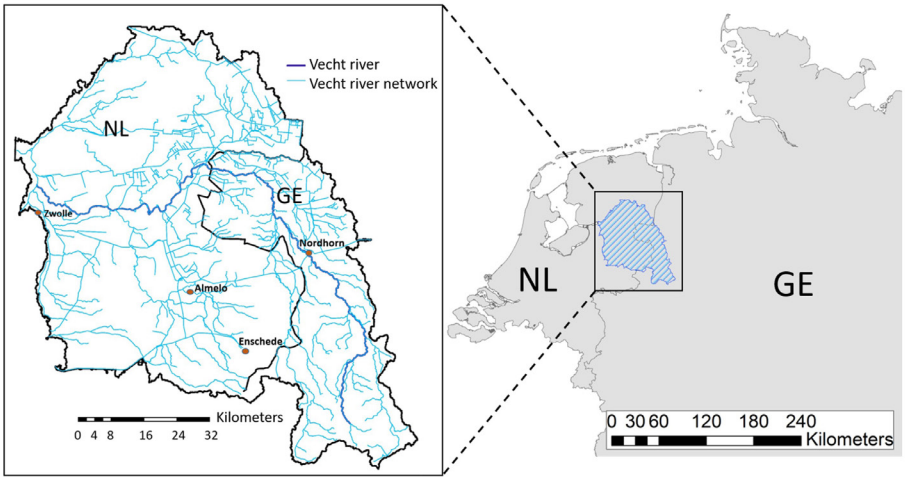


Figure A1. The Vecht river catchment, indicating the German (GE) and Dutch (NL) part of the catchment.

A 1.3. Input data human pharmaceutical loads

Data on pharmaceutical sales for GE and NL were obtained from IQVIA[2] and SFK[3] respectively. Data for the Vecht catchment at the level of grouped municipalities were provided by IQVIA and SFK as well. The reference year for all pharmacy sales data is 2017. It is assumed that the amount of sold pharmaceuticals equals the amount consumed pharmaceuticals. Furthermore, local hospitals in the Vecht catchment were approached to obtain the pharmaceutical dispersion through their hospital pharmacies. For hospitals in the region that did not provide data, pharmaceutical dispersion was extrapolated from the others, differentiating between German and Dutch hospitals.

The excreted fraction from the human body varies among pharmaceuticals. We focus here on what is excreted in the same form as the parent compound. For this study, excreted fractions were determined from literature. A comprehensive list is presented in Table A2.

In GE and NL the connection rates to public wastewater treatment plants (WWTPs) are 97% and 99%, respectively (OECD, 2015). In both countries, households are responsible to treat their wastewater if they are not connected to public WWTPs. Therefore, we assume for our estimations of pharmaceutical loads that all wastewater undergoes treatment. The removal of pharmaceutical residues during treatment is dependent on substance properties and WWTP characteristics such as treatment steps, plant size and retention time (Jelić et al., 2012, Yang et al., 2011). In GE and NL, tertiary treatment (a combination of mechanical, biological treatment and nutrient removal) is predominant (OECD, 2015). Conventional treatment is not designed to specifically remove pharmaceuticals or other micropollutants (Jelić et al., 2012) and depending on the substance, fractions of pharmaceuticals are not eliminated during the treatment process. Removal fractions of pharmaceuticals were determined from literature (Table A3). We preferentially considered literature that describes pharmaceutical removal determined with flow measurements over at least 24 hours within plants with tertiary treatment and used median values for our estimations when multiple suitable data sets were identified. In case of multiple measurements for one treatment plant, average values were determined.

2 IQVIA is an Institute for Human Data Science. Data retrieved from IQVIA is based on drug prescriptions that are retailed by pharmacies. Sales data for OTC-compounds are included by extrapolating data from pharmacy questionnaires.

3 SFK is the Dutch Foundation of Pharmaceutical Statistics and collects pharmaceutical sales data for 95% of the Dutch community pharmacies. The data retrieved from SFK include an extrapolation to all pharmacy pharmaceutical sales. According to SFK, an additional 7% of pharmaceutical sales are not included in the data by SFK because these drugs are dispersed by private practitioners. We accounted for this by an increase of pharmacy sales by 7%.

Table A2. As parent compound excreted fraction used for the grey water footprint estimations.

Substance	Excreted fraction [%]	Reference
Amantadine	86	Moffat et al. (2011)
Amoxicillin	60	Moffat et al. (2011)
Carbamazepine	6	Kümmerer et al. (2011)
Ciprofloxacin	67	Lienert et al. (2007)
Diclofenac	33.3	Kümmerer et al. (2011)
Doxycycline	40	Moffat et al. (2011)
Erythromycin	84	Kümmerer et al. (2011)
Ethinylestradiol	59	Lienert et al. (2007)
Metformin	70	Moffat et al. (2011)
Metoprolol	10	Moffat et al. (2011)
Oxazepam	10	Moffat et al. (2011)
Oxytetracycline	81	Hirsch et al. (1999)
Sulfamethazine	7.5	Moffat et al. (2011)
Tetracycline	85	Hirsch et al. (1999)
Valsartan	87	Moffat et al. (2011)

For substances where a negative median removal was determined, we assumed that there is no elimination. For amantadine no data for removal during tertiary treatment was available. In this case, a removal fraction of 42.3% reported for biological treatment was used (Ghosh et al., 2010). No distinctions were examined for different WWTP sizes or operations. From the WWTP discharge, the wastewater is released into the aquatic environment as a point source.

A 1.4. Method and input data veterinary pharmaceutical loads

The amounts of administered substances distinguishing between livestock types are not publicly accessible, neither in GE nor in NL. For GE national substance-specific data of total antibiotic annual sales for 2017 were obtained from Wallmann et al. (2018). Data on total antibiotic sales for individual substances on postcode level (first two dig-

Table A3. Removed pharmaceutical fractions in wastewater treatment plants selected from literature considering plants with tertiary treatment.

Substance	Removed fraction in %	References	Median removed fraction in %
Carbamazepine	-193; -6.6; 0; 0; 0; 2; 2.6; 3; 5; 9; 9.5; 10; 11; 58	(Abbeglen and Siegrist, 2012, de Jesus Gaffney et al., 2017, Feldmann, 2005, Gurke et al., 2015, Oosterhuis et al., 2013, Radjenovic et al., 2009, Rosal et al., 2010, Sacher and Thoma, 2014, Ternes et al., 2007, Vieno et al., 2007, Zuehlke et al., 2006)	2.8
Ciprofloxacin	57; 58; 59; 74; 79; 80.5; 82.5; 90; 92; 95.5;	(de Jesus Gaffney et al., 2017, Feldmann, 2005, Guerra et al., 2014, Lindberg et al., 2005, Mauer, 2011, Rosal et al., 2010, Vieno et al., 2007, Zorita et al., 2009)	79.8
Diclofenac	-105; -9; 0; 14; 21.8; 23; 28; 33; 37; 40; 44;	(Abbeglen and Siegrist, 2012, de Jesus Gaffney et al., 2017, Feldmann, 2005, Oosterhuis et al., 2013, Radjenovic et al., 2009, Sacher and Thoma, 2014, Ternes et al., 2007, Zorita et al., 2009)	23
Doxycycline	-174; -173; 33; 52.2	(Lindberg et al., 2005, Rosal et al., 2010, Ternes et al., 2007)	-84
Erythromycin	-2; 4.3; 14; 25; 35.4; 48.5	(de Jesus Gaffney et al., 2017, Feldmann, 2005, Guerra et al., 2014, Radjenovic et al., 2009, Rosal et al., 2010, Ternes et al., 2007)	19.5
Ethinylestradiol	70.5	(Zuehlke et al., 2006)	70.5
Metformin	96; 96; 97; 98; 99; 99.2	(de Jesus Gaffney et al., 2017, Oosterhuis et al., 2013, Sacher and Thoma, 2014)	97.5
Metoprolol	-8.6; 2; 6.5; 16.7; 21; 21; 24.7; 25; 25; 29; 31; 65	(de Jesus Gaffney et al., 2017, Gurke et al., 2015, Maurer et al., 2007, Oosterhuis et al., 2013, Radjenovic et al., 2009, Rosal et al., 2010, Sacher and Thoma, 2014, Ternes et al., 2007, Vieno et al., 2007, Zuehlke et al., 2006)	22.9
Oxazepam	-46; 0	(Bijlsma et al., 2012, de Jesus Gaffney et al., 2017)	-23
Valsartan	24.4; 95	(Gurke et al., 2015, Oosterhuis et al., 2013)	59.7

its) for the German part of the Vecht catchment were provided by the German Federal Office of Consumer Protection and Food Safety (Wallmann, 2017). The reference year is 2016. For NL, the most accurate data available are the national antibiotic sales per substance group (e.g. tetracyclines). From this information, an amount sold per substance was estimated proportionally to the amounts of substance sold from each group in GE. In NL, 98% of all antibiotics are sold to the livestock sector (Van Geijlswijk et al., 2018). Since more specific data is lacking, we assume that the same applies for GE. In 2016 the cattle, pig and poultry livestock population accounted for 97% of the total livestock population in both GE and NL (Eurostat, 2019). In NL, 99% of antibiotics used in the livestock sector are given to cows, pigs and chicken[4] (Van Geijlswijk et al., 2018). As no other data are available for GE, we assume that the same ratio applies here. For the GWF estimations we differentiate between pharmaceutical loads from beef cattle[5], dairy cattle, pigs, broilers and laying hens. The overall pharmaceutical use in the livestock sector is allocated to each animal type based on their relative weight as there is no substance-specific information about the number and frequency of treatments per animal. For this reason, we take into account the number of animals per livestock type as well as the average body weight per livestock type. Livestock density data on national and regional scale were taken from CBS (2019), DESTATIS (2019b), IT.NRW (2019) and LSN (2019). Average body weights per animal type were defined based on data from CVPM (2016). No region-specific data on antibiotic usage or sales data were available for the Dutch part of the Vecht catchment. Therefore, national data were translated to regional level proportional to the livestock densities in the Vecht catchment.

Data for excreted fractions of veterinary pharmaceuticals are scattered and not comprehensively available by substance and animal type, while often not differentiating between parent compounds and metabolites (Feinman and Matheson, 1978, Halling-Sorensen et al., 2001, Kim et al., 2010a). Due to this data gap, we take excretion data from the human metabolism as the most suitable option for our estimations.

According to Montforts (1999), pigs and chicken spend the whole year inside housing. Cattle are partly outside grazing, which results in direct dung distribution on pasture land. To determine the load directly emitted to pasture land, we account for one thirds of cattle grazing for half a year (BMEL, 2018). For inside animal housing, manure is generally collected and stored before it is applied to the fields. As antibiotics are known to decay during manure storage (Dolliver et al., 2008, Song and Guo, 2014, Wang and Yates, 2008, Wang et al., 2006), this process of the excreted compounds is considered in order to determine the load emitted to fields. We assume a constant

4 Assuming that the category "other poultry farming sectors" exclusively includes the chicken farming sector.

5 All veal were counted as beef cattle.

input of manure into the storage over one storage period. Even though antibiotic dissipation can depend on parameters such as temperature or manure moisture content (Wang and Yates, 2008), different studies indicate the validity of antibiotic dissipation following a first order decay as a plausible approximation (Ray et al., 2017, Wang and Yates, 2008). We therefore follow this approach for our estimations and express the constant input into storage while antibiotics are decaying as:

$$\frac{dS}{dt} = I - kS \tag{A1}$$

where S [kg] is the quantity of substance in stored manure, I [kg day^{-1}] is the constant substance input with manure input into the storage and k [day^{-1}] is the decay constant. A schematic overview of the process is shown in Figure S2. The solution of this differential equation with starting condition S(t=0) = 0 is:

$$S(t) = \frac{I}{k} \cdot (1 - e^{-k \times t}) \tag{A2}$$

The average storage time of manure differs per animal type and for solid and liquid manure; data are adopted from Mackay et al. (2005). Fractions of liquid versus solid manure were obtained from DESTATIS (2019a). Substance-specific half-lives for liquid and solid manure for the different animal types were derived from Berendsen et al. (2018) and Boxall et al. (2004). In the Netherlands, 30% of chicken manure is incinerated (Leenstra et al., 2014) and therefore does not enter the environment. We consider this by assuming that the daily load from chicken excretions is reduced by 30%. This study does not account for possible degradation and transformation processes of pharmaceuticals during manure fermentation for biogas production as there is an ambiguous picture about these processes due to various influential conditions and parameters (Spielmeyer et al., 2014, UBA, 2018) and the fact that fermentation residues are generally distributed to agricultural fields after biogas production (Leenstra et al., 2014). From the loads emitted daily on pasture land and being stored over one storage period, we determine yearly loads that enter the environment.

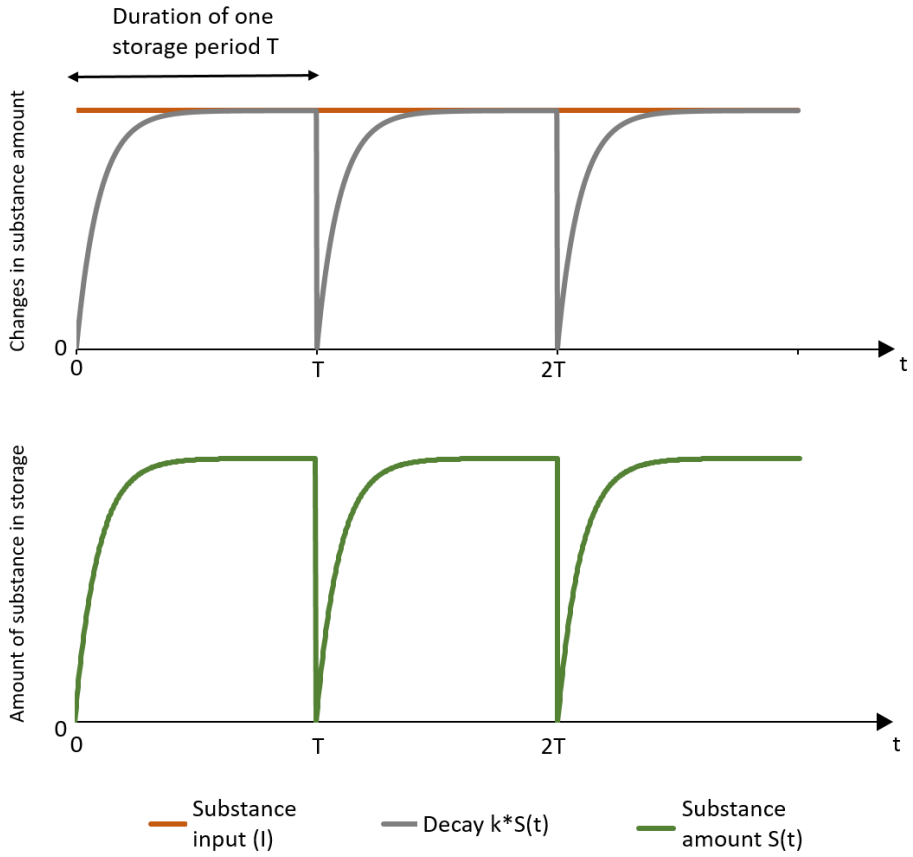


Figure A2. Schematic overview of the inflow of new pharmaceuticals in the manure storage (I) and decay of pharmaceuticals in the manure storage (kS) (upper graph) and the amount of pharmaceuticals in the manure storage (S) (lower graph). The graphs represent the example of amoxicillin (decaying with k=0.14 day^{-1}) used in beef cattle and excreted in liquid manure which is stored for 75 days on average.

A 1.5. PNEC values

PNEC values that are based on ecotoxicological data are used as limit concentrations for the GWF estimation. Table A4 provides an overview of applied PNEC values.

Table A4. Predicted no effect concentrations (PNEC) values selected for the grey water footprint estimations.

Substance	PNEC in µg/L	Reference
Amoxicillin	0.0156	Bergmann et al. (2011)
Carbamazepine	2.5	Bergmann et al. (2011)
Ciprofloxacin	0.036	Bergmann et al. (2011)
Diclofenac	0.1	Bergmann et al. (2011)
Doxycycline	0.054	Bergmann et al. (2011)
Erythromycin	0.206	Bergmann et al. (2011)
Ethinylestradiol	0.00001	Bergmann et al. (2011)
Metformin	60	Bergmann et al. (2011)
Metoprolol	3.2	Bergmann et al. (2011)
Oxazepam	0.0019	Orias and Perrodin (2013)
Oxytetracycline	1.1	Bergmann et al. (2011)
Sulfamethazine	1	Bergmann et al. (2011)
Tetracycline	0.251	Bergmann et al. (2011)
Valsartan	90	Furtmann (2015)

A 2. Results

A 2.1. National GWFs from human and veterinary pharmaceutical use

Table A5 presents GWFs of human pharmaceuticals for selected compounds for Germany and the Netherlands. The results are based on pharmacy sales to households and do not include dispersion through hospitals. Table A6 shows GWFs of veterinary pharmaceuticals for both countries. The results are presented per animal category and per substance. The contribution of each animal category to the overall GWF per country is displayed in Figure A3.

Table A5. Grey water footprints related to human pharmaceutical consumption in Germany and the Netherlands.

Substance	Grey water footprint [10^6 m^3 yr^{-1}]	
	Germany	Netherlands
Amantadine	10,537	1,116
Carbamazepine	888	156
Ciprofloxacin	75,624	13,014
Diclofenac	146,600	11,432
Doxycycline	38,472	7,200
Erythromycin	54,837	1,271
Ethinylestradiol	190,063	193,338
Metformin	382	93
Metoprolol	3,121	575
Oxazepam	34,625	59,050
Valsartan	283	32

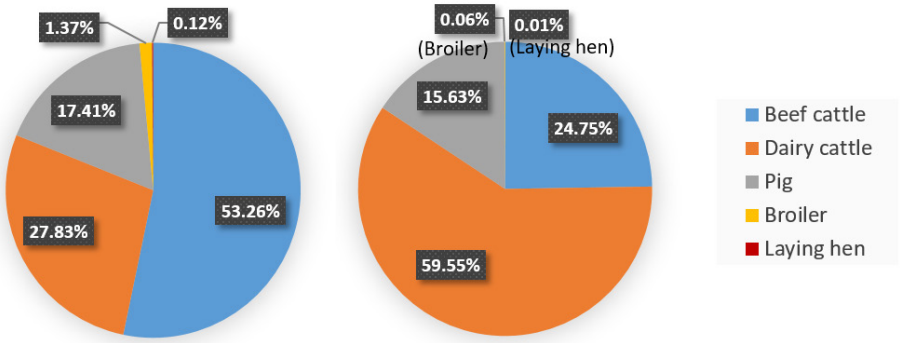


Figure A3. Relative contribution of different animal types to the overall grey water footprint of amoxicillin in Germany (left) and the Netherlands (right).

Table A6. Grey water footprints related to veterinary pharmaceutical use in Germany and the Netherlands.

Substance	Livestock type	Grey water footprint [10^6 m^3 yr^{-1}]	
		Germany	Netherlands
Amoxicillin	Beef cattle	782,335	63,429
	Dairy cattle	408,787	152,615
	Pig	255,777	40,056
	Broiler	20,156	143
	Laying hen	1,757	24
	Total	1,468,812	256,267
Doxycyclin	Beef cattle	136,343	21,285
	Dairy cattle	71,242	51,213
	Pig	39,571	16,653
	Broiler	4,939	94
	Laying hen	544	20
	Total	252,639	89,265
Oxytetracycline	Beef cattle	819	126
	Dairy cattle	428	305
	Pig	355	149
	Broiler	35	1
	Laying hen	5	0.2
	Total	1,642	581
Sulfamethazine	Beef cattle	197	57
	Dairy cattle	103	137
	Pig	18	11
	Broiler	3	0.1
	Laying hen	0.3	0.01
	Total	321	205
Tetracycline	Beef cattle	18,322	3,239
	Dairy cattle	9,573	7,793
	Pig	9,262	3,898
	Broiler	1,497	29
	Laying hen	324	12
	Total	38,977	14,970

Table A7. Annual GWFs per animal type for selected substances in Germany (GE) and the Netherlands (NL).

Animal type		Grey water footprint									
		Amoxicillin		Doxycycline		Oxytetracycline		Sulfamethazine		Tetracycline	
		GE	NL	GE	NL	GE	NL	GE	NL	GE	NL
Beef cattle	$m^3\ yr^{-1}$	99,683	52,744	17,373	17,699	104	105	25	47	2,334	2,693
Dairy cattle	$m^3\ yr^{-1}$	99,683	52,744	17,373	17,699	104	105	25	47	2,334	2,693
Pig	$m^3\ yr^{-1}$	9,672	3,230	1,496	1,343	13	12	1	1	350	314
Broiler	$m^3\ animal^{-1}$	22	0.2	5	0.2	0.04	0.001	0.003	0.0001	2	0.05
Laying hen	$m^3\ yr^{-1}$	42	0.49	13	0.41	0.11	0.003	0.01	0.0003	8	0.24

Table A8. Grey water footprint of human pharmaceuticals for the German and the Dutch part of the Vecht catchment.

Substance	Grey water footprint ($10^6\ m^3\ yr^{-1}$)		
	German part of the Vecht catchment	Dutch part of the Vecht catchment	Total Vecht catchment
Amantadine	40	90	130
Carbamazepine	3	15	18
Ciprofloxacin	308	1,157	1,465
Diclofenac	537	904	1,443
Doxycycline	180	681	861
Erythromycin	318	90	408
Ethinylestradiol	798	15,306	16,104
Metformin	1	8	9
Metoprolol	11	56	67
Oxazepam	159	4940	5,099
Valsartan	0.9	3	4
Inhabitants	304,000	1,244,000	1,548,000

Table A9. Estimated loads and grey water footprints (GWFs) of veterinary pharmaceuticals per animal category in the Vecht catchment, distinguished between Germany (GE) and the Netherlands (NL).

Substance	Animal type	Load GE Vecht [kg yr^{-1}]	Load NL Vecht [kg yr^{-1}]	GWF GE Vecht [10^6 m3 yr^{-1}]	GWF NL Vecht [10^6 m^3 yr^{-1}]	GWF total Vecht [10^6 m^3 yr^{-1}]
Amoxicillin	Beef cattle	161	172	10,345	11,021	21,366
	Dairy cattle	83	421	5,329	26,983	32,313
	Pig	483	88	30,948	5,658	36,605
	Broiler	47	0.33	3,003	21	3,024
	Laying hen	4	0.05	267	4	270
	Total	778	682	49,891	43,687	93,578
Doxycycline	Beef cattle	213	200	13,631	12,802	26,434
	Dairy cattle	110	489	7,022	31,343	38,366
	Pig	257	127	16,483	8,142	24,625
	Broiler	40	0.74	2,533	48	2,580
	Laying hen	4	0.16	284	10	294
	Total	623	817	39,953	52,346	92,299
Oxytetracycline	Beef cattle	22	24	705	3,782	4,487
	Dairy cattle	11	59	2,500	1,474	3,974
	Pig	39	23	321	7	328
	Broiler	5	0.11	38	2	40
	Laying hen	0.6	0.03	4,974	6,804	11,778
	Total	78	106	608	844	1,452
Sulfamethazine	Beef cattle	n.d.	10	0	633	633
	Dairy cattle	n.d.	24	0	1,550	1,550
	Pig	n.d.	1.6	0	100	100
	Broiler	n.d.	0.01	0	1	1
	Laying hen	n.d.	0.00	0	0	0
	Total	n.d.	36	0	2,284	2,284

Substance	Animal type	Load GE Vecht [kg yr^{-1}]	Load NL Vecht [kg yr^{-1}]	GWF GE Vecht [10^6 m3 yr^{-1}]	GWF NL Vecht [10^6 m^3 yr^{-1}]	GWF total Vecht [10^6 m^3 yr^{-1}]
Tetracycline	Beef cattle	94	141	6,041	9,055	15,097
	Dairy cattle	49	346	3,112	22,170	25,282
	Pig	247	138	15,853	8,858	24,711
	Broiler	49	1.1	3,155	67	3,222
	Laying hen	11	0.44	695	28	723
	Total	450	627	28,857	40,178	69,035

Table A7 shows the annual GWFs per animal type in Germany and the Netherlands for all substances considered. As broiler have a lifetime below one year, we do not display annual GWFs for broiler, but the GWF per lifetime. The largest average annual GWFs per animal was determined for beef and dairy cattle. Broiler showed the smallest GWF per animal, resulting also from the estimated lifetime of 37.5 days on average (Santonja et al., 2017).

A 2.2. Grey water footprints of veterinary pharmaceuticals in the Vecht catchment

Table A8 presents the GWFs of human pharmaceutical consumption for the Vecht catchment as a whole and for the German and Dutch parts individually. Table A9 shows loads and GWFs per animal category for the veterinary antibiotics considered in the research.

A 2.3. Sensitivity analysis for the national and river basin level

To understand the effects of input data and underlying assumptions on the results, a sensitivity analysis has been carried out for several parameters considered in the national human and veterinary GWF estimations: sales and consumption data, excretion rates, removal in WWTPs, degradation during manure storage, leaching and runoff after manure application to fields.

In the GWF analysis we assume that the amount of sold pharmaceuticals equals the consumption of pharmaceuticals. Several studies report about pharmaceutical waste resulting from medicines that were not taken by patients due to e.g. change in prescription, expired products or death of patients (Bekker, 2018, Besse and Garric, 2010, Götz and Keil, 2007, Paut Kusturica et al., 2017, Persson et al., 2009, West et al.,

2014). Pharmaceutical fractions that were not taken by patients that are mentioned by Besse and Garric (2010) and Götz and Keil (2007) vary from 0% to 50%. Following this range, we chose a 25% fraction of untaken pharmaceuticals for the sensitivity analysis. The same value was chosen for the analysis of veterinary pharmaceuticals.

Uncertainty further exists regarding excreted pharmaceutical fractions as these are not only influenced by the pharmacokinetics of the substance but also by factors such as the dosage form and the age or sex of the target body (Feldmann, 2005, Mauer, 2011), which were not specifically considered within this study. To understand the effect of varying excreted fractions on the study results, we apply a 10% increase or decrease of the excreted fraction used for the GWF assessment within the sensitivity analysis. For WWTP removal efficiencies, the literature presents ranges for various substances. Per substance, the median determined from a selection of literature values was used within this study. For the sensitivity analysis, the minimum and maximum values from the literature selection were applied, also including negative removal rates. In case of single values available, a deviation of 10% was used as minimum and maximum. The sensitivity to the degradation rate of pharmaceuticals during manure storage was evaluated by assuming changes in manure storage. While we used storage times specified per animal type and manure type, Weinfurtner (2011) estimates a general storage time between 1 and 4 month depending on the vegetation period. For the sensitivity analysis we therefore assume 1 and 4 month storage time. Pharmaceutical leaching and runoff to water bodies was not modelled within this study, taking the precautionary approach of assuming that all pharmaceuticals applied to the field could end up in water. For the sensitivity analysis we consider leaching-runoff fractions below 100%. Several studies investigating the leaching of pharmaceuticals report different environmental behaviour in soil water matrices for different antibiotic groups (Hamscher et al., 2005, Kay et al., 2005, Kim et al., 2010b, Lahr et al., 2017, Ostermann et al., 2013, Pan and Chu, 2016, Pan and Chu, 2017). Even though systematic understanding of leaching behaviour of individual substances is poor, these studies jointly indicate that sulfonamides are more mobile than tetracyclines and therefore more likely to leach to groundwater. For amoxicillin Kim et al. (2012) predict high mobility. Compiling this information, we qualitatively determine a high risk of leaching for amoxicillin and sulfamethazine and a low risk of leaching for doxycycline, oxytetracycline and tetracycline. For the sensitivity analysis we express this as 95% and 5% of the initially applied mass entering water bodies for a high and low risk respectively. Overland runoff is much less than leaching. Following model results by Bailey (2015), we assume an overland runoff to water bodies of 0.15% of the initially applied load.

The effects of changing input parameters on the GWF estimations are presented in Tables A10 and A11. The sensitivity of the GWF results was assessed towards a combination of changing input parameters. Depending on the substance, human GWFs substantially respond to changes in input parameters. As no country-specific parameters were adjusted, the effect of changing input parameters on the results is identical for GE and NL. A 75% consumption of the sold pharmaceuticals, results in a 25% decrease of GWF for all substances. Changing the input parameters of excreted fraction as well as WWTP removal, effects results differently per substance. The effect of adjusting those parameters on the results considerable. Especially for the combination of larger excreted fractions and minimal WWTP removal, there is a large effect on the GWF results. For five out of the 11 substances, GWF increases by over 100% even though only 75% of the sold pharmaceuticals are assumed to be consumed. This reflects the importance of reliable data regarding these parameters for GWF estimations.

Table A10. Changes in human GWF results due to changed input parameters.

	75% appliance						
		-10% excreted fraction			+10% excreted fraction		
			min WWTP removal	max WWTP removal		min WWTP removal	max WWTP removal
Amantadine	-25%	-33%	-21%	-44%	-18%	-3%	-32%
Carbamazepine	-25%	-33%	+103%	-71%	-18%	+149%	-64%
Ciprofloxacin	-25%	-33%	+43%	-85%	-18%	+75%	-82%
Diclofenac	-25%	-33%	+78%	-51%	-18%	+118%	-40%
Doxycycline	-25%	-33%	+85%	-68%	-18%	+126%	-61%
Erythromycin	-25%	-33%	-14%	-57%	-18%	+5%	-47%
Ethinylestradiol	-25%	-33%	-16%	-49%	-18%	+10%	-45%
Metformin	-25%	-33%	+8%	-78%	-18%	+32%	-74%
Metoprolol	-25%	-33%	-5%	-69%	-18%	+16%	-63%
Oxazepam	-25%	-33%	-1%	not assessed[6]	-18%	+20%	not assessed[6]
Valsartan	-25%	-33%	+27%	-92%	-18%	+55%	-90%

For the sensitivity analysis of the national veterinary GWF estimations, country-specific input parameters were changed and results are presented in Table A11. Especially the excreted fraction as well as the manure storage time appear to influence the results.

6 The maximum WWTP removal for Oxazepam was found as 0. As the median was determined negative, we selected 0 removal for the GWF assessment and did not further assess this in the sensitivity analysis.

Table A11. Changes in veterinary GWF results due to changed input parameters.

		75% appliance										
			-10% excreted fraction					+10% excreted fraction				
				1 month manure storage		4 months manure storage			1 month manure storage		4 months manure storage	
					runoff, leaching		runoff, leaching			runoff, leaching		Runoff, leaching
Germany	Amoxicillin	-25%	-29%	-21%	+35%	+43%	-38%	-30%	26%	+34%	-42%	-34%
	Doxycycline	-25%	-27%	-23%	+23%	+26%	-40%	-36%	-94%	-94%	-97%	-97%
	Oxytetracycline	-25%	-27%	-23%	+20%	+24%	-39%	-36%	-94%	-94%	-97%	-97%
	Sulfamethazine	-25%	-29%	-21%	+22%	+30%	-41%	-34%	+14%	+21%	-45%	-38%
	Tetracycline	-25%	-27%	-23%	+39%	+43%	-38%	-34%	-93%	-93%	-97%	-97%
Netherlands	Amoxicillin	-25%	-30%	-20%	+14%	+25%	-35%	-25%	+7%	+17%	-40%	-30%
	Doxycycline	-25%	-28%	-22%	+18%	+24%	-38%	-32%	-94%	-94%	-97%	-97%
	Oxytetracycline	-25%	-28%	-22%	+17%	+22%	-37%	-32%	-94%	-94%	-97%	-97%
	Sulfamethazine	-25%	-30%	-20%	+3%	+14%	-38%	-27%	-3%	+6%	-42%	-32%
	Tetracycline	-25%	-29%	-21%	+28%	+35%	-37%	-30%	-94%	-93%	-97%	-97%

Appendix B: An appendix to Chapter 3

B 1. Methods and data

B 1.1. Characteristics of the Vecht river catchment

The Vecht river has its source near Laer in Germany (GE) and discharges into the Zwarte Water that flows into the Lake IJssel in the Netherlands (NL). Larger tributaries of the Vecht include the Steinfurter Aa, Dinkel and Regge. The river's hydrological system has experienced severe human intervention. From hydrological as well as from EU water policy perspective it belongs to the larger Rhine basin (ICPR, 2015). The transboundary catchment area that stretches out over approximately 6,000 km^2 is illustrated in Figure B1. 80% of the 1.5 million inhabitants live in NL, 20% in GE. Several larger sized cities are located in the area (e.g. Nordhorn, Enschede, Zwolle). The catchment is characterized by intensive agricultural activity. About 3,600 km^2 (1460 km^2 in GE and 2240 km^2 in NL) of the catchment's area are arable and grassland. Livestock densities with over 1.4 livestock units per hectare of utilized agricultural area are high compared to the EU average (Eurostat, 2019). In total, there are 1,200,000 cattle (25% GE, 75% NL), 4,200,000 pigs (50% GE, 50% NL) and 33,500,000 chicken (43% GE, 57% NL) registered in the area (CBS, 2019, IT.NRW, 2019, LSN, 2019). More than 90% of the agricultural area's soil is sand, loamy sand and sandy loam with pHs between 3.7 and 5.3 and organic carbon contents from 0.0% to 44.1% (Ballabio et al., 2016, Jones et al., 2005b, Panagos et al., 2012). The soil's dry bulk densities range between 926 kg m^{-3} and 1556 kg m^{-3} (Ballabio et al., 2016). Soil porosities were calculated from bulk densities and a particle density of 2650 kg m^{-3} (Schjønning et al., 2017) and range from 0.39 to 0.64 m^3 m^{-3}.

B 1.2. Modelled processes per time step in VANTOM

Figure B2 illustrates all processes that are modelled within one time step in VANTOM. At the beginning of a time step a soil as well as VA mass are set. In the first modelled timestep, liquid and solid soil masses are calculated based on area, soil profile, porosity, density and pore water content. For the following timesteps, solid soil masses result from the previous timestep, liquid soil masses are re-calculated with monthly changing pore water levels. VA masses for the model initialization base on previous conditions, for all further timesteps on the previous one. The second process modelled is the fertilizer application. Here, manure containing VA is homogene-

ously mixed in the plough layer. As mass is added to the modelled soil matrix and the plough layer has a fixed depth, the sub-plough layer depth is adapted. Following fertilizing, the VA sorption is modelled. An equilibrium of VA mass in the solid and liquid soil phase is defined. Afterwards, the time-dependent degradation is modelled. The time interval for degradation equals the duration of one timestep. VA remaining after degradation can either remain in the soil until the end of a time step or be transported overland to surface waters. Transportation occurs due to soil erosion and surface runoff that both are driven by a modelled rainfall event (Bailey, 2015).

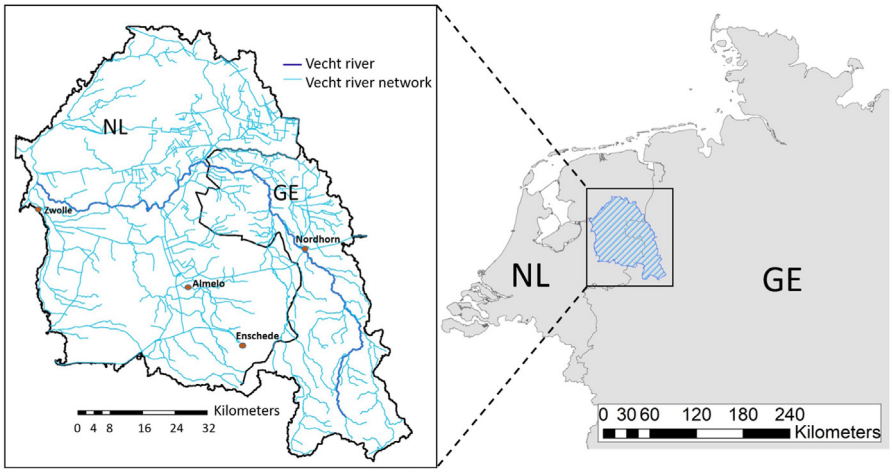


Figure B1. The Vecht river catchment, indicating the German (GE) and Dutch (NL) part of the catchment, obtained from Wöhler et al. (2020b).

B 1.3. Substance specific sorption coefficients

In VANTOM the equilibrium of VAs between the liquid and solid phase in soil is determined by the sorption coefficient K_d. To obtain an overview of sorption coefficients available, we carried out a literature review and clustered K_d values by soil texture, pH and organic carbon content as these environmental parameters are most influential to VA sorption (Wegst-Uhrich et al., 2014) (Table B1). Soil maps for soil texture, pH and organic carbon content were retrieved from the European Soil Data Centre and base on work by Ballabio et al. (2016), Panagos et al. (2012) and Jones et al. (2005b).

Literature K_d values for conditions that fairly match conditions in the Vecht catchments are identified (sand, loamy sand and sandy loam, pH between 3.7 and 5.3, OC from 0% to 44.1%). Given an observed absence of correlations between these three soil parame-

ters and the limited number of K_d values for different soil property combinations found in literature, we assume one K_d value per VA to represent the entire study area. When several matching values were found, the median was taken. For amoxicillin, where no value within the pH conditions was found, the closest to the range was selected.

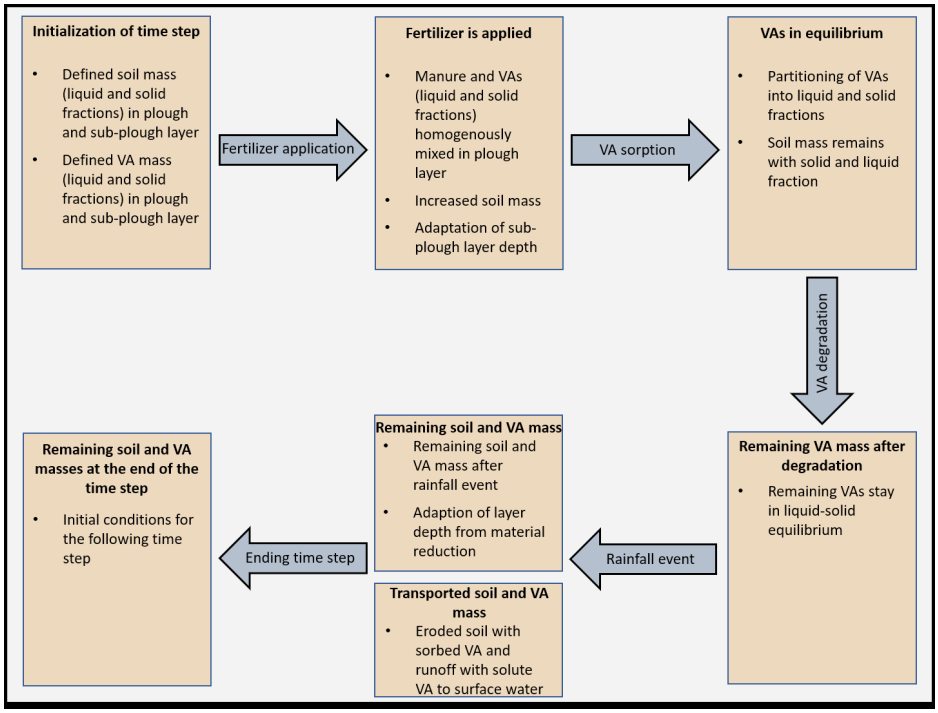


Figure B2: Detailed overview of processes modelled within each time step in VANTOM.

Table B1. Sorption coefficients (Kd) for amoxicillin, doxycycline, oxytetracycline, sulfamethazine and tetracycline, differentiated by soil texture and listed with according pH and organic carbon content (OC). Sorption coefficients that fairly match soil characteristics in the Vecht catchment and were considered to determine one coefficient as model input, are marked bold.

Substance	Soil texture	K_d [L kg^{-1}] (pH [-], OC [%])	References
Amoxicillin	Sandy loam	4.2 (8.5, 0.82); 4.6 (7, 0.82); **5 (5.5, 0.82)**; 5.3 (8.13, 2); 5.6 (8.13, 4); 6 (8.13, 6)	Kim et al. (2012)
	Silt loam	4.3 (8.5, 1.83); 5 (7, 1.83); 5.5 (5.64, 2); 5.7 (5.64, 4); 6.4 (5.64, 6); 6.5 (5.5, 1.83)	Kim et al. (2012)

Substance	Soil texture	K_d [L kg^{-1}] (pH [-], OC [%])	References
Doxycycline	Sandy loam	550 (7.2, 2.53); **603 (5.3, 1.9)**; 813 (7.2, 2.53); **1047 (5.3,1.9)**; **1820 (3.88, 7.26)**; **3890 (3.88, 7.26)**	Teixidó et al. (2012)
	Silt loam	1318 (6.5, 8.78); 1820 (6.5, 8.78)	Teixidó et al. (2012)
	Silty clay	776 (6.2, 5.12); 871 (6.7, 5.41); 1047 (6.7, 5.41); 1072 (6.2, 5.12)	Teixidó et al. (2012)
	Silty clay loam	617 (8.2, 1.14); 977 (8.2, 1.14)	Teixidó et al. (2012)
	Loam	398 (8.2, 1.45); 427 (8.2, 1.45); 603 (7.9, 2.62); 661 (6, 1.7); 692 (7.9, 2.62); 912 (6, 1.7); 1148 (5, 1); 1738 (5, 1)	Teixidó et al. (2012)
	Clay loam	324 (8, 1); 339 (8, 1); 490 (8.1, 2.3); 537 (8.1, 2.3)	Teixidó et al. (2012)
Oxytetracycline	Sand	**41 (5.11, 1.7)**; 120 (7.01, 1.7); 210 (8.47, 1.7); **486 (4.1, 1.78)**; **618 (3.8, 1.68)**; 670 (5.6, 1.4)	Figueroa-Diva et al. (2010), Jones et al. (2005a), Rabølle and Spliid (2000)
	Sandy loam	140 (7.04, 0.3); 140 (8.37, 0.3); **160 (5.05, 0.3)**; 175 (8.5, 0.82); 180 (7, 0.82); 213 (8.13, 2); 220 (5.5, 0.82); 237 (8.13, 4); 270 (8.13, 6); **309 (5.3, 1.9)**; 346 (7.2, 2.53); 549 (5.3, 1.9); 616 (7.2, 2.53); 680 (6.1, 1.6); 771 (3.6, 0.78); 781 (5.4, 0.18); 1026 (5.6, 1.1); **1435 (4.8, 0.05)**; **1445 (3.88, 7.26)**; 1837 (5.5, 4.13); **2398 (3.88, 7.26)**; **2818 (4.4, 0.3)**; 2876 (5.6, 4.56); **3129 (5.3, 0.35)**; **3174 (5.1, 0.2)**; **3426 (4.5, 0.04)**;	Figueroa-Diva et al. (2010), Jones et al. (2005a), Kim et al. (2012), Rabølle and Spliid (2000), Teixidó et al. (2012)
	Loamy sand	310 (6.6, 2.2); 417 (6.3, 1.5); **2519 (4.5, 2.46)**; 2900 (6.99, 2.5); 3100 (8.36, 2.5); **3900 (5.1, 2.5)**; 4200 (6.6, 2.2)	Figueroa-Diva et al. (2010), Jones et al. (2005a), Rabølle and Spliid (2000), Ter Laak et al. (2006)
	Sandy clay loam	1613 (6, 0.23); 3646 (4.6, 0.79)	Jones et al. (2005a)
	Silt loam	190 (8.5, 1.83); 200 (7, 1.83); 210 (7.04, 1.9); 237 (5.64, 2); 260 (5.64, 4); 290 (4, -); 310 (5.64, 6); 313 (5.5, 1.83); 380 (5.13, 1.9); 510 (8.37, 1.9); 750 (4, -); 760 (4, -); 812 (6.5, 8.78); 1023 (6.5, 8.78); 1454 (5.6, 3.08); 1504 (5, 1.87); 2020 (4, -); 2507 (5.2, 2.48); 3135 (4.2, 0.84)	Figueroa-Diva et al. (2010), Jones et al. (2005a), Kim et al. (2012), Teixidó et al. (2012), Vaz (2016)
	Silty clay	490 (6.2, 5.12); 513 (6.7, 5.41); 691 (6.2, 5.12); 707 (6.7, 5.41); 2034 (7.5, 0.47); 4377 (6.6, 1.21)	Jones et al. (2005a), Teixidó et al. (2012)
	Silty clay loam	295 (8.2, 1.14); 316 (8.2, 1.14)	Teixidó et al. (2012)
	Loam	190 (8.2, 1.45); 251 (8.2, 1.45); 380 (7.9, 2.62); 407 (6, 1.7); 478 (7.9, 2.62); 616 (6, 1.7); 812 (5, 1); 1258 (5, 1); 1586 (3.6, 2.58); 2305 (4.5, 1.95); 2886 (5.6, 2.75); 3616 (4.7, 0.16); 4500 (8.07, 8.9); 7200 (6.93,8.9); 7600 (6.93, 8.9); 12047 (3.2, 8.93)	Figueroa-Diva et al. (2010), Jones et al. (2005a), Teixidó et al. (2012)
	Clay	380 (8.6, 3.9); 620 (8.4, 0.46); 790 (5.02, 3.9); 920 (7.01, 3.9); 1250 (5.16, 0.46); 1300 (6.09, 0.46); 1751 (7.2, 3.94); 2038 (7.2, 1.31); 2885 (6.8, 4.16); 3436 (6.6, 0.74); 4897 (5.2, 0.46)	Figueroa-Diva et al. (2010), Jones et al. (2005a)
	Clay loam	114 (8, 1); 128 (8, 1); 186 (8.1, 2.3); 208 (8.1, 2.3); 630 (6.8, 3.1); 4740 (6.8, 3.1)	Teixidó et al. (2012), Ter Laak et al. (2006)

Substance	Soil texture	K_d [L kg^{-1}] (pH [-], OC [%])	References
Sulfamethazine	Sand	0.96 (6.9, 1.1); 5.54 (7, 0)	Fan et al. (2011), Srinivasan et al. (2014)
	Sandy loam	0.23 (9, 0.1); 0.32 (8, 0.1); 0.48 (6, 0.1); 0.49 (9, 1.4); 0.55 (8, 1.4); 0.58 (5.5, 0.1); 0.64 (7, 0.1); 0.78 (5.44, -); 0.9 (9, -); 0.98 (7, 1.4); 1.17 (5.44, -); 1.18 (6, 1.4); 1.22 (5.5, 1.4); 2.03 (5.44, -); 4.88 (5.44, -); 5.1 (7, -); 6.9 (5, -); 9.8 (7.7, 2.1); 10 (7.2, 2.1); 14 (6.7, 2.1); 17 (5.7, 2.1); 22 (5.4, 2.1)	Bailey et al. (2016), Kurwadkar et al. (2007), Lertpaitoonpan et al. (2009), Wegst-Uhrich et al. (2014)
	Loamy sand	0.99 (6.25, 1); 2.5 (7.4, 1); 3.9 (5.6, 1); **4.6 (5.3, 1)**; 7.4 (3.5, 1); 30 (2.3, 1)	Carter et al. (2014), Kurwadkar et al. (2007)
	Silt loam	0.74 (7.4, 1.61); 0.79 (7.5, 1.61); 0.84 (6.6, 1.3); 1.17 (7.2, -); 1.46 (7.8, 9.2); 2.24 (7.2, -); 2.4 (7, 1.61); 2.85 (4.7, 2.3); 3 (7.2, -); 4.1 (7.2, -)	Bailey et al. (2016), Chu et al. (2013), Fan et al. (2011), Thiele-Bruhn and Aust (2004), Thiele-Bruhn et al. (2004)
	Silty clay loam	1.25 (7.9, 7.5); 1.66 (6.1, 2.1); 2.61 (6.7, 5); 2.92 (5.8, 4)	Fan et al. (2011), Srinivasan et al. (2014)
	Loam	1.05 (9, 2.2); 1.16 (9, 3.8); 1.33 (8, 2.2); 1.45 (6.9, 1.1); 1.7 (8, 3.8); 1.98 (7, 2.2); 1.99 (7.9, 7.5); 2.42 (6, 2.2); 2.84 (7, 3.8); 2.52 (5.5, 2.2); 3.05 (6, 2.7); 3.1 (7.3, 1.1); 3.77 (5.5, 2.7); 4 (7.2, 1.1); 4.5 (5.6, 1.1); 5.08 (5.7, 8.2); 10 (3.4, 1.1); 17 (3.1, 1.1)	Fan et al. (2011), Kurwadkar et al. (2007), Lertpaitoonpan et al. (2009), Srinivasan et al. (2014)
	Clay loam	0.34 (8.2, 5.3)	Fan et al. (2011)
Tetracycline	Sand	**41 (4.99, 1.7)**; 120 (7.01, 1.7); 320 (8.52, 1.7)	Figueroa-Diva et al. (2010)
	Sandy loam	130 (8.38, 0.3); **140 (5.02, 0.3)**; 170 (7.02, 0.3); 174 (5.44, -); 241 (7.6, 2.83); 254 (7.6, 2.83); 272 (7.6, 2.83); 281 (7.6, 2.83); 401 (5.44, -); 407 (7.2, 2.53); **427 (5.3, 1.9)**; 676 (7.2, 2.53); **759 (5.3, 1.9)**; 1253 (5.44, -); 1489 (5.44, -); 1585 (**3.88, 7.26**); **2754 (3.88, 7.26**)	Bailey et al. (2016), Chessa et al. (2016), Figueroa-Diva et al. (2010), Teixidó et al. (2012)
	Loamy sand	1500 (8.38, 2.5); 2300 (7.01, 2.5); **6100 (5.04, 2.5)**	Figueroa-Diva et al. (2010)
	Silt loam	270 (5.07, 1.9); 350 (7.04, 1.9); 390 (8.41, 1.9); 794 (6.5, 8.78); 1148 (6.5, 8.78); 1290 (7.2, -); 1996 (7.2, -); 2154 (7.2, -); 2751 (7.2, -)	Bailey et al. (2016), Figueroa-Diva et al. (2010), Teixidó et al. (2012)
	Silty clay	501 (6.2, 5.12)575 (6.7, 5.41); 708 (6.2, 5.12); 776 (6.7, 5.41)	Teixidó et al. (2012)
	Silty clay loam	708 (8.2, 1.14); 794 (8.2, 1.14)	Teixidó et al. (2012)
	Loam	295 (8.2, 1.45); 398 (8.2, 1.45); 417 (6, 1.7); 437 (7.9, 2.62); 550 (7.9, 2.62); 617 (6, 1.7); 1000 (5, 1); 1778 (5, 1); 5600 (8.13, 8.9); 7800 (6.93, 8.9); 8300 (5.04, 8.9)	Figueroa-Diva et al. (2010), Teixidó et al. (2012)
	Clay	979 (5.77, 4); 993 (5.77,4); 1200 (5.3, 3.9); 1200 (8.63, 3.9); 1400 (5.77, 4); 1495 (5.77, 4); 2200 (5.04, 0.46); 2600 (7.02, 0.46); 2800 (8.38, 0.46); 2800 (7.23, 3.9);	Chessa et al. (2016), Figueroa-Diva et al. (2010)
	Clay loam	295 (8. 1); 372 (8, 1); 447 (8.1, 2.3); 525 (8.1, 2.3)	Teixidó et al. (2012)

B 1.4. Substance-specific degradation parameters

VANTOM accounts for VA degradation by adopting a first-order-decay model. Degradation rates or according half-lives for each substance are required inputs, and were obtained from a literature review. Table B2 clusters all half-lives retrieved from literature by soil texture, pH and organic carbon content. Degradation rates refer to the bulk soil and are assumed to be identical for the solid and liquid soil phase.

Table B2. Half-lives (DT50) for amoxicillin, doxycycline, oxytetracycline, sulfamethazine and tetracycline, differentiated by soil texture and listed with according pH and organic carbon content (OC). Half-lives used to determine degradation rates as VANTOM inputs are marked bold.

Substance	Soil type	DT50 [d] (pH [-], OC [%])	References
Amoxicillin	Loam	0.57 (4.6, 2.18)	Braschi et al. (2013)
	Loamy sand	<1 (6.3, 0.4)	Boxall et al. (2006)
	Clay loam	0.43 (8.1, 0.77)	Braschi et al. (2013)
Doxycyclin	Sand	59.4 (7.35, 0.63); 66.5 (7.35, 0.63); 76.3 (7.35, 0.63)	Szatmári et al. (2012)
	Sandy clay loam	46.5 (4.2, 1.42); 62 (4.2, 1.42); 68.2 (4.2, 1.42); 533 (5.6, 1.7)	Shi et al. (2019), Walters et al. (2010)
	Unknown	9.9 (-, -); 12.21 (6.18, 1.086); 14.44 (6.18, 1.086); 15.42 (6.18, 1.086); 15.43 (6.18, 1.086)	Wen et al. (2018), Yan et al. (2018)
Oxytetracycline	Sandy loam	21 (6.2-6.6, 1.4); 33 (7.2, 0.92); 43 (7.89, 2.04); 46 (7.2, 0.35); 56 (7.2, 0.92); 89 (7.89, 2.04)	Blackwell et al. (2007), Li et al. (2016), Wang and Yates (2008), Yang et al. (2009)
	Loamy sand	30.2 (6.92, 0.68); <103 (6.3, 0.4)	Boxall et al. (2006), Li et al. (2010)
	Sandy clay loam	37 (4.3, 1.14)	Yang et al. (2009)
	Silt loam	20 (7.46, 3.8); 28 (7.46, 3.8)	Li et al. (2016)
	Loam	23 (7.3, 1.14)	Aga et al. (2005)
	Silty clay loam	30 (8.5, 2.57)	Yang et al. (2009)
	Clay	39.4 (4.55, 1.64)	Li et al. (2010)
	Unknown	12.81 (7.3, 0.921); 16.66 (7.3, 0.921); 18.89 (7.3, 0.921)	Chen et al. (2014)

Substance	Soil type	DT50 [d] (pH [-], OC [%])	References
Sulfamethazine	Sand	21.2 (7.2, 0.94)	Accinelli et al. (2007)
	Loamy sand	0.99 (6.25, 1)	Carter et al. (2014)
	Silt loam	1.3 (7.5, 3.4); 5.3 (7.5, 3.4); 16.8 (7.5, 18)	Accinelli et al. (2007), Topp et al. (2013)
	Loam	1.2 (6.4, 2.6); 1.2 (6.4, 2.6); 1.3 (6.4, 2.6); 1.9 (6.4, 2.6); 3.2 (6.4, 2.6); 4.1 (6.4, 2.6); 5.9 (6.4, 2.6); 6.6 (6.4, 2.6)	Lertpaitoonpan et al. (2015)
	Clay loam	24.8 (6.45, 0.8)	Pan and Chu (2016)
Tetracycline	Sandy loam	28 (7.89, 2.04); 82 (7.89, 2.04)	Li et al. (2016)
	Loamy sand	20.9 (6.92, 0.67)	Li et al. (2010)
	Sandy clay loam	578 (5.6, 1.7)	Walters et al. (2010)
	Silt loam	17 (7.46, 3.8); 26 (7.46, 3.8)	Li et al. (2016)
	Clay	21.7 (4.55, 1.64)	Li et al. (2010)
	Clay loam	31.5 (6.45, 0.8)	Pan and Chu (2016)

B 1.5. PESERA model and use of PESERA outputs in VANTOM

The present study uses the Pan-European Soil Erosion Risk assessment (PESERA) model (Kirkby et al., 2008) to obtain soil moisture deficits, surface runoff and soil erosion as inputs for VANTOM. Bailey (2015) adopted hydrologically based inputs from PESERA as well to calculate VA emissions across Germany. PESERA is a process-based model which uses 128 input layers (covering climate, land use, crop planting, soil use and topographic data) to estimate runoff and soil erosion (Kirkby et al., 2008). These outputs are monthly averages typically at a cell size in the range 100 m^2 - 1 km^2 (Kirkby et al., 2008). The model was originally designed to generate soil erosion and runoff estimates across Europe and (despite incomplete data for calibration or validation on European scale) shown to successfully predict relative patterns of soil erosion across Belgian and Czech agricultural land (Van Rompaey et al., 2003). For the first Europe-wide model implementation - the PESERA map - the developers used different cross-continental datasets covering eight monthly data layers with climate inputs, 25 data layers for land-use, crops and planting dates, six data layers for soil parameters and one layer for the relief (Kirkby et al., 2008, Kirkby et al., 2004). In spite of an overall satisfying performance on European scale, the authors suggest the potential for improvement of erosion estimates by using region-specific climate data (Kirkby et al., 2004) which was done in the current research. Climate data layers required for PESERA cover the mean monthly temperature range corrected for altitude, monthly temperature range, mean monthly potential evapotranspiration, mean monthly rainfall, mean monthly

rainfall per rain day and coefficient of variation of monthly rainfall per rain day (Kirkby et al., 2008). For the present study we generated PESERA outputs based on climate averages for the period 1970 until 2000. The mean monthly temperature range corrected for altitude as well as the monthly temperature range were obtained from the worldclim database (version 2.1) (Fick and Hijmans, 2017), which provides gridded climate datasets on 1 km^2 spatial resolution. The data originates from weather station records and was interpolated using best-fit regional models (Fick and Hijmans, 2017). The mean monthly potential evapotranspiration was retrieved from the Global Aridity and PET database which uses worldclim, and therefore national weather station data, as a basis (Zomer et al., 2008). The mean monthly rainfall, mean monthly rainfall per rain day and coefficient of variation of monthly rainfall per rain day were calculated based on the E-OBS dataset (version 22.0e) (Cornes et al., 2018). E-OBS daily precipitation data bases on weather station information that is provided by national meteorological services across Europe (Cornes et al., 2018). The PESERA input data layers on land use, crop planting, soil use and topography remained as used and described for the PESERA map by Kirkby et al. (2004) and Kirkby et al. (2008).

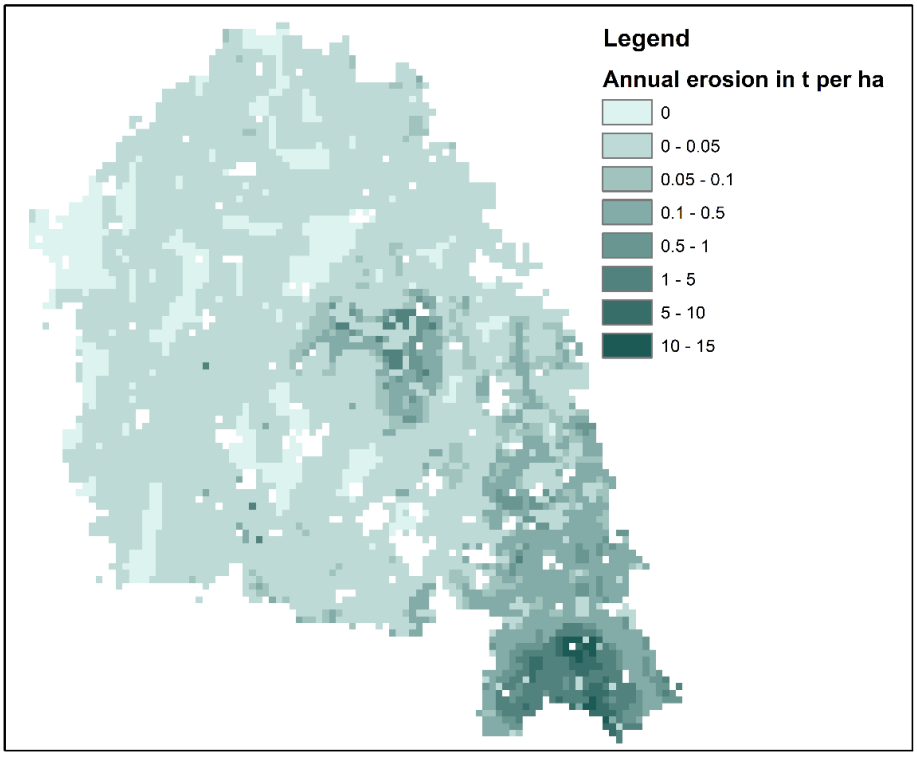


Figure B3. Annual soil erosion in the Vecht catchment modelled with PESERA on a 1 km2 spatial resolution.

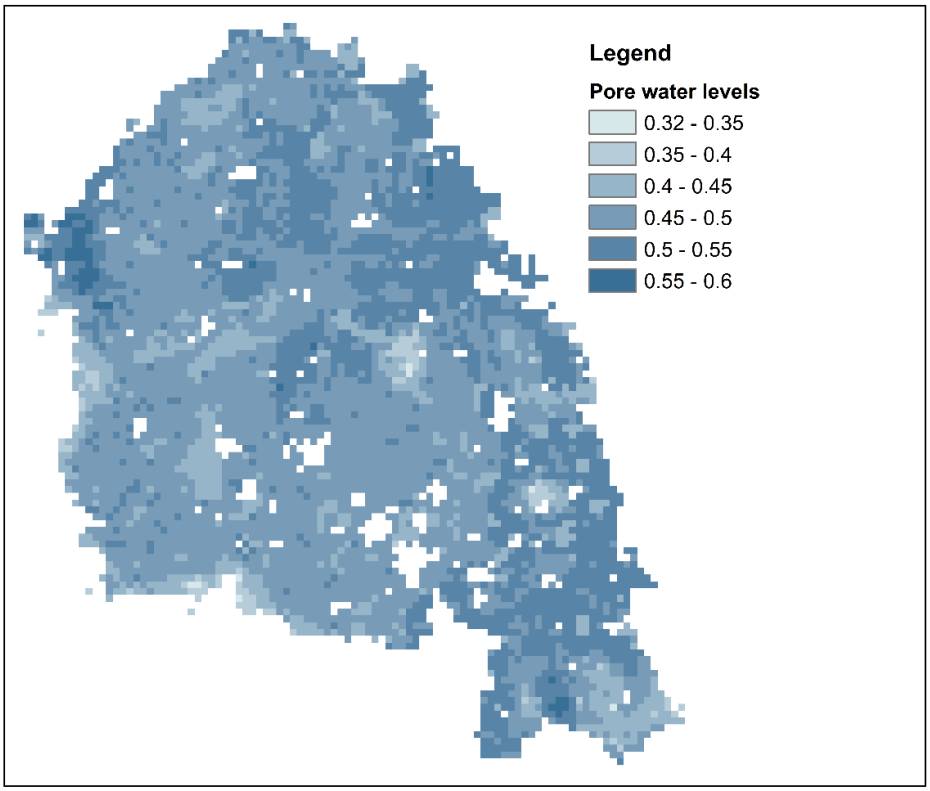


Figure B4. Annual average pore water levels in the Vecht catchment at 1 km² spatial resolution.

Output data from PESERA were used as VANTOM inputs. One of these is the gridded soil erosion data for the Vecht catchment with a monthly time step. The accumulated soil erosion for one year at a 1 km² spatial resolution is presented in Figure B3. The figure shows that there is less erosion occurring throughout the west of the catchment. PESERA predicts higher erosion in the east, especially in the south east of the catchment, which is the German part (see Figure B1). This seems plausible due to steeper slopes combined with predominant arable land cover in that region. The Dutch catchment area is flat and prevalently characterized by grassland. Note that only erosion on agricultural land (arable and pasture) was considered as VANTOM input.

Surface runoff was determined by PESERA as well. VANTOM uses the occurrence of surface runoff to indicate that there is liquid transport of VA in the according time step (if there is runoff, VA transport in liquid is modelled). For the Vecht catchment, PESERA results project runoff in every month. In VANTOM, the transported liquid soil mass is determined based on the erodible layer depth (5 mm) and the pore

water levels. We calculated pore water levels by subtracting saturated deficits generated by PESERA from soil porosities. Latter were determined based on a particle density of 2650 kg m-3 and bulk densities from Ballabio et al. (2016). A map of average annual pore water levels in the Vecht catchment is displayed in Figure B4.

B 1.6. Uncertainties and Sensitivities

To assess uncertainties related to the VA emission modelling in the IMA presented, we combine extremes of individual parameters to estimate uncertainty ranges. Inasmuch as we assume hydrological uncertainties not to be dominant, these are not in the focus of this uncertainty assessment. Instead, we concentrate on model inputs and assumptions related to agricultural practices and the VA fate and transport: fertilizer application, plough layer depth, sorption coefficients and degradation rates.

As described in section 2.3 of the manuscript, fertilizer application is permitted from February until late summer (August to October). An assumption in the demonstration of our IMA for the Vecht catchment is that fertilizer is applied three times annually - in February, May and August. Considering limits to storage capacity, but a minimum required capacity between 6 and 10 months in GE and NL (Fraters et al., 2016, Weinfurtner, 2011), a minimum of two application events (in February and August) seems a plausible assumption to capture the uncertainty range. Contrary to this minimum, we assume a monthly fertilizer application from February to August as the maximum. Note that next to the number of fertilizing events also the manure storage times and therefore the VA load applied to the field differs.

The plough layer depth is another parameter influential to VANTOM outcomes. Ploughing is a commonly practiced on arable land at a depth of 25 cm (see section 2.4 in the manuscript). A variation of +/- 5 cm for VA presence in the soil under arable land seems to be realistic considering VA presence in the soil's depth profile studied by Spielmeyer et al. (2020). For grassland, we assumed manure injection within a layer of 7.5 cm. Considering that manure could be sprayed or percolate deeper than 7.5 cm, we also varied the plough layer depth with +/- 5 cm under grassland.

Minimum and maximum values for sorption coefficients and degradation rates were determined from findings of the comprehensive literature study summarized under sections 1.3. and 1.4 respectively. Table B3 presents the values used.

Table B3. Veterinary antibiotics' minimum and maximum sorption coefficients K_d and half-lives used to determine uncertainty ranges of GWF results.

Substance	K_d [L kg^{-1}]		DT_{50} [d]	
	Minimum	Maximum	Minimum	Maximum
Amoxicillin	4.2	6.5	0.43	1
Doxycycline	324	3890	9.9	533
Oxytetracycline	41	12047	12.81	103
Sulfamethazine	0.23	30	0.99	24.8
Tetracycline	41	8300	17	578

B 2. Results

B 2.1. GWF

Table B4 presents substance specific GWFs for the German, the Dutch and the entire Vecht catchment, differentiating between livestock sectors. Moreover, GWFs resulting from externalized VA emissions due to manure exports from the Vecht region (35% and 65% for GE and NL respectively) are displayed, assuming identical VA fate and transport routines than the average in the Vecht catchment.

Table B4. Grey water footprints for the German and Dutch part of the Vecht catchment as well as for the entire catchment resulting from VA field application in the region as well as total grey water footprints including externalized VA emissions.

Substance	Livestock type	Grey water footprints [m^3 yr^{-1}]			
		Germany	Netherlands	Total	Total including VA exports
Amoxicillin	Beef cattle	4.5×10^{-5}	6.1×10^{-6}	5.1×10^{-5}	8.6×10^{-5}
	Dairy cattle	7.5×10^{-5}	4.9×10^{-5}	1.2×10^{-4}	2.5×10^{-4}
	Pig	1.5×10^{-2}	1.7×10^{-3}	1.6×10^{-2}	2.7×10^{-2}
	Broiler	5.4×10^{-3}	6.9×10^{-4}	6.1×10^{-3}	1.0×10^{-2}
	Laying hen	4.8×10^{-4}	1.1×10^{-4}	6.0×10^{-4}	1.1×10^{-3}
	Total	2.1×10^{-2}	2.6×10^{-3}	2.3×10^{-2}	3.9×10^{-2}

Substance	Livestock type	Grey water footprints [m^3 yr^{-1}]			
		Germany	Netherlands	Total	Total including VA exports
Doxycycline	Beef cattle	117808	25279	143087	253468
	Dairy cattle	480	489	969	2136
	Pig	71880	13615	85495	149486
	Broiler	9112	7488	16601	35414
	Laying hen	3773	1269	5042	9431
	Total	203052	48142	251194	449935
Oxytetracycline	Beef cattle	1930	17291	19221	52371
	Dairy cattle	31	1322	1353	3824
	Pig	469	3497	3966	10714
	Broiler	0	0	0	0
	Laying hen	0	0	0	0
	Total	2430	22110	24539	66909
Sulfamethazine	Beef cattle	62	14	76	134
	Dairy cattle	0	0	0	0
	Pig	0	0	0	0
	Broiler	1500	98	1598	2587
	Laying hen	228	28	256	430
	Total	1790	139	1929	3151
Tetracycline	Beef cattle	20356	8903	29259	56755
	Dairy cattle	10486	21797	32284	78411
	Pig	21047	7875	28922	54879
	Broiler	3218	1337	4554	8769
	Laying hen	2310	1819	4129	8752
	Total	57417	41731	99148	207566

B 2.2. WPL

Table B5 presents subcatchment specific GWFs for all investigated substances as well as the annual available runoff and resulting WPLs per subcatchment of the Vecht river basin.

Table B5. Grey water footprints (GWFs) of amoxicillin (AMX), doxycycline (DXY), oxytetracycline (OXY), sulfamethazine (SMX) and tetracycline (TC), the available runoff and water pollution levels (WPL) per sub-catchment.

Sub-catchment	GWF [m^3 yr^{-1}]					Runoff in 1000 m^3 yr^{-1}	WPL
	AMX	DXY	OXY	SMX	TC		
1	1.5×10^{-3}	30434	370	135	7432	70146	4.3×10^{-4}
2	1.8×10^{-3}	54327	666	160	12616	69385	7.8×10^{-4}
3	2.5×10^{-3}	14141	164	220	4828	39850	3.5×10^{-4}
4	1.1×10^{-3}	6007	70	97	2073	62025	9.7×10^{-5}
5	3.6×10^{-3}	42655	887	308	12011	149530	2.9×10^{-4}
6	6.4×10^{-5}	343	4	6	118	5027	6.8×10^{-5}
7	4.0×10^{-4}	2227	26	35	760	14366	1.6×10^{-4}
8	5.3×10^{-5}	280	3	5	98	1141	2.5×10^{-4}
9	1.5×10^{-3}	7318	84	134	2667	43096	1.7×10^{-4}
10	4.4×10^{-4}	2116	24	38	767	17554	1.2×10^{-4}
11	2.1×10^{-3}	12850	712	179	4996	84886	1.5×10^{-4}
12	1.1×10^{-3}	6911	85	98	2279	32255	2.1×10^{-4}
13	3.2×10^{-4}	1420	16	28	537	7781	1.8×10^{-4}
14	7.6×10^{-4}	3432	54	66	1300	27274	1.3×10^{-4}
15	2.4×10^{-4}	11276	137	205	4110	50787	2.2×10^{-4}
16	4.6×10^{-4}	6504	96	40	1718	28311	2.3×10^{-4}
17	1.1×10^{-4}	1044	67	9	365	14140	7.4×10^{-5}
18	1.3×10^{-4}	2465	1133	7	2128	110089	2.2×10^{-5}
19	1.6×10^{-4}	2969	1363	9	2579	105027	2.8×10^{-5}
20	1.2×10^{-5}	238	109	1	204	13854	1.7×10^{-5}
21	1.5×10^{-5}	286	132	1	247	22090	1.3×10^{-5}
22	3.3×10^{-4}	4280	1650	22	3351	115414	3.7×10^{-5}
23	1.1×10^{-5}	197	91	1	172	25503	7.7×10^{-6}
24	9.0×10^{-5}	1464	622	6	1186	74658	2.0×10^{-5}

Sub-catchment	GWF [m^3 yr^{-1}]					Runoff in 1000 m^3 yr^{-1}	WPL
25	8.8×10^{-5}	1473	619	5	1190	55377	2.7×10^{-5}
26	5.3×10^{-5}	982	451	3	853	43377	2.3×10^{-5}
27	5.7×10^{-6}	101	46	3×10^{-1}	88	10869	9.3×10^{-6}
28	1.1×10^{-4}	947	211	9	557	29248	3.2×10^{-5}
29	4.9×10^{-6}	91	42	0	79	2449	3.7×10^{-5}
30	4.2×10^{-5}	775	356	2	675	26664	2.9×10^{-5}
31	8.8×10^{-5}	1737	802	5	1470	38558	4.5×10^{-5}
32	1.5×10^{-4}	2706	1242	8	2346	62299	4.3×10^{-5}
33	1.8×10^{-4}	3410	1565	10	2963	86944	3.9×10^{-5}
34	1.4×10^{-4}	776	80	12	368	8617	9.0×10^{-5}
35	1.8×10^{-5}	331	152	1	288	14326	2.3×10^{-5}
36	9.0×10^{-5}	1678	770	5	1459	40020	4.2×10^{-5}
37	1.6×10^{-4}	3069	1409	9	2664	61678	5.0×10^{-5}
38	7.2×10^{-5}	1357	623	4	1175	62762	2.2×10^{-5}
39	1.2×10^{-5}	224	103	1	195	11588	1.9×10^{-5}
40	6.3×10^{-5}	1159	532	3	1009	34496	3.4×10^{-5}
41	9.1×10^{-5}	1661	762	5	1446	32793	5.1×10^{-5}
42	1.3×10^{-4}	2475	1135	7	2155	47742	5.2×10^{-5}
43	7.9×10^{-5}	1452	667	4	1262	33519	4.3×10^{-5}
44	3.2×10^{-4}	5934	2723	17	5169	91757	6.5×10^{-5}
45	8.2×10^{-5}	1525	700	4	1328	27202	5.6×10^{-5}
46	1.1×10^{-4}	2146	985	6	1870	32305	6.6×10^{-5}

B 2.3. Uncertainties

The uncertainty ranges of VA-related GWFs between the least and most conservative estimates are presented in Figure B5. Conclusions are drawn based on the average uncertainty ranges for the Vecht catchment, whereby Figure B5 illustrates minimum and maximum GWFs for each, the German and the Dutch part of the catchment.

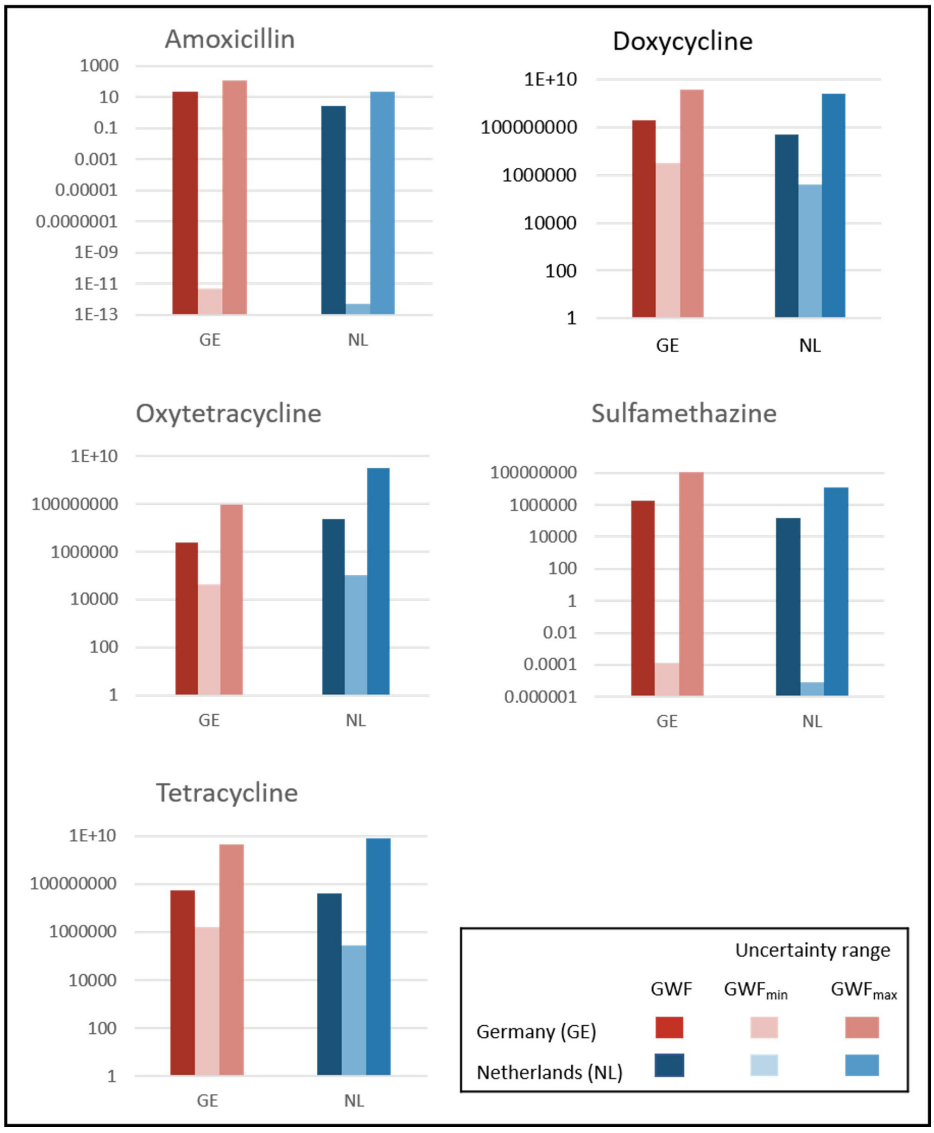


Figure B5. Uncertainty ranges for grey water footprints (GWFs) in L yr¹ of different veterinary antibiotics, showing the result of this study as GWF, the least conservative estimate as GWF_{min} and the most conservative results as GWF_{max}.

Appendix C: An appendix to Chapter 4

C 1. Methods and data

C 1.1. Description of livestock sectors

For the livestock types cattle (meat and dairy), pigs, and poultry (broilers and laying hens) we conducted a short review on the production sectors in the EU, and specifically in Germany and the Netherlands.

Cattle sector: EU-wide bovine numbers are predicted to decrease in the coming years, whereby a more efficient meat and dairy production is projected. It is to be noted that the German and Dutch productions operate at comparatively high efficiencies already (European Commission, 2020a). Bovine meat production exists as primary production as well as by-product from dairy farming. For latter, meat is either produced from old dairy cows or from (especially) male calves that are useless for the dairy sector (Bundesinformationszentrum Landwirtschaft, 2021, de Vries et al., 2015, van der Peet et al., 2018). Specifically in the Netherlands, the meat producing sector has specialized in veal production, where the average farm has several hundred animals (van der Peet et al., 2018). For all cattle, the average Dutch herd counts 150 heads (CBS, 2019). In Germany this number is 85 (Bundesanstalt für Landwirtschaft und Ernährung and Bundesinformationszentrum Landwirtschaft, 2021). Approximately 5% of the German beef cattle production is organic (BMEL, 2018). The share of organic beef cattle farming is unknown in the Netherlands, specifically for calves it is 0.2% (van der Peet et al., 2018).

Dairy production bases on a cycle of cows' pregnancy and birth in order to continuously yield milk. Dairy herds count on average less heads than bovine herds for meat production (BMEL, 2021, van der Peet et al., 2018). Around 40% of the German dairy cattle is (at least partially) pasture-based (BMEL, 2021). In the Netherlands around 80% of the dairy farms practice pasture-based farming (van der Peet et al., 2018). It is not clear what percentage of animals this refers to. The EU's agricultural outlook states that alternative production systems (e.g. pasture-based, hay-based, GM-free fed) could increase in the coming years (European Commission, 2020a). The EU's share of organic milk production is expected at 10% in 2030, compared to 3.5% in 2018 (European Commission, 2020a). 3.4% and 1.6% of the milk produced is organic in Germany and the Netherlands, respectively (BMEL, 2018, van der Peet et al., 2018).

Pig sector: With 38% the EU is the global leader in pig meat exports. The EU commission predicts that this leading role will remain over the coming 10 years (European Commission, 2020a). There is a large diversity of pig farms in the EU – from small scale mixed animal farms with just one or a few pigs to highly industrialized farms with thousands of pigs (European Parliament, 2020). In latter, pigs are raised in various production steps where individual farms focus on: pigs for breeding, piglets and fattening pigs of different weight categories (BMEL, 2018, van der Peet et al., 2018). Typically pigs reach their weight of slaughter (120kg) at the age of six months (BMEL, 2018, van der Peet et al., 2018). In Germany over 75% of pigs live on farms that count between 400 and 4999 heads (BMEL, 2021). In the Netherlands the average number of pigs per farm is 2800 (van der Peet et al., 2018). 0.6% and 0.8% of all pigs are raised organically in Germany and the Netherlands, respectively (BMEL, 2018, van der Peet et al., 2018). While the share in organic pig meat production is low in entire Europe, a study describing the organic pig production in eight European countries, recognized an increasing trend (Früh et al., 2014).

Poultry sector: In the EU, the poultry meat production has been growing and is projected to continue growing until 2030 (European Commission, 2020a). It is the most intensive farming sector within the EU, characterized by high stocking densities, fast growth rates, very large holdings and indoor rearing (Augere-Granier, 2019, Caspari et al., 2010). In Germany organic chicken meat has a share of 1% (BMEL, 2018, BMEL, 2019). In the Netherlands less than 0.5% of the total broiler production is organic (van der Peet et al., 2018). Eggs are produced by hatcheries. After hatching, chicks are transported to the fattening farm in groups that fill one stable. According to the interviewed veterinarians in this study, a standard stable size for broilers is 40 000 and 45 000 animals (in Germany and the Netherlands respectively), also farms with several stables exist. The duration of the fattening period is 5-9 weeks in Germany and on average 6 weeks in the Netherlands (BMEL, 2018, van der Peet et al., 2018).

Laying hen farms are keeping large stocks as well. In Germany 24% of all hens live on farms that count between 10 000 and 30 000 hens; another 21% of all hens are kept on holdings with more than 200 000 animals (BMEL, 2021). In the Netherlands the average animal count per farm is 40 000 (van der Peet et al., 2018). The laying hen sector is the only livestock production sector in the EU where an EU-wide legal classification system applies, depending on the rearing system. In the EU chicken are kept as follows: 53% enriched cage, 27% barn, 15% free range; 5% organic. In Germany this distribution is: 7% enriched cage, 63% barn, 19% free range; 12% organic. In the Netherlands hens are kept in: 18% enriched cage, 60% barn, 16% free range; 6% organic.

C 1.2. Data collection

Interviews: To obtain data about pharmaceutical administration in different livestock production systems, interviews with seven German and seven Dutch veterinarians were conducted. Interviews with German interviewees were conducted in German. In the interviews with Dutch veterinarians questions were asked in English and depending on the participants preference, answers were given in English or Dutch. The interview's setup was semi-structured following a questionnaire that contained seven sections. The first section targeted to get to know the interviewees background, the last section aimed to resolve unanswered questions and/or to make additional statements. The five sections in between were content-related. A detailed overview of the questionnaire's sections and individual questions is presented in Table C1.

Table C1. Interview questionnaire (English version).

Opening words	• Introduction of the researcher • Explanation of information brochure and informed consent • Outline of the research context • Permission to record the interview • Explanation how the data will be processed and used for the research
Section 1	**Participants' background** • Job description • Specialization • Affiliation(s)
Section 2	**General aspects about pharmaceutical use in livestock production systems** • Please outline the general procedure of pharmaceutical administration in livestock production systems (specifically for the livestock animals you specialize in): • When and to what purposes is a pharmaceutical treatment done? • How is the organizational procedure? - What are tasks of the farmer, what are tasks of the veterinarian? • What are the most treated and/or prevented diseases (per livestock type)? • What are regulations for pharmaceutical use in food producing animals?

Section 3 **Factors and drivers influencing pharmaceutical use in livestock production**

- What factors influence pharmaceutical use in livestock animals? Could you please list them?

  - What are reasons and circumstances that foster/support/increase pharmaceutical administration?
  - What are reasons and circumstances that prevent/reduce pharmaceutical administration?
  - Do [extend by other factors from literature or previous interviews] also play a role according to your opinion?

- What livestock types are these factors relevant for?

- What are drivers for and against each of the factors?

Section 4 **Differences among livestock production systems**

- What differences exist among different livestock production systems regarding the mentioned factors? (different production systems under investigation are: organic/ conventional, animal welfare categories for laying hens)

  - How important or pronounced are the mentioned factors that influence pharmaceutical use in different livestock production systems?

- Are there other production systems (that are defined/ classified) which you see relevant in terms of differences in pharmaceutical use?

Section 5 **Indicator pharmaceuticals**

- What are relevant substance groups per livestock type?

- Can you please name the most relevant substances (indicator substances per substance group)? → relevance refers to amounts and frequencies used

- Are there differences in the most relevant substances among different livestock production systems?

- For these substances: Which of the abovementioned factors play a role and what differences exist for different livestock production systems?

Section 6 **Assessing the pharmaceutical lifecycle**

- If we do not only look at pharmaceutical use, but at their lifecycle up to the environmental emission: What other aspects do you consider relevant that could increase or decrease such emissions (in general and for the named substances)?

- What do you know about the environmental presence of veterinary pharmaceuticals in general and for the named substances in specific?

- Do you know of any impacts (environmental and human) that veterinary pharmaceuticals and specifically those you named before have? If yes, what impacts are these?

- What are responses to the environmental emission of veterinary pharmaceuticals and specifically those you mentioned?

Section 7 **Comments and questions**

- Do you have any comments or questions?

Literature: Quantitative data that indicates substance specific pollution potential in the pilot assessment was obtained for the lifecycle stages metabolization, manure, environmental behaviour, and environmental impact. To indicate the metabolization in the target body, livestock type specific excretion rates were used as a proxy. Degradation during manure storage (specifically the substance's half-life) was taken as quantitative indicator for pollution potential resulting from the period during which pharmaceuticals reside in manure. Where available, half-lives for livestock type specific manure were used. Half-lives that describe degradation in soil was often available for different soil characteristics. We therefore retrieved all substance-specific half-lives from literature and listed the median in the pilot assessment. The environmental impact was described using the predicted no effect concentration (PNEC). For all parameters indicating pollution potential we used these in combination with individual substance names as search terms.

C 2. Results

C 2.1. Factors influential to pharmaceutical use and pollution

For the pharmaceutical lifecycle stage of pharmaceutical administration, factors that can cause or avoid pharmaceutical pollution were identified based on interviews with veterinarians. We categorized and grouped the factors as part of the thematic data analysis. To ensure that factors are interpreted correctly by future researchers using the framework, we present a description to all factors based on interviewee's insights in Table C2.

Table C2. Factors influencing pharmaceutical administration in livestock production systems along with their description.

Factor group	Factor	Description	Applies to				
			Beef cattle	Dairy cattle	Pigs	Broiler chickens	Laying hens
Production system independent factors	Accidents	• technical, management accidents	yes	yes	yes	yes	yes
	Outdoor climate	• stress for animals outside • influential to indoor climate	yes	yes	yes	yes	yes
	Presence of pathogens	• disease outbreak in certain regions, airborne transitions	yes	yes	yes	yes	yes
	Follow up diseases	• animal with weak immune status after one health problem are prone to get other health issues	yes	yes	yes	yes	yes
Systematic facors	Herd size	• depending on animal numbers, time of littering is influenced by pharmaceutical treatment • for poultry: herd size too big to survey individual animals	no	yes	yes	yes	yes
	Product innovation	• bioavailability • vaccine development	yes	yes	yes	yes	yes
	System specific health problems	• delivery aftercare	no	yes	yes	no	no
	Disease eradication	• diseases that are eradicated do not need any treatment	yes	yes	yes	yes	yes
Policies	Pharmaceutical policies	• regulations (e.g. for waiting time) can determine pharmaceuticals' suitability for usage • policies to specifically use, not use or reduce substances	yes	yes	yes	yes	yes
	Animal welfare policies	• injured animals should be treated, should not suffer	yes	yes	yes	yes	yes
	Monitoring	• control about animal welfare indicators in slaughterhouses • control about substance use (specifically antibiotics)	yes	yes	yes	yes	yes
	Reduction measures	• obligatory measures against high antibiotic use • restrictive substance use following a protocol	yes	yes	yes	yes	yes

Factor group	Factor	Description	Applies to				
			Beef cattle	Dairy cattle	Pigs	Broiler chickens	Laying hens
Management	All-in-all-out system	• fattening animals come to the stable, are raised, leave to the slaughterhouse, stable is disinfected	no	no	yes	yes	no
	Animals origin	• health/immune status of animals upon arrival on a farm; • number of origins determines the number of health status in one herd/stable/farm	yes	no	yes	yes	yes
	Contact between age groups	• animals with different ages in one herd/stable/farm have different health status	yes	no	yes	yes	yes
	Health status new animals	• disease transmission from parent animals • for poultry: hatchery management (age of layers, frequency of egg collection, egg hygiene, egg storage)	yes	no	yes	yes	yes
	Choice of breeds	• top-athletes vs. slow-growing • for pigs: number of piglets born in one litter	yes	yes	yes	yes	yes
	Feed (and water)	• feed quality • feed composition	yes	yes	yes	yes	yes
	Hygiene	• stable hygiene (disinfection after rounds) • equipment hygiene	yes	yes	yes	yes	yes
	Prevention	• vaccines • probiotics • feed additives (e.g. vitamins) • deworming	yes	yes	yes	yes	yes
	Animal surveillance	• veterinary controls • behavior observation • separation of sick animals	yes	yes	yes	yes	yes
	Animal wellfare	• managing animals based on their demand	yes	yes	yes	yes	yes
	Other working procedures	• fertility management • pasture management	yes	yes	yes	no	no

Factor group	Factor	Description	Applies to				
			Beef cattle	Dairy cattle	Pigs	Broiler chickens	Laying hens
Treatment strategy/ management	Treatment scale	• from individual to herd treatment	yes	yes	yes	no	no
	Treatment timing	• strategic balancing (e.g. an earlier treatment with small amounts (because animals weigh less) can prevent a treatment with large amounts at a later stage)	yes	no	yes	yes	no
	Strategic substance choice	• strategic choice of substances (e.g. Trim/Sulfa counting as 2 treatments)	yes	yes	yes	yes	yes
	Natural cure	• attempt to have the animals cure themselves	yes	yes	yes	yes	yes
Housing	Stable quality	• housing adapted to animals needs	yes	yes	yes	yes	yes
	Separation of compartments	• control of disease spreading between animals/compartments	yes	yes	yes	no	no
	Animal density in stable	• housing size matching animal numbers • the higher the density, the easier diseases can spread	no	no	yes	yes	yes
	Ventilation and heating	• quality of stable climate	yes	yes	yes	yes	yes
	Technical aids	• sensors, automatic systems, systems working with AI	yes	yes	yes	yes	yes
	Outdoor contact	• climate as triggering factor for an infection • pesticide infestation • for cattle: grazing influential for claw health	yes	yes	yes	yes	yes
Staff	Farmer's skills	• talent, education	yes	yes	yes	yes	yes
	Farmer's health-risk perspective	• habits/tradition • demand for pharmaceuticals	yes	yes	yes	yes	yes
	Veterinarian's skills	• education • time of disease detection • time of problem recognition • experience, specialization, and equipment	yes	yes	yes	yes	yes
	Veterinarian's professional perspective	• working routines in diagnostics, pathology, treatment • remuneration • awareness	yes	yes	yes	yes	yes

Influential factors for pharmaceutical pollution within the lifecycle stages pharmaceuticals in manure and pharmaceuticals applied to agricultural land were determined based on literature and are presented in Tables C3 and C4, respectively. Note that the references given should be seen as exemplary sources - especially for the factor manure treatment we found a large number of studies that investigated degradation of pharmaceuticals during manure treatment under diverse study settings. Besides reviewing literature, we studied current valid policy documents to determine factors deriving from regulations. Whereas legal obligations for the application of manure to agricultural land exist, there are no binding rules for manure management that have relevance for pharmaceutical pollution.

Table C3. Factors influencing pharmaceutical pollution within the lifecycle stage pharmaceuticals in manure.

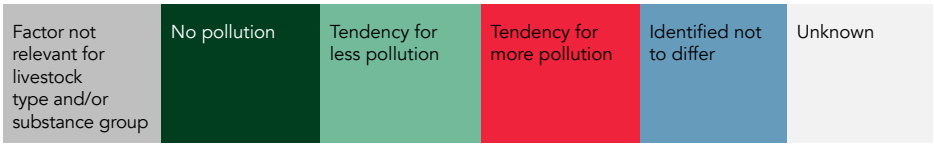
Factor	Description	Reference
Manure storage time	pharmaceuticals biodegrade over time in manure, thus storage time influences the amount degraded	Berendsen et al. (2018); Kemper et al. (2008)
Manure treatment	Stimulation of pharmaceutical degradation by: composting methods (where aeration, temperature, pH, organic carbon, nitrogen, phosphorus, and metal content are influential to pharmaceutical degradation) anaerobic digestion anaerobic/aerobic lagooning	Ho et al. (2013); Massé et al. (2014); Schlüsener et al. (2006); Van Epps and Blaney (2016)

Table C4. Factors influencing pharmaceutical pollution within the lifecycle stage pharmaceuticals in manure.

Factor	Description	Reference
manure policies	policies regulating manure application to agricultural land (e.g. application period and method)	Netherlands Enterprise Agency (2020) Federal Ministry of food and agriculture (2020) Düngemittelverordnung Meststoffenwet
direct application from grazing animals		Bair et al. (2017); Boxall et al. (2002); Kemper (2008)
manure application technologies	manure spraying (broadcasting) manure narrow-band application manure injection	Huijsmans et al. (2001); Huijsmans et al. (2003); Saeys et al. (2008)

C 2.2. Pilot assessment

For the pilot assessment we compared the pollution potential between conventional and organic production systems for each of the factors related to administration based on insights from the conducted interviews. This analysis was carried out for the substance groups antibiotics, antiparasitics, hormones and NSAIDs individually for each livestock type. We display qualitative comparative pollution potentials in the Tables C5 to C9 and used the following colour codes:



For the cases where a difference in pollution potential was identified between organic and conventional production we further added a short description to explain the logics behind this tendency.

Table C5. Pharmaceutical pollution potential for influential factors in pharmaceutical administration compared for different substance groups in conventional and organic beef cattle production.

Factor group	Factor	Conventional			Organic		
		Antibiotics	Antiparasitics	NSAIDs	Antibiotics	Antiparasitics	NSAIDs
Coincidental/ uninfluenceable factors	Accidents						
	Outdoor climate						
	Presence of pathogens						
	Follow up diseases						
Systematic facors	Herd size						
	Product innovation						
	System specific health problems						
	Disease eradication						
Policies	Pharmaceutical policies	less restrictive use; no policies that apply specifically to conventional farming			more restrictive use		
	Animal welfare policies						
	Monitoring						
	Reduction measures						

Factor group	Factor	Conventional			Organic		
		Antibiotics	Antiparasitics	NSAIDs	Antibiotics	Antiparasitics	NSAIDs
Management	All-in-all-out system						
	Animals origin						
	Contact between age groups						
	Health status new animals						
	Choice of breed	common choice of breeds that maximize production, consequently top athletes that are very sensitive to getting diseases		common choice of breeds that maximize production, consequently top athletes that are very sensitive to getting diseases	choice for breeds that are no top athletes		choice for breeds that are no top athletes
	Feed (and water)						
	Hygiene	especially highly industrialized farms work professionally hygienic		especially highly industrialized farms work professionally hygienic	tendency for less strict hygiene procedures; concerns to use disinfectants		tendency for less strict hygiene procedures; concerns to use disinfectants
	Prevention	Due to less restrictions in pharmaceutical use, less attention is given to prevention		Due to less restrictions in pharmaceutical use, less attention is given to prevention	due to more restricted pharmaceutical use, more attention given to prevention		due to more restricted pharmaceutical use, more attention given to prevention
	Animal surveillance						
	Animal wellfare						
	Other working procedures						

Factor group	Factor	Conventional			Organic		
		Antibiotics	Antiparasitics	NSAIDs	Antibiotics	Antiparasitics	NSAIDs
Treatment strategy/ management	Treatment scale	Full herd treatment possible		Full herd treatment possible	herd treatment is strictly regulated		herd treatment is strictly regulated
	Treatment timing						
	Strategic substance choice						
	Natural cure	Due to less restrictions in pharmaceutical use, less attempts for natural cure		Due to less restrictions in pharmaceutical use, less attempts for natural cure	due to more restricted pharmaceutical use, more attempts for natural cure[a]		due to more restricted pharmaceutical use, more attempts for natural cure[a]
Housing	Stable quality						
	Compartment separation						
	Animal density in stable						
	Ventilation and heating						
	Technical aids						
	Outdoor contact	less outdoor contact in conventional farming prevents infections	less outdoor contact in conventional farming prevents parasites	less outdoor contact in conventional farming prevents infections	obligatory outdoor contact in organic farming supports infections	obligatory outdoor contact in organic farming supports parasites	obligatory outdoor contact in organic farming supports infections

Factor group	Factor	Conventional			Organic		
		Antibiotics	Antiparasitics	NSAIDs	Antibiotics	Antiparasitics	NSAIDs
Staff	Farmer's skills	farmers competing in the conventional system are often good (health) managers		farmers competing in the conventional system are often good (health) managers	organic farmers who were not able to compete in the conventional system because of poor management skills remain with poor skills negatively affecting animal's health status		organic farmers who were not able to compete in the conventional system because of poor management skills remain with poor skills negatively affecting animal's health status
	Farmer's health-risk perspective	no ideology of farmers to not use pharmaceuticals		no ideology of farmers to not use pharmaceuticals	organic farmers who ideologically do not want to administer pharmaceuticals[a]		organic farmers who ideologically do not want to administer pharmaceuticals[a]
	Veterinarian's skills						
	Veterinarian's professional perspective						

[a] *not administering pharmaceuticals could potentially lead to more pharmaceutical use in case that the infection gets worse and/or spreads out.*

Table C6. Pharmaceutical pollution potential for influential factors in pharmaceutical administration compared for different substance groups in conventional and organic dairy cattle production.

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Coincidental/ uninfluenceable factors	Accidents								
	Outdoor climate								
	Presence of pathogens								
	Follow up diseases								
Systematic facors	Herd size			Treatment for reproductory interventions in large herds				Treatment for reproductory interventions is prohibited	
	Product innovation								
	System specific health problems								
	Disease eradication								

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Policies	Pharmaceutical policies	less restrictive use; no policies that apply specifically to conventional farming		less restrictive use; no policies that apply specifically to conventional farming	less restrictive use; no policies that apply specifically to conventional farming	more restrictive use		only allowed for heath treatment, not for reproductory interventions	more restrictive use
	Animal welfare policies								
	Monitoring								
	Reduction measures								

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Management	All-in-all-out system								
	Animals origin								
	Contact between age groups								
	Health status new animals								
	Choice of breed	common choice of races that maximize production, consequently top athletes that are very sensitive to getting diseases			common choice of races that maximize production, consequently top athletes that are very sensitive to getting diseases	choice for races that are no top athletes			choice for races that are no top athletes
	Feed (and water)								
	Hygiene	especially highly industrialized farms work professionally hygienic			especially highly industrialized farms work professionally hygienic	tendency for less strict hygiene procedures; concerns to use disinfectants			tendency for less strict hygiene procedures; concerns to use disinfectants

Prevention	Due to less restrictions in pharmaceutical use, less attention is given to prevention			Due to less restrictions in pharmaceutical use, less attention is given to prevention	due to more restricted pharmaceutical use, more attention given to prevention			due to more restricted pharmaceutical use, more attention given to prevention
Animal surveillance			treatment for fertility management				good surveillance necessary because hormone use for fertility management is prohibited	
Animal wellfare								
Other working procedures			treatment for fertility management				good surveillance necessary because hormone use for fertility management is prohibited	

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Treatment strategy/ management	Treatment scale	Full herd treatment possible			Full herd treatment possible	herd treatment is strictly regulated			herd treatment is strictly regulated
	Treatment timing								
	Strategic substance choice								
	Natural cure	Due to less restrictions in pharmaceutical use, less attempts for natural cure			Due to less restrictions in pharmaceutical use, less attempts for natural cure	due to more restricted pharmaceutical use, more attempts for natural cure[a]			due to more restricted pharmaceutical use, more attempts for natural cure[a]

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Housing	Stable quality								
	Compartment separation								
	Animal density in stable								
	Ventilation and heating								
	Technical aids								
	Outdoor contact	less outdoor contact in conventional farming prevents infections	less outdoor contact in conventional farming prevents parasites		less outdoor contact in conventional farming prevents infections	obligatory outdoor contact in organic farming supports infections	obligatory outdoor contact in organic farming supports parasites		obligatory outdoor contact in organic farming supports infections

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Staff	Farmer's skills	farmers competing in the conventional system are often good (health) managers			farmers competing in the conventional system are often good (health) managers	organic farmers who were not able to compete in the conventional system because of poor management skills remain with poor skills negatively affecting animal's health status			organic farmers who were not able to compete in the conventional system because of poor management skills remain with poor skills negatively affecting animal's health status
	Farmer's health-risk perspective	no ideology of farmers to not use pharmaceuticals		no ideology of farmers to not use pharmaceuticals	no ideology of farmers to not use pharmaceuticals	organic farmers who ideologically do not want to administer pharmaceuticals[a]		organic farmers who ideologically do not want to administer pharmaceuticals	organic farmers who ideologically do not want to administer pharmaceuticals[a]
	Veterinarian's skills								
	Veterinarian's professional perspective								

[a] *not administering pharmaceuticals could potentially lead to more pharmaceutical use in case that the infection gets worse and/or spreads out.*

Table C7. Pharmaceutical pollution potential for influential factors in pharmaceutical administration compared for different substance groups in conventional and organic pig production.

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Coincidental/ uninfluenceable factors	Accidents								
	Outdoor climate								
	Presence of pathogens								
	Follow up diseases								
Systematic facors	Herd size			Treatment for reproductory interventions in large herds				Treatment for reproductory interventions is prohibited	
	Product innovation								
	System specific health problems								
	Disease eradication								

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Policies	Pharmaceutical policies	less restrictive use; no policies that apply specifically to conventional farming		less restrictive use; no policies that apply specifically to conventional farming	less restrictive use; no policies that apply specifically to conventional farming	more restrictive use		only allowed for heath treatment, not for reproductory interventions	more restrictive use
	Animal welfare policies								
	Monitoring								
	Reduction measures								

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Management	All-in-all-out system	frequent procedure to reduce disease spreading	frequent procedure to reduce parasite spreading		frequent procedure to reduce disease spreading	less strictly done and consequently disease spreading is more likely	less strictly done and consequently parasite spreading is more likely		less strictly done and consequently disease spreading is more likely
	Animals origin								
	Contact between age groups	stricter separation of animal ages			stricter separation of animal ages	different animal ages kept together frequently			different animal ages kept together frequently
	Health status new animals								
	Choice of breed	common choice of races that maximize production, consequently top athletes that are very sensitive to getting diseases; high number of piglets born in one litter of which some are smaller and do not fit in the working round			common choice of races that maximize production, consequently top athletes that are very sensitive to getting diseases; high number of piglets born in one litter of which some are smaller and do not fit in the working round	choice for races that are no top athletes			choice for races that are no top athletes

	Feed (and water)	tendency for highly optimized feed			tendency for highly optimized feed	feed with lower quality/ less suitable composition			feed with lower quality/ less suitable composition
	Hygiene	especially highly industrialized farms work professionally hygienic	especially highly industrialized farms work professionally hygienic		especially highly industrialized farms work professionally hygienic	tendency for less strict hygiene procedures; concerns to use disinfectants	tendency for less strict hygiene procedures; concerns to use disinfectants		tendency for less strict hygiene procedures; concerns to use disinfectants
	Prevention	Due to less restrictions in pharmaceutical use, less attention is given to prevention			Due to less restrictions in pharmaceutical use, less attention is given to prevention	due to more restricted pharmaceutical use, more attention given to prevention			due to more restricted pharmaceutical use, more attention given to prevention
	Animal surveillance			treatment for fertility management				good surveillance necessary because hormone use for fertility management is prohibited	
	Animal wellfare								
	Other working procedures			treatment for fertility management				good surveillance necessary because hormone use for fertility management is prohibited	

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Treatment strategy/ management	Treatment scale	Full herd treatment possible			Full herd treatment possible	herd treatment is strictly regulated			herd treatment is strictly regulated
	Treatment timing								
	Strategic substance choice								
	Natural cure	Due to less restrictions in pharmaceutical use, less attempts for natural cure			Due to less restrictions in pharmaceutical use, less attempts for natural cure	due to more restricted pharmaceutical use, more attempts for natural cure[a]			due to more restricted pharmaceutical use, more attempts for natural cure[a]

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Housing	Stable quality								
	Compartment separation								
	Animal density in stable	higher animal density leading to more disease outbreaks and spreading	higher animal density leading to more parasite spreading		higher animal density leading to more disease outbreaks and spreading	organic farming regulations requires less animal density which leads to less disease outbreaks and spreading	organic farming regulations requires less animal density which leads to less parasite spreading		organic farming regulations requires less animal density which leads to less disease outbreaks and spreading
	Ventilation and heating								
	Technical aids								
	Outdoor contact	less outdoor contact in conventional farming prevents infections	less outdoor contact in conventional farming prevents parasites		less outdoor contact in conventional farming prevents infections	obligatory outdoor contact in organic farming supports infections	obligatory outdoor contact in organic farming supports parasites		obligatory outdoor contact in organic farming supports infections

Factor group	Factor	Conventional				Organic			
		Antibiotics	Antiparasitics	Hormones	NSAIDs	Antibiotics	Antiparasitics	Hormones	NSAIDs
Staff	Farmer's skills	farmers competing in the conventional system are often good (health) managers			farmers competing in the conventional system are often good (health) managers	organic farmers who were not able to compete in the conventional system because of poor management skills remain with poor skills negatively affecting animal's health status			organic farmers who were not able to compete in the conventional system because of poor management skills remain with poor skills negatively affecting animal's health status
	Farmer's health-risk perspective	no ideology of farmers to not use pharmaceuticals		no ideology of farmers to not use pharmaceuticals	no ideology of farmers to not use pharmaceuticals	organic farmers who ideologically do not want to administer pharmaceuticals[a]		organic farmers who ideologically do not want to administer pharmaceuticals	organic farmers who ideologically do not want to administer pharmaceuticals[a]
	Veterinarian's skills								
	Veterinarian's professional perspective								

[a] *not administering pharmaceuticals could potentially lead to more pharmaceutical use in case that the infection gets worse and/or spreads out.*

Table C8. Pharmaceutical pollution potential for influential factors in pharmaceutical administration compared for different substance groups in conventional and organic broiler chicken production.

Factor group	Factor	Conventional		Organic	
		Antibiotics	Antiparasitics	Antibiotics	Antiparasitics
Coincidental/ uninfluenceable factors	Accidents				
	Outdoor climate				
	Presence of pathogens				
	Follow up diseases				
Systematic facors	Herd size				
	Product innovation				
	System specific health problems				
	Disease eradication				
Policies	Pharmaceutical policies	less restrictive use; no policies that apply specifically to conventional farming		more restrictive use	
	Animal welfare policies				
	Monitoring				
	Reduction measures				

Factor group	Factor	Conventional		Organic	
		Antibiotics	Antiparasitics	Antibiotics	Antiparasitics
Management	All-in-all-out system	frequent procedure to reduce disease spreading	frequent procedure to reduce parasite spreading	less strictly done and consequently disease spreading is more likely	less strictly done and consequently parasite spreading is more likely
	Animals origin				
	Contact between age groups				
	Health status new animals				
	Choice of breed	common choice of breeds that maximize production, consequently top athletes that are very sensitive to getting diseases		choice for breeds that are no top athletes	
	Feed (and water)	highly optimized and high quality feed		feed with lower quality[b]	
	Hygiene	especially highly industrialized farms work professionally hygienic	especially highly industrialized farms work professionally hygienic	tendency for less strict hygiene procedures; concerns to use disinfectants	tendency for less strict hygiene procedures; concerns to use disinfectants
	Prevention	Due to less restrictions in pharmaceutical use, less attention is given to prevention		due to more restricted pharmaceutical use, more attention given to prevention	
	Animal surveillance				
	Animal wellfare				
	Other working procedures				

Factor group	Factor	Conventional		Organic	
		Antibiotics	Antiparasitics	Antibiotics	Antiparasitics
Treatment strategy/ management	Treatment scale				
	Treatment timing				
	Strategic substance choice				
	Natural cure	Due to less restrictions in pharmaceutical use, less attempts for natural cure		due to more restricted pharmaceutical use, more attempts for natural cure[a]	
Housing	Stable quality				
	Compartment separation				
	Animal density in stable	higher animal density leading to more disease outbreaks and spreading	higher animal density leading to more parasite spreading	organic farming regulations requires less animal density which leads to less disease outbreaks and spreading	organic farming regulations requires less animal density which leads to less parasite spreading
	Ventilation and heating				
	Technical aids				
	Outdoor contact	hardly outdoor contact in conventional production	hardly outdoor contact in conventional production	more outdoor contact that supports infections	more outdoor contact supports parasites

Factor group	Factor	Conventional		Organic	
		Antibiotics	Antiparasitics	Antibiotics	Antiparasitics
Staff	Farmer's skills				
	Farmer's health-risk perspective	no ideology of farmers to not use pharmaceuticals		organic farmers who ideologically do not want to administer pharmaceuticals[a]	
	Veterinarian's skills				
	Veterinarian's professional perspective				

[a] *not administering pharmaceuticals could potentially lead to more pharmaceutical use in case that the infection gets worse and/or spreads out.*
[b] *differing descriptions among interviewees were identified, one reported that organic feed quality has improved over the years and is not a problem anymore*

Table C9. Pharmaceutical pollution potential for influential factors in pharmaceutical administration compared for different substance groups in conventional and organic laying hen production.

Factor group	Factor	Conventional		Organic	
		Antibiotics	Antiparasitics	Antibiotics	Antiparasitics
Coincidental/ uninfluenceable factors	Accidents				
	Outdoor climate				
	Presence of pathogens				
	Follow up diseases				
Systematic facors	Herd size				
	Product innovation				
	System specific health problems				
	Disease eradication				
Policies	Pharmaceutical policies	less restrictive use; no policies that apply specifically to conventional farming		more restrictive use	
	Animal welfare policies				
	Monitoring				
	Reduction measures				

Factor group	Factor	Conventional		Organic	
		Antibiotics	Antiparasitics	Antibiotics	Antiparasitics
Management	All-in-all-out system				
	Animals origin				
	Contact between age groups				
	Health status new animals				
	Choice of breed	common choice of races that maximize production, consequently top athletes that are very sensitive to getting diseases		choice for races that are no top athletes	
	Feed (and water)	highly optimized and high quality feed		feed with lower quality[b]	
	Hygiene	especially highly industrialized farms work professionally hygienic	especially highly industrialized farms work professionally hygienic	tendency for less strict hygiene procedures; concerns to use disinfectants	tendency for less strict hygiene procedures; concerns to use disinfectants
	Prevention	Due to less restrictions in pharmaceutical use, less attention is given to prevention		due to more restricted pharmaceutical use, more attention given to prevention	
	Animal surveillance				
	Animal wellfare				
	Other working procedures				

Factor group	Factor	Conventional		Organic	
		Antibiotics	Antiparasitics	Antibiotics	Antiparasitics
Treatment strategy/ management	Treatment scale				
	Treatment timing				
	Strategic substance choice				
	Natural cure	Due to less restrictions in pharmaceutical use, less attempts for natural cure		due to more restricted pharmaceutical use, more attempts for natural cure[a]	
Housing	Stable quality				
	Compartment separation				
	Animal density in stable	higher animal density leading to more disease outbreaks and spreading	higher animal density leading to more parasite spreading	organic farming regulations requires less animal density which leads to less disease outbreaks and spreading	organic farming regulations requires less animal density which leads to less parasite spreading
	Ventilation and heating				
	Technical aids				
	Outdoor contact	less outdoor contact in conventional production	less outdoor contact in conventional production	more outdoor contact that supports infections	more outdoor contact supports parasites

Factor group	Factor	Conventional		Organic	
		Antibiotics	Antiparasitics	Antibiotics	Antiparasitics
Staff	Farmer's skills				
	Farmer's health-risk perspective	no ideology of farmers to not use pharmaceuticals		organic farmers who ideologically do not want to administer pharmaceuticals[a]	
	Veterinarian's skills				
	Veterinarian's professional perspective				

[a] *not administering pharmaceuticals could potentially lead to more pharmaceutical use in case that the infection gets worse and/or spreads out*
[b] *differing descriptions among interviewees were identified, one reported that organic feed quality has improved over the years and is not a problem anymore*

Table C10 lists the indicator substances per substance group that were identified from the interviews. Specifically we asked interviewees for the most relevant substances and defined relevant as most administered in terms of quantities and/or frequencies. German and Dutch veterinarians partially named different indicator substances (as indicated in the table). This could indicate that most used substances differ in the countries. It is also possible that different veterinarians have preference for specific substances and we therefore received different answers. Some interviewees listed several most relevant substances, while others named only one. This could also be a (rather coincidental) reason for this observed imbalance between the countries. For the substance-specific pilot assessment we selected substances named in both countries with priority. A second criterion were the substances named most often.

Table C10. Indicator substances listed by interviewed veterinarians.

Animal type	Indicator pharmaceuticals				
	Antibiotics	Antiparasitics	Hormones	NSAIDs	Others
Dairy cattle	Amoxicillin[a] Cephalosporin[b] Cloxacillin[b] Oxytetracycline[b] Penincillin[b]	Moxidectin[b]	Gonadotropin-releasing hormone (GnRH)[a] Prostaglandin F2alpha	Meloxicam	
Beef cattle	Amoxicillin[a] Doxycycline[b] Tilmicosin[b]	Moxidectin[b]		Meloxicam[a] Natriumsalicytat[b]	Bromhexine[b]
Pigs	Amoxicillin[a] Doxycycline Florfenicol[b] Oxytetracycline[b] Penincillin[b] Trimethoprim- Sulfonamid[a]	Fenbendazole[a] Flubendazole Ivermectine[a] Piperazin[a]	Altrenogest Pregnant mare's serum gonatropin (PMSG)[a] Prostaglandin F2alpha[b]	Acetylsalicylic acid[a] Paracetamol[a]	
Broiler	Amoxicillin Ampicillin[a] Colistin[a] Doxycycline Enrofloxacin[a] Flumequin[b] Neomycin[a] Trimethoprim- Sulfonamid Tylosin[a]	Fenbendazole[a] Flubendazole[b]			
Laying hens	Amoxicillin Doxycycline[b] Flumequin[b] Trimethoprim- Sulfonamid	Fenbendazole[a] Flubendazole[b]			

[a] *substances exclusively named by German interviewees*
[b] *substances exclusively named by Dutch interviewees*

Figures C1 to C13 present the substance specific pilot assessments exemplary for each livestock type and substance group combination. A substance-specific assessment is necessary because the quantitative information on excretion, degradation and PNEC are highly substance-specific values. For prioritization in policies, the overall ranking across substances, livestock types and production systems as well as a ranking of substances per livestock type can be useful. Following legends indicate the assessment's pollution potential for the qualitative comparison of production systems (top) as well as for the quantitative comparison of production system independent parameters (bottom).

Factor not relevant for livestock type and/or substance	No pollution	Tendency for less pollution	Tendency for more pollution	Identified not to differ	Unknown

Pollution potential		low	moderate	medium	high
Excretion rate	not available	0-25 %	25-50 %	50-75 %	75-100 %
Degradation manure (DT_{50})	not available	<10 days	10-30 days	30-90 days	>90 days
Degradation soil (DT_{50})	not available	<10 days	10-30 days	30-90 days	>90 days
Predicted no effect concentration (PNEC)	not available	>1 µg/L	0.1-1 µg/L	0.01-0.1 µg/L	<0.01 µg/L

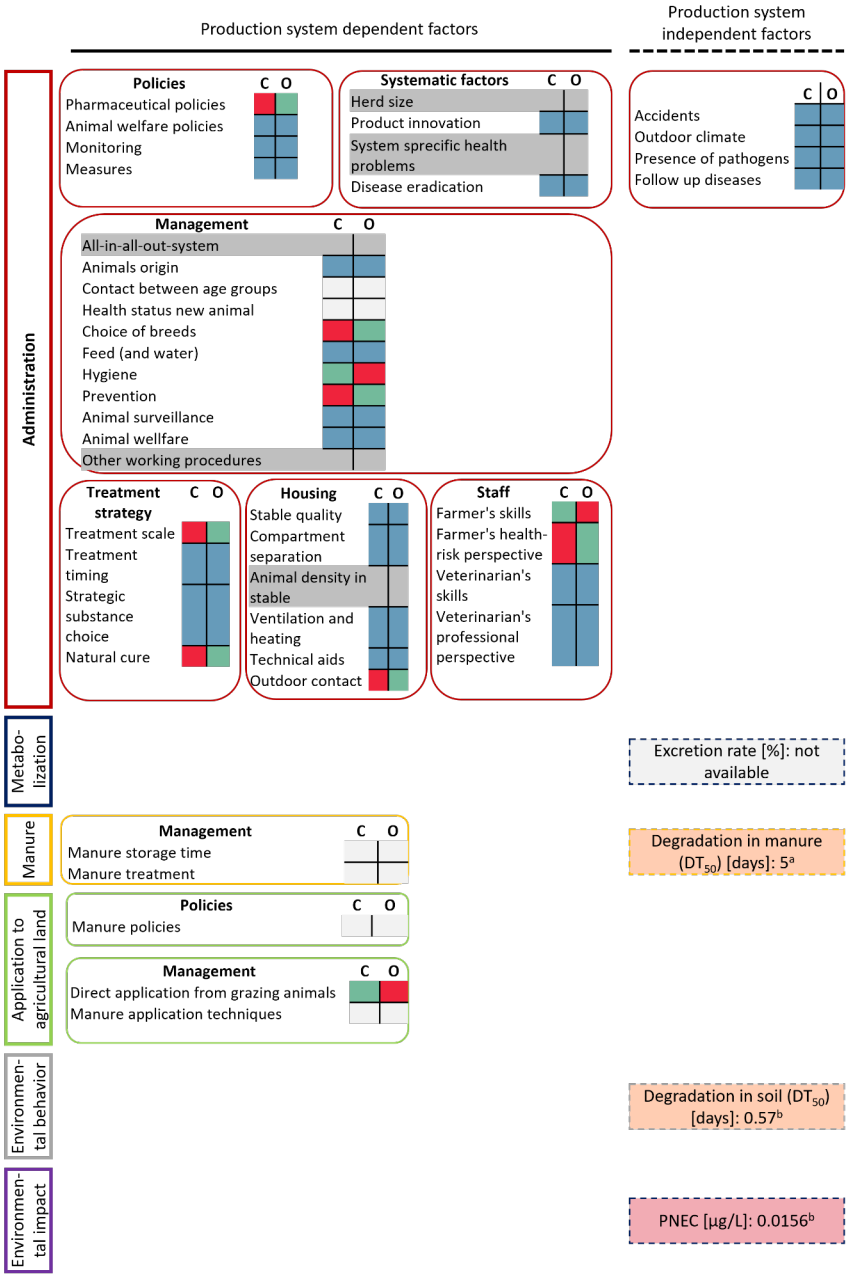


Figure C1. Pilot assessment for amoxicillin pollution from beef cattle production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] *DT_{50} for beta-lactams (Boxall et al., 2004);* [b] *median DT_{50} (Boxall et al., 2006, Braschi et al., 2013);* [c] *predicted no effect concentration (PNEC) (Bergmann et al., 2011).*

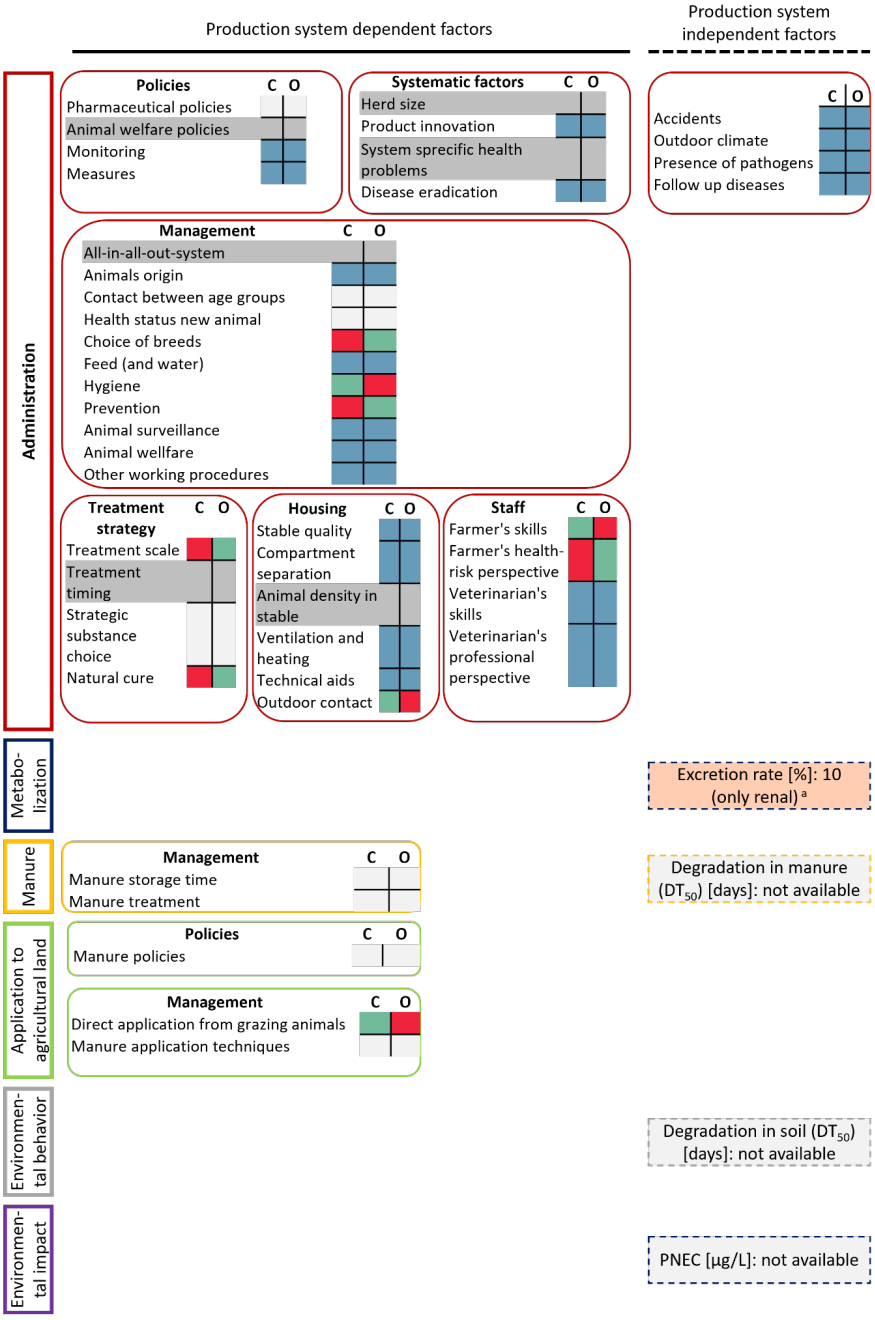


Figure C2. Pilot assessment for meloxicam pollution from beef cattle production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] (EMEA, 1999).

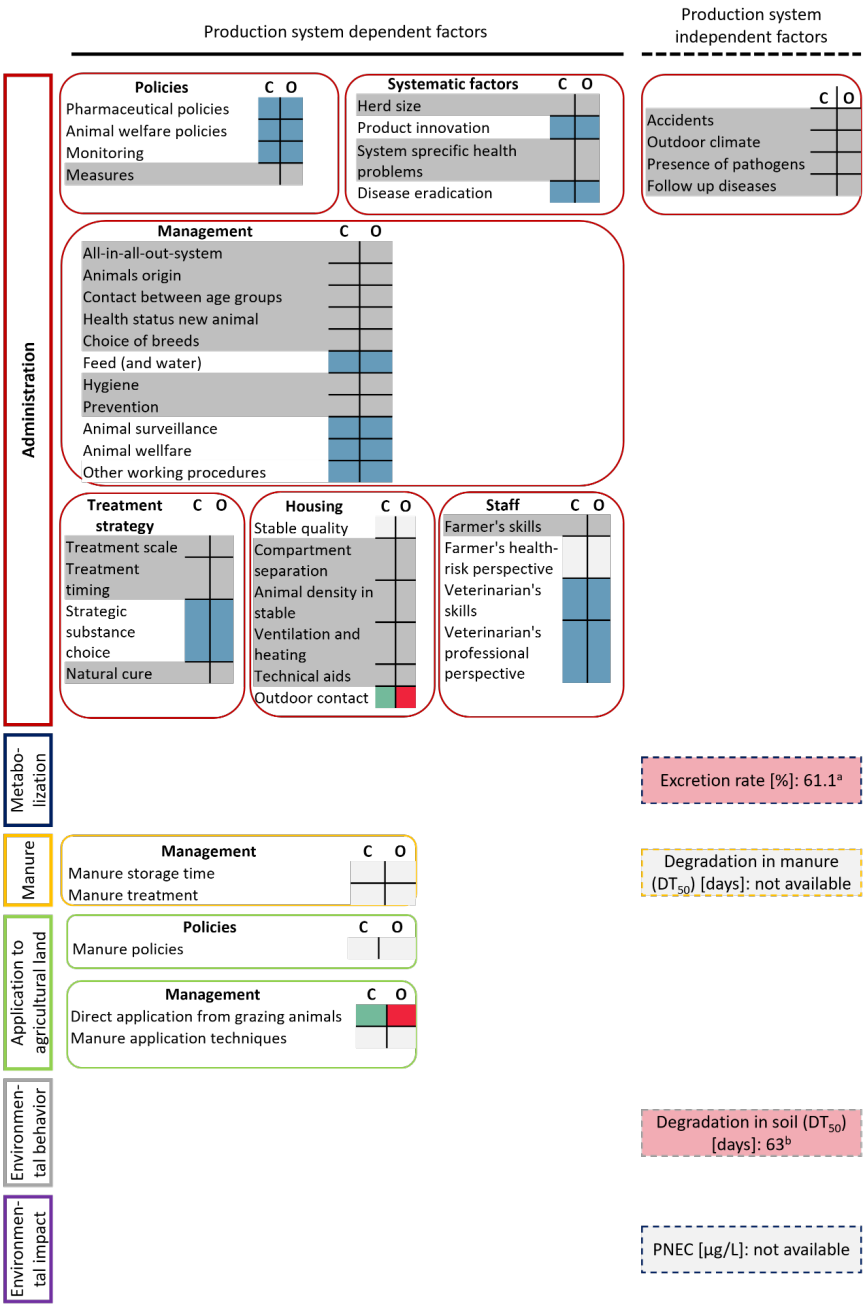


Figure C3. Pilot assessment for moxidectin pollution from dairy cattle production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] (Zulalian et al., 1994); [b] median DT_{50} (de Oliveira Ferreira et al., 2019, EMA, 2017, Fort Dodge Animal Health, 1997).

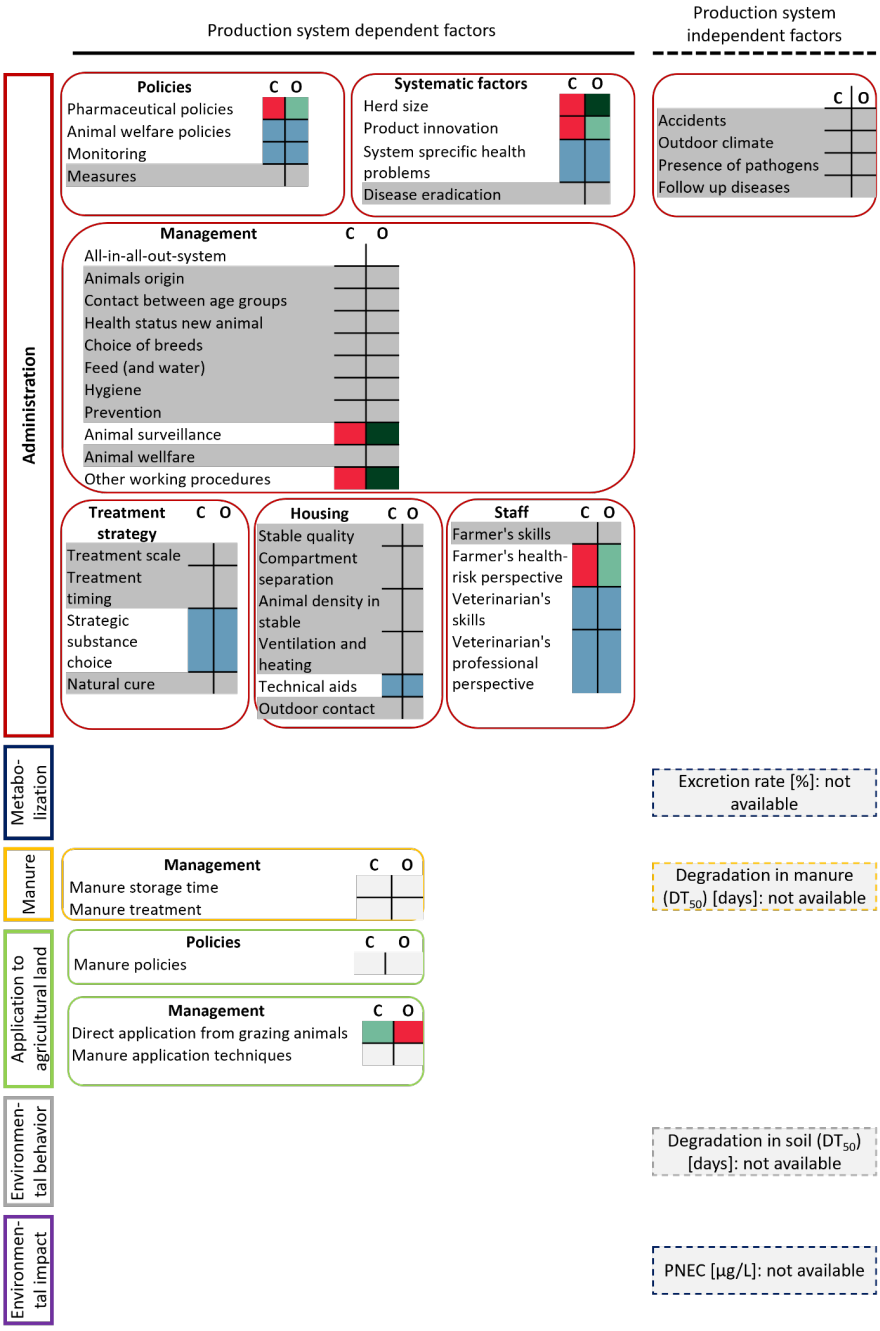


Figure C4. Pilot assessment for prostaglandin F2alpha pollution from dairy cattle production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews.

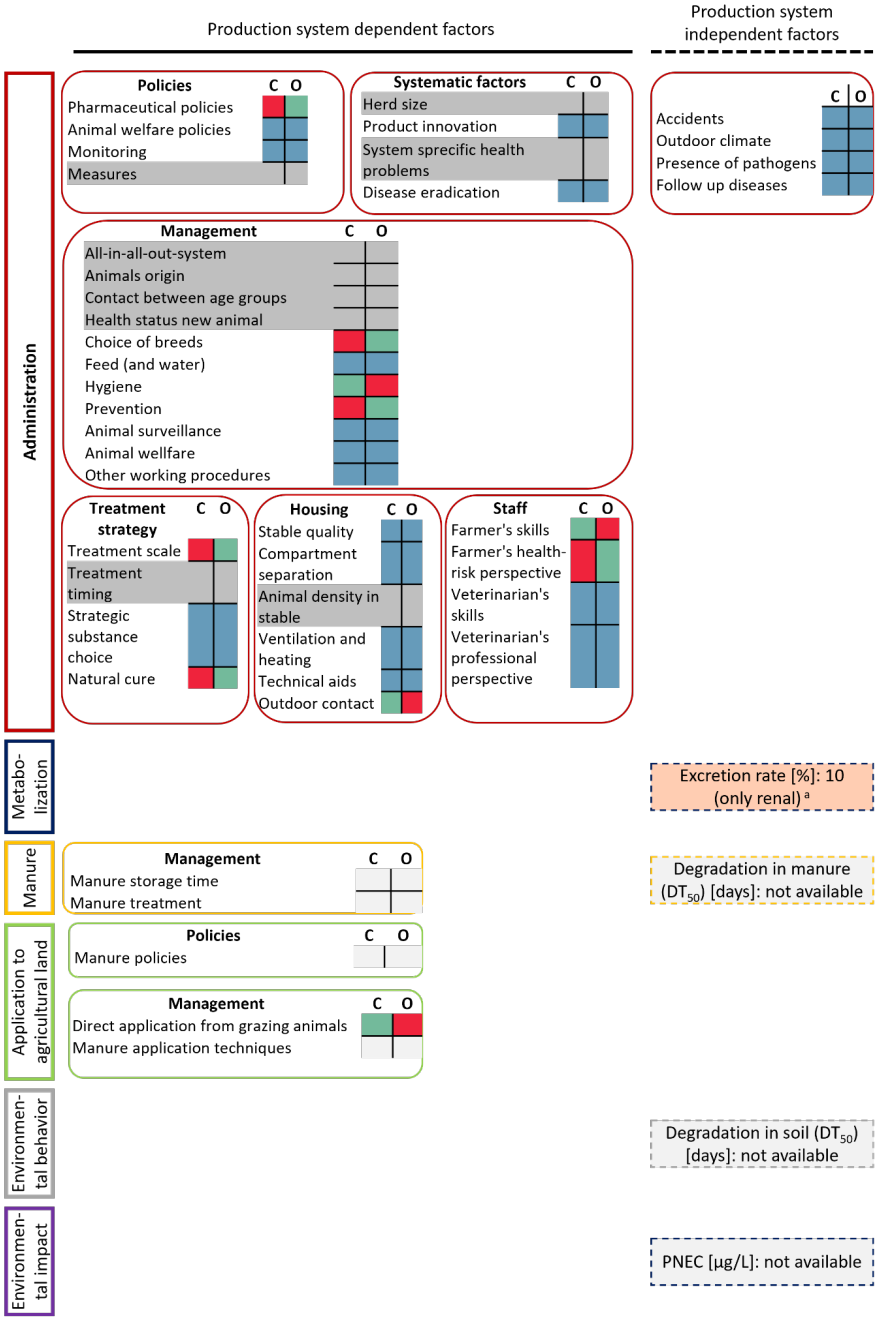


Figure C5. Pilot assessment for meloxicam pollution from dairy cattle production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] (EMEA, 1999).

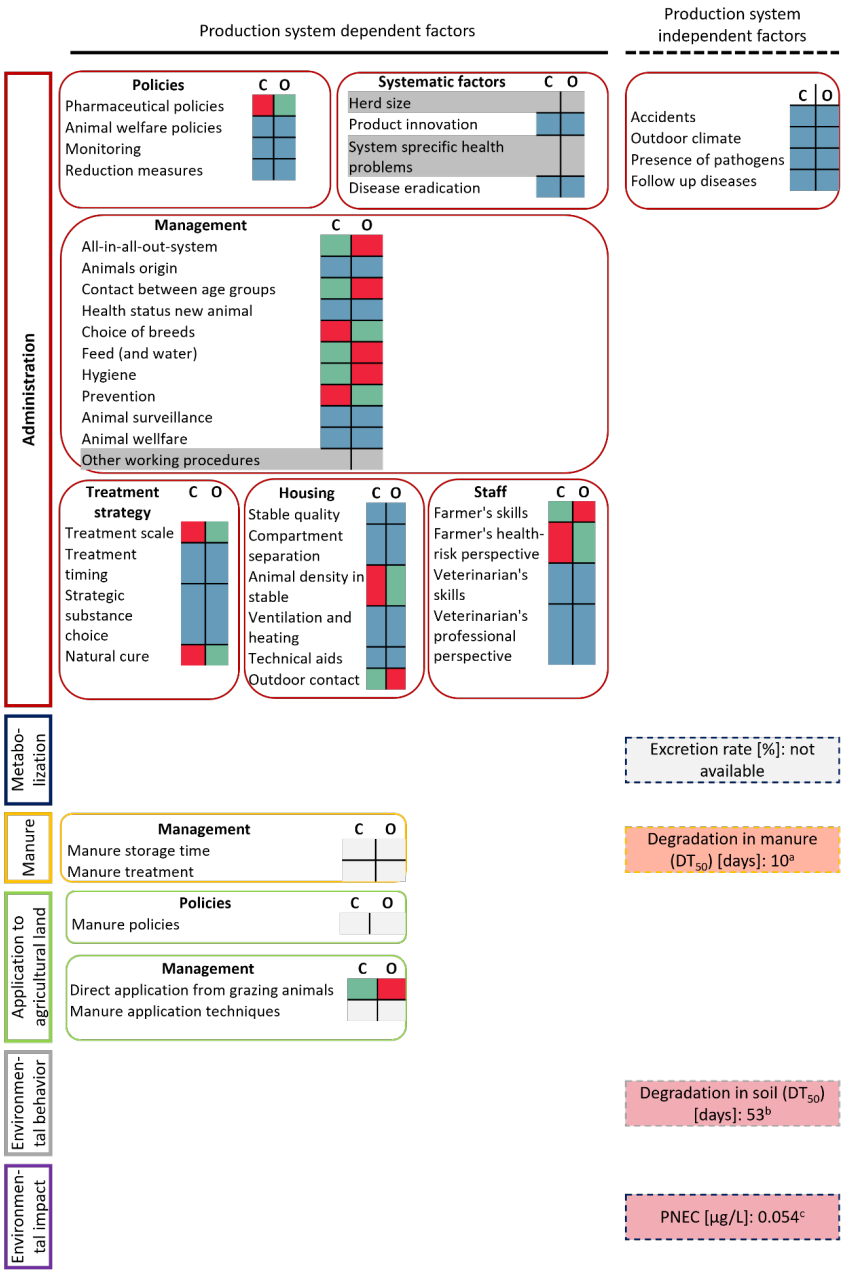


Figure C6. Pilot assessment for doxycycline pollution from pig production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] *(Berendsen et al., 2018);* [b] *median* DT_{50} *(Shi et al., 2019, Szatmári et al., 2012, Walters et al., 2010, Wen et al., 2018, Yan et al., 2018);* [c] *predicted no effect concentration (PNEC) (Bergmann et al., 2011).*

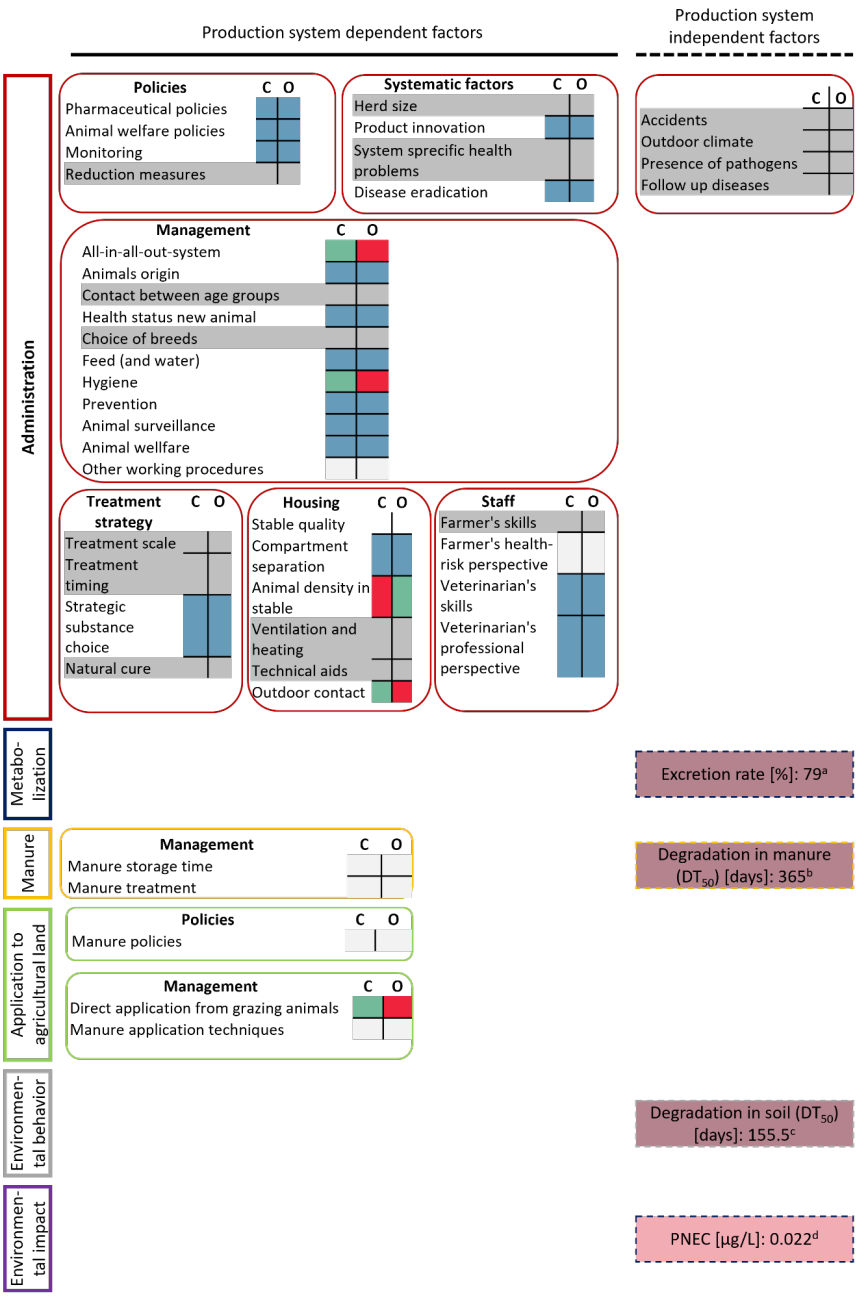


Figure C7. Pilot assessment for flubendazole pollution from pig production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] *(FAO, 1992);* [b] *(Lagos et al., 2021);* [c] *median* DT_{50} *(Kreuzig et al., 2007a);* [d] *predicted no effect concentration (PNEC) (Bundschuh et al., 2016).*

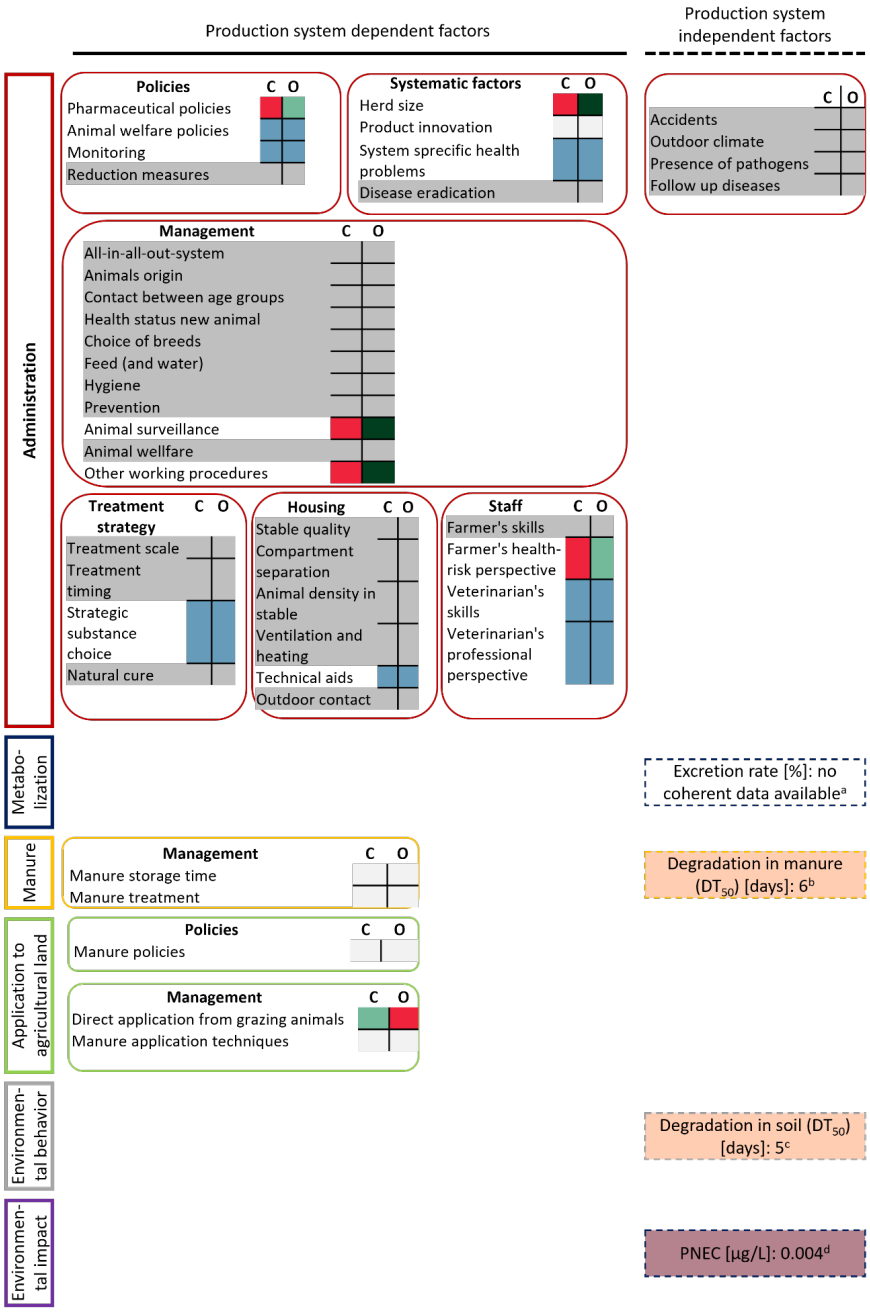


Figure C8. Pilot assessment for altrenogest pollution from pig production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] (Liesenfeld et al., 2022); [b] (EMA, 2016); [c] median DT_{50} (EMA, 2016); [d] predicted no effect concentration (PNEC) (EMA, 2016).

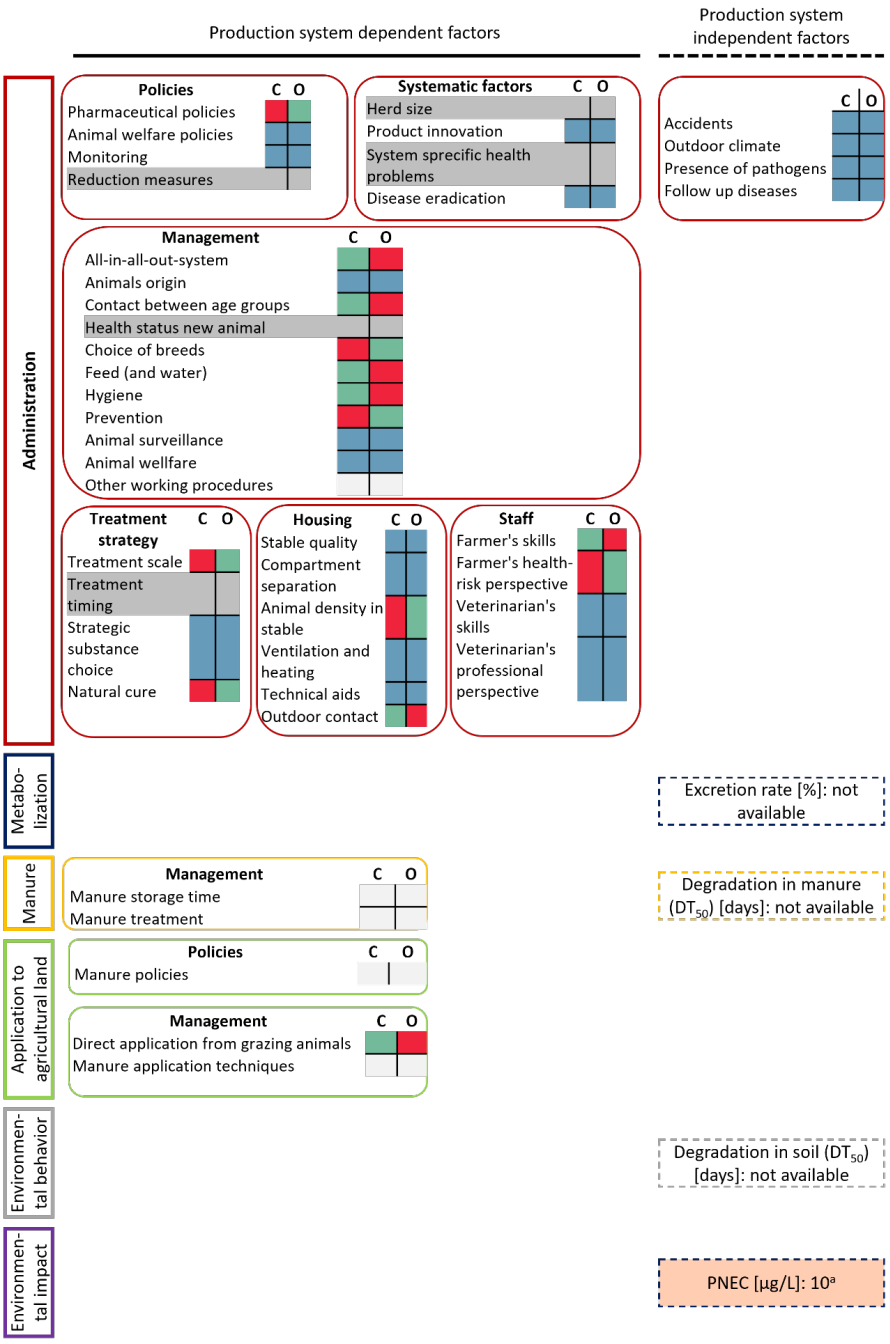


Figure C9. Pilot assessment for acetylsalicylic acid pollution from pig production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] predicted no effect concentration (PNEC) (Bergmann et al., 2011).

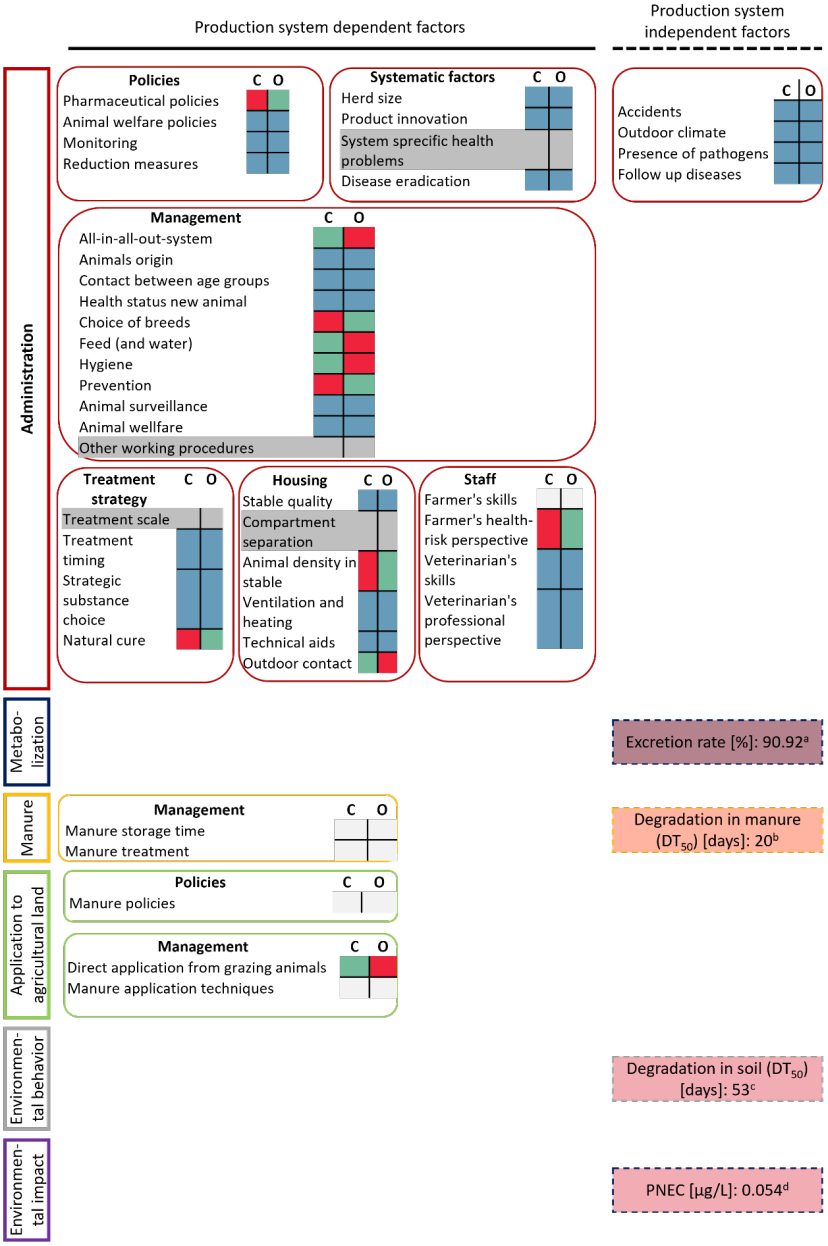


Figure C10. Pilot assessment for doxycycline pollution from broiler production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] average excretion rate (Peng et al., 2016); [b] (Berendsen et al., 2018); [c] median DT_{50} (Shi et al., 2019, Szatmári et al., 2012, Walters et al., 2010, Wen et al., 2018, Yan et al., 2018); [d] predicted no effect concentration (PNEC) (Bergmann et al., 2011).

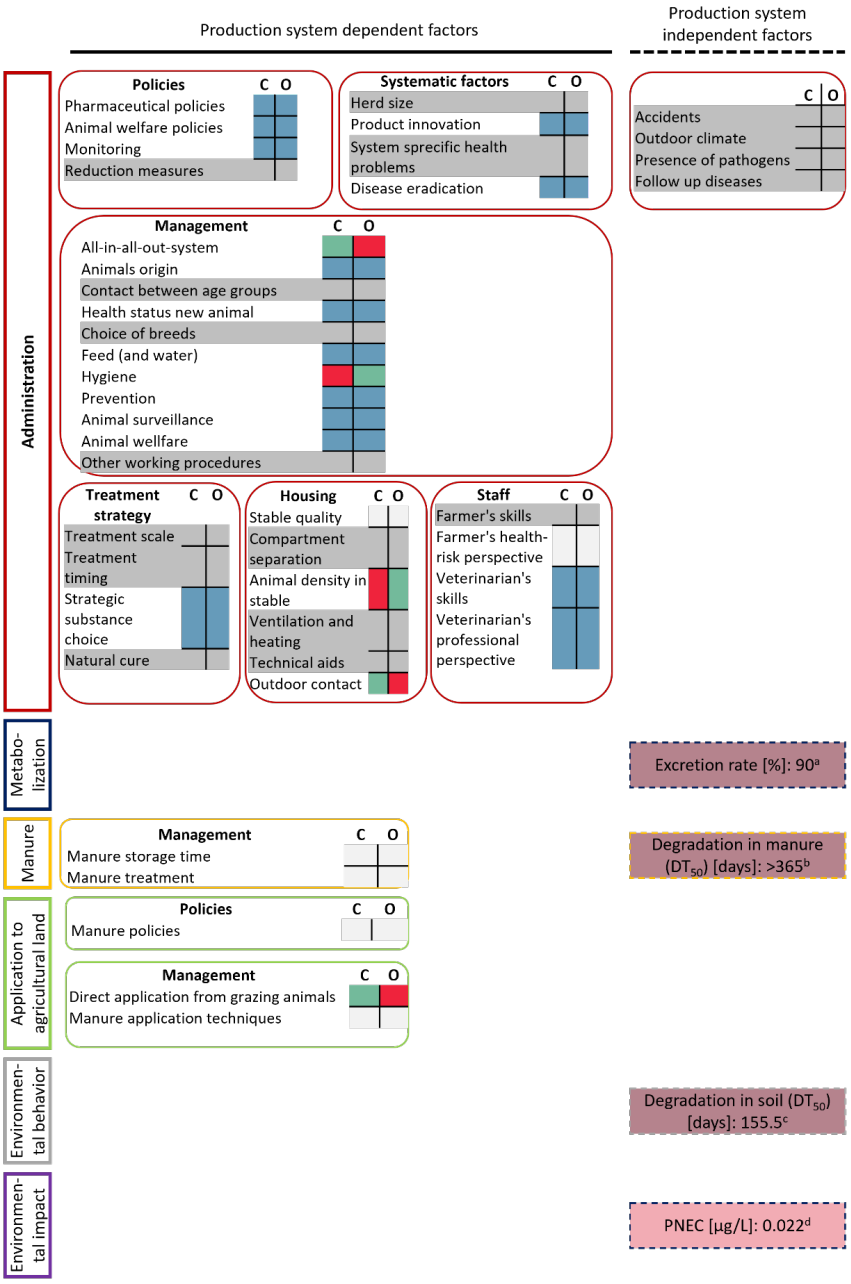


Figure C11. Pilot assessment for flubendazole pollution from broiler production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] (EMEA, 2006); [b] (Lagos et al., 2021); [c] median DT_{50} (Kreuzig et al., 2007a); [d] predicted no effect concentration (PNEC) (Bundschuh et al., 2016).

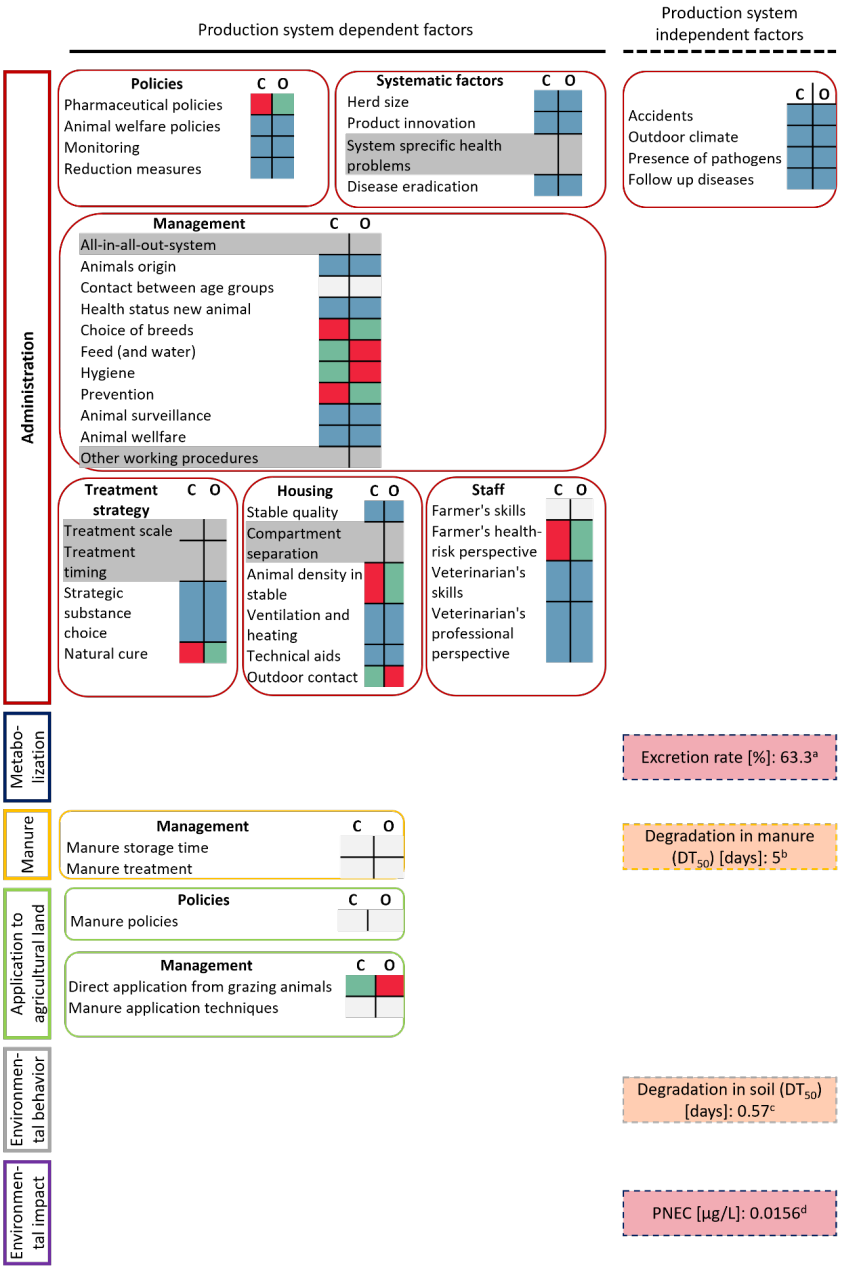


Figure C12. Pilot assessment for amoxicillin pollution from laying hen production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] average excretion rate (Peng et al., 2016); [b] DT_{50} for beta-lactams (Boxall et al., 2004); [c] median DT_{50} (Boxall et al., 2006, Braschi et al., 2013); [d] predicted no effect concentration (PNEC) (Bergmann et al., 2011).

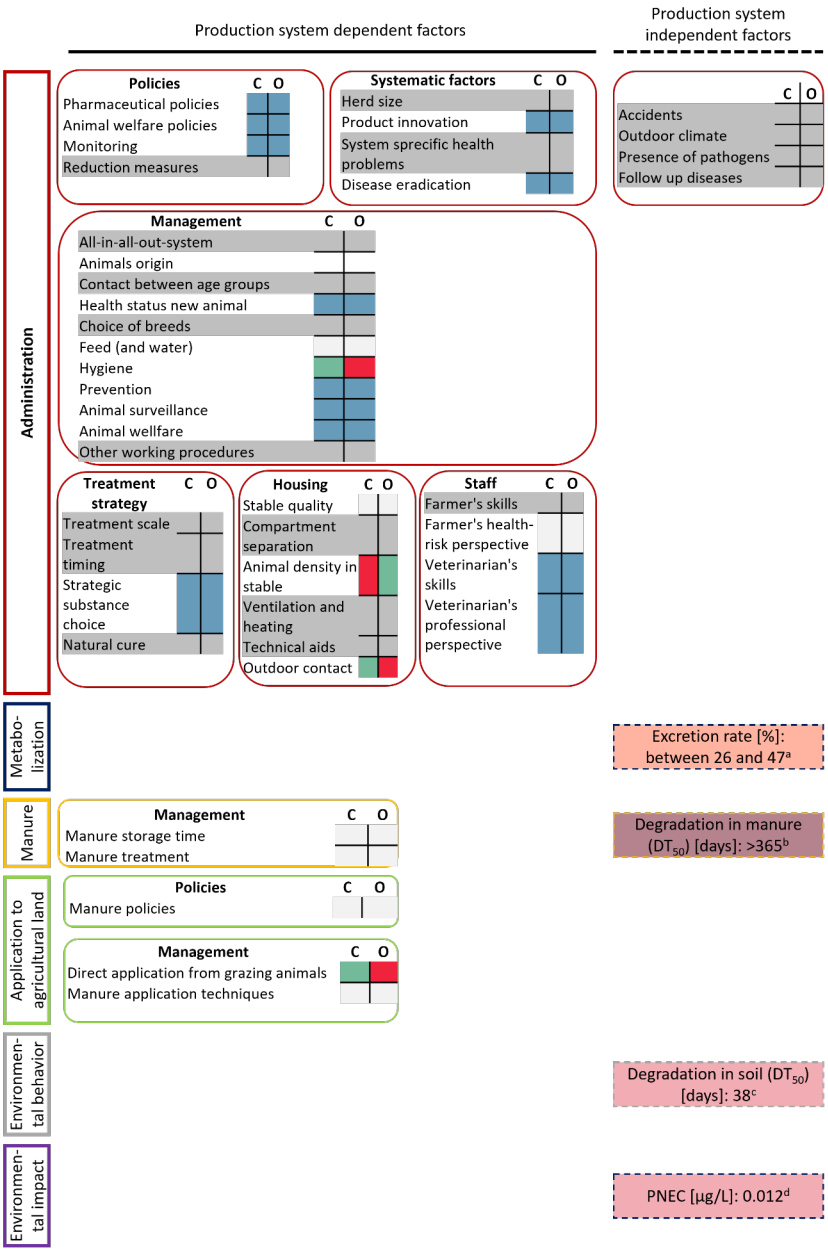


Figure C13. Pilot assessment for fenbendazole pollution from laying hen production comparing conventional (c) and organic (o) systems; data for comparison between production systems from interviews; [a] *(Short et al., 1988);* [b] *(Lagos et al., 2021);* [c] *median* DT_{50} *(Kreuzig et al., 2007a, Kreuzig et al., 2007b);* [d] *predicted no effect concentration (PNEC) (Bundschuh et al., 2016).*

Appendix D: An appendix to Chapter 5

D 1. Theoretical framework, methods and data

D 1.1. Multi-level Perspective

To identify different solutions to PIE this study follows the theory of transition paths by Geels and Schot (2007). The authors describe six different paths that outline and define diverse futures. 1) *Reproduction process*, which is a continuation of the current regime, hence adoption of niche innovations does not take place despite their possible existence. There is no landscape pressures leading to a regime shift. 2) The *transformation* path is characterized as a regime change due to moderate landscape pressure without momentum of fully developed niche-innovations. This leads to a regime reorientation with gradual adjustments, not to a regime shift. 3) *De-alignment and re-alignment* is a two-fold process where the existing regime is de-aligned through a sudden or incremental landscape change and a niche-innovation forms the centre for re-alignment of a new regime. Thereby the theory conceptualized that niche-innovations are still under development and therefore competing. One of these becomes dominant, leading to a re-alignment. 4) The *technological substitution* represents a path with matured landscape pressure while niche-innovations exist in their full development. An immediate breakthrough of the innovations substituted the existing regime. 5) In the *reconfiguration* pathway the new regime grows from the previous regime as symbiotic innovations are implemented in different domains of the system over time. Landscape can create opportunities for these. The regime reconfiguration takes place while regime actors remain. 6) *Disruptive landscape change* can lead to a sequence of transition pathways, a chain of combinations of transformation, reconfiguration, technological substitution and de- and re-alignment (Geels and Schot, 2007).

D 1.2. Data collection

We investigate the current socio-technical system of pharmaceutical lifecycle as well as potential future systems. Besides data collection through pertinent literature, interviews with regime actors were conducted. Therefore, current regime actors that are linked to the societal function of pharmaceutical supply were identified. These cover representatives from the pharmaceutical industry, healthcare sector and agricultural sector. Umbrella organizations of these sectors in Germany and the Neth-

erlands were approached for contacts of potential interviewees. In a second step, interviewed stakeholders were involved to acquire contacts of further stakeholders. Between November 2019 and February 2020, we conducted three interviews within the pharmaceutical industry, and six each in the healthcare and agricultural sector. Interviews with German participants were carried out in German. Dutch interviewees were questioned in English, while they had the opportunity to answer in Dutch.

Semi-structured interviews were conducted following an interview manuscript. The manuscript consists of an introduction, which are opening words for the interview, plus six sections which cover the content of the interview. For each section we formulated main questions and for several of these sub-questions. Sub questions were used as follow up or as alternative questions if it was difficult for the participants to immediately answer the overall questions. As the interview was conducted with actors having diverse backgrounds, interview questions are formulated broadly. The method of semi-structured interviews was chosen and considered suitable due to it's proven appropriateness to study insights and perceptions of participants from diverse backgrounds along with the possibility of including further questions during the interview (Kallio et al., 2016). The latter was especially helpful to understand system dynamics and actor's routines. Table D1 presents the sections of the interview manuscript.

One interview was conducted with two participants due to preference of the interviewees. The recording of one interview was only partially successful and therefore extended with a report from memory based on notes taken during the interview.

Table D1. Interview manuscript in English.

Opening words	• Organizational details • Explanation about the context of the research • Introduction of the research team • Permission for interview recording • Explanation how the data will be processed and used later on
Section 1	**General**
	• Do you have any comments or questions that you would like to bring up? • Personal details - Job title • Sector and type of organization the stakeholder is affiliated to

Section 2 **Problem description – today's situation:**

- What do you know about the topic of pharmaceuticals in the environment? / How would you describe the situation?
- Do you see pharmaceutical residues in the environment as a problem?

  - If yes, could you describe what kind of problem?
  If no, why not?

- Is the topic discussed within your everyday work life?

  - Please describe

- How do you consider the urgency of addressing the topic of pharmaceuticals in the environment (1 to 10, where 1 has the lowest urgency)?
- Do you recognize developments in addressing the topic of pharmaceuticals in the environment?

  - If yes, what developments are these?

- Do you recognize counter developments in the field?

  - If yes, what counter developments are these?

Section 3 **Potential solutions – the future:**

- How do you see the future regarding the topic of pharmaceuticals in the environment?

  - Do you think the situation is going to change?

- What (different) potential solutions do you see for the problem of pharmaceuticals in the environment that you just described?

Section 4 **Requirements for potential solutions:**

- What conditions and requirements do you think are necessary to reach these potential solutions?

  - How should an enabling environment look like?
    What Societal trends, legislative and policy developments, political changes, cultural dynamics, etc. are necessary?
  - What innovations do you consider necessary for these potential solutions?
    Technological innovations, non-technical tools and measures

- What developments (specific innovation and broader societal developments) do you foresee to realistically happen or not to happen?

Section 5 **Who:**

- Who do you see responsible for putting these conditions and requirements into place?

  - If you look at the different actors and their roles in the pharmaceutical domain today (pharmaceutical companies, health sector, agricultural sector, water sector etc.), do you think that roles and responsibilities have to shift in order to implement your suggested solutions? How?

- How do you see your/ your organizations role/ responsibility in regard to these solutions?

Section 6 **Reflecting on potential solutions:**

- How realistic do you see your potential solutions (from 1 to 10 where 1 least realistic)
- What hurdles do you see?
- Do you foresee (societal) consequences or tradeoffs for such solutions?

D 2. Results

D 2.1. Niche innovations

Figure 5-2 in the manuscript presents an overview of the identified niche innovations that developed along the pharmaceutical lifecycle to reduce PIE. Table D2 presents these niche innovations, including a selection of different identified approaches for the innovations and references as information source.

Table D2. Overview niche innovations.

Niche innovation	Approaches	Sources
Awareness raising	• Education of medical and veterinary staff • Awareness raising among patients	(Daughton and Ruhoy, 2009, Klatte et al., 2017, Kümmerer, 2008b, Sivén et al., 2020)
Considering environmental aspects during drug discovery process	• Benign by design • Benign by nature • Increasing bioavailability of pharmaceuticals	(Kümmerer, 2008b, Kümmerer, 2019, Kümmerer and Hempel, 2010, Straub, 2016)
Avoiding emissions from manufacturing, considering environmental standards	• Transparency of production chain • Environmental emission regulations • Pollution control along supply chain	(Bengtsson-Palme et al., 2018, Changotra et al., 2020, Ding, 2018, Larsson, 2014)

Niche innovation	Approaches	Sources
Changing prescription towards less pharmaceutical emissions	• promoting prescription of pharmaceuticals with less environmental relevance • Replacing pharmaceutical treatment with alternative • Deprescribing	(Ågerstrand et al., 2009, Deffner and Götz, 2008, Goetz, 2013, Seinen and Feil, 2019, Thompson and Farrell, 2013)
Reducing consumption (human health sector)	• Prevention • Disease specific application (e.g. no antibiotics for viral infections)	(Daughton and Ruhoy, 2011, Deffner and Götz, 2008)
Reducing, limiting pharmaceutical use (livestock sector)	• limit consumption to health-related purposes • pharmaceutical treatment exclusively for sick animals • management, e.g. separation of sick animals, vaccines, appropriate animal keeping	(Kemper, 2008, Klatte et al., 2017, Vidaurre et al., 2016)
Avoiding incorrect disposal	• avoiding leftovers • correctly disposing leftovers in households and health care institutions • pharmaceutical recycling	(Afanasjeva and Gruenberg, 2019, Daughton and Ruhoy, 2011, Persson et al., 2009), Petrovic and Barcelo (2007)
Excreta collection and disposal	• urine collection system • toilets for separated excreta collection	(Derksen et al., 2015, Niederste-Hollenberg et al., 2018)
Decentralized wastewater treatment	• special treatment for hotspots/ specific pollutions	(Batelaan et al., 2013, Krarup et al., n.y.)
Centralized advanced wastewater treatment	• Activated carbon • Nanofiltration, reverse osmosis • H2O2 and UV-radiation • phytoremediation	(Dobner et al., 2013, Fröhlich et al., 2019, Ganiyu et al., 2015, Homem and Santos, 2011, Reungoat et al., 2012, Schroder et al., 2012, Snyder et al., 2007)
Manure treatment	• composting • heating • drying • pasteurisation • incineration	(Derksen et al., 2015, Vidaurre et al., 2016)
Reducing runoff and leaching	• improved manure application techniques • buffer zones to surface waters • application adjusted to climate and soil conditions	Vidaurre et al. (2016)

D 2.2. Niche innovation awareness raising and requirements

Awareness raising was identified as an overarching measure to the implementation of niche innovations. Table D3 lists the different awareness raising elements mentioned by the interviewees.

Table D3. Different elements of awareness raising about pharmaceuticals in the environment (PIE) and their requirements expressed by the interviewed regime actors.

Awareness raising elements	Requirements
General awareness raising	• Information understandable for everyone • Information and knowledge originating from independent experts • Funds for knowledge transfer, campaigns etc. • Collaboration among sectors to exchange expertise
Communication about PIE to patients and general public	• Continuously addressing the topic in media (constant marketing) • Focus on positive communication: how everyone can contribute rather than telling people what they should not do • Leaflet about PIE enclosed to each medicine
Patient's education towards more critical drug use	• Reliable information from independent research
Communication about PIE for doctors	• Include environmental criteria in existing guidelines that are regularly updated • Availability and easy accessibility of information, knowledge and evidence • Include PIE theme in education of healthcare staff
Awareness raising about PIE among animal owners	• Availability of Information, knowledge and evidence • Include critical perspectives in the farmers' educations (also on PIE)
Informing consumers about pharmaceutical use in livestock animals	• Product specific consumer information
Exchange best practice examples among regime actors	
School subject "health" to increase general knowledge about healthy living, health risk due to PIE etc.	

D 2.3. Niche innovations human health sector and their requirements

Different niche innovations were identified for the human health sector: The change of prescription routines, alternative treatments and the appropriate use of pharmaceuticals. For each of these we identified elements that describe different approaches to implement the niche innovations. Table D4 presents niche innovations along with their detailed elements and requirements.

D 2.4. Responsibilities and barriers

Different solutions to pharmaceuticals in the environment were identified. For each of these solutions, interviewees named requirements and who they see responsible for putting these requirements in place. Table D5 illustrates actors, actor groups, organization, institutions or sectors that were mentioned by participants in this context.

The interview analysis elucidated barriers that regime actors see to the solutions they proposed. These include barriers to individual measures, but likewise more broad barriers to change. A detailed list categorizing all barriers is provided in Table D6.

Table D4. Niche innovations targeting human pharmaceutical prescription and use along with their requirements.

Niche innovation	Detailed elements	Requirement
Changing prescription routines towards less pharmaceutical emissions	More restrictive drug prescribing by doctors	• Adapt payment system for doctors if necessary
	Prescriptions considering environmental aspects	• Awareness raising • Environmental risks have to be known and included in information materials that prescribers use anyway • Benchmarks for drugs with environmental risk, so prescribers can compare their prescription behavior to that of colleagues • Prioritize, e.g. start with the "big 5"
	Doctors diagnose and pharmacists decide on drug use	
	Prioritizing treatment options without pharmaceuticals over pharmaceutical treatment	• Doctor's responsibility • Information about non-pharmaceutical treatment has to be made easily accessible to prescribers • Societal acceptance for people to take a recovering time (e.g. when they are missing work)
	Deprescribing	• Use of co-effects as deprescibing can not only be done for environmental purposes • Centralized information system where different medication of patients are saved and can be re-evaluated (plus technical and regulatory prerequisites)
Alternative treatments resulting in less pharmaceutical emissions	Evaluation if pharmaceutical treatment is unavoidable	• Evidence on when it makes sense to wait for natural positive course
	Household remedies or medicinal plants	• Availability and functioning of household remedies or medicinal plants
	Non-medical therapy instead of medication for mental diseases	• Increasing numbers of doctors and therapists to increase their capacity as non-medical treatment is mostly more time intensive

Niche innovation	Detailed elements	Requirement
Appropriate use of pharmaceuticals leading to reduced pharmaceutical emissions		• awareness of pharmaceutical impact on environment • if patients would have to pay for pharmaceuticals, they would be more critical about their use
	Patients' expectations are frequently pharmaceutical oriented, they need to understand and be informed about appropriate use (e.g. non-functioning of antibiotics for viral infections)	• Explanation to patients by doctors • Change of attitude by patients (demanding patients leave the doctor with more medicine than non-demanding patients. Not because they are more sick, but because they demand)
	many complaints and diseases have a positive natural course, patients need to know that in these cases pharmaceutical use is not essential	• evidence on when it makes sense to wait for natural positive course • patients need to trust in their bodies own healing capacity • societal acceptance for people to take a recovering time (e.g. when they are missing work)
	Encompassing informing of patients about positive and negative effects of using pharmaceuticals, thus they can make a critical choice. (E.g. life-prolonging drugs might increase life expectancy, but at the same time cause severe side effects during this time. If a patient is informed with full transparency, he/she can make a suitable decision)	• educating patients to be critical on drug use
	more critical use of OTC products, government should control that more strictly	• public awareness • increase price of OTC products • prohibit OTC products that pose environmental risk

Table D5. List of those responsible for the different solutions according to the interviewed regime actors.

Solution	Function	Responsible
Accepting PIE		
Implementing niche innovations	Strategy setting	• Governments (from local to national) • Legislators
	Pressuring	• People in power positions • Governments • Food producing sector • Environmentalists
	Knowledge generation and distribution	• Educational and research institutions • Experts • Authorities • Media
	Implementation of innovations in different sectors	• Educational institutions • Pharmaceutical developers • Pharmaceutical producers • Procurers in pharmaceutical industry • Prescribers • Doctors • Hospital owners • Pharmacists • Patients • Veterinarians • Farmers • Water authorities • Representing organizations
	Financing	• Governments • Banks • Health insurance companies • Animal product consumers
	"Watchdog"	• NGOs • Authorities

Solution	Function	Responsible
System change veterinary pharmaceuticals	Knowledge acquisition and distribution	• Universities • Media
	Consulting	• Representing organizations
	Enforcement	• Governments
	Pressure	• Public • Consumers
	Financing	• Banks • Society • Retailers • Consumers
System change human pharmaceuticals	Awareness	• Society

Table D6. List of barriers to solutions mentioned by interviewees.

Category	Barrier
Financial barriers	• Costs for testing environmental concentrations • Rules and monitoring costs • In some countries medicine choice is influenced by medicine cost and therefore not always ideal treatment is applied • Unattractive business case to develop specific new pharmaceuticals, e.g. antibiotics • Health care system is oriented towards economic efficiency, working on additional topics such as environmental topics is not being paid for • Choice between alternative therapies is based on costs not on environmental aspects • Farm efficiency more important than environmental aspects • Financial pressure on farmers • Pharmaceutical treatment for animals cheaper than management measures • Veterinarians earning money with selling pharmaceuticals • Investments for innovations • Proposed innovations require more work force • Not clear who should pay for measures (patients, pharma industry, insurances, taxpayers etc.)

Category	Barrier
Knowledge barriers	• No coherence in water quality data • Scarcity of evidence based knowledge about PIE • Poor knowledge about metabolites • Lack of knowledge about PIE among health care professionals and policy makers • Lack of demand for alternatives due to scarce knowledge about PIE • Deficits in knowledge distribution • Lack of knowledge about "where to start" • Polarization of topic hinders solutions • Insufficient evidence based evaluation of innovations • Pharmaceutical industry could be at disadvantage if they share information • Intransparent agreements between pharmaceutical industry and health sector
Cultural barriers	• Corupt practices regarding environmental standards • Established practices, resistance to change • Cultural barriers about the perception of medicine use • Patients trust prescribers blindly • Starting a (long-term) medical treatment is easy, stopping it is difficult
Regulatory barriers	• Short term thinking rather than long term thinking • Implementation of regulations is time intensive • Regulations prioritizing other aspects than environment • Different national policies make it difficult do find a one fits all solution • No regulatory pressure to include environmental aspects in pharmaceutical development • Different policies lead to different procurement standards, possibly leading to disincentivizing companies to compete everywhere • Rules by representing organizations could lead to members withdrawal from the organization • Shortcomings in current environmental risk assessment regulation for pharmaceutical authorization • Pharmaceutical authorization barriers for veterinary pharmaceuticals, e.g. first choice products have larger excreted fractions than second choice
Responsibility barriers	• Different perceptions of who is the polluter • People perceive others responsible for changing behaviour • Differentiation between what can every individual (actor) do and what do we have to do as a society • Priority of involved sectors lies elsewhere (e.g. health care), sector has no interest in having a responsibility for other topics • Politicians fear consequences of prohibiting • No coherent responsibilities of who collects leftover drugs
Technical barriers	• Measures target specific emission sources or substances, but do not capture everything • What works in theory, does not necessarily work in practice • Non-practicability of certain measures, e.g. urine bags • Several established drugs function effectively, there is no incentive to develop products (with less environmental risk) which could replace these • Alternative drugs might not always exist

Category	Barrier
Organizational barriers	• Established global system • Established sectoral structures • Some innovations require global demand • Global market competition for animal products • Influential position of pharmaceutical industry • Implementation of measures can result in increased workload for medical staff • Lack of (future) professionals in farming due to unattractiveness of the job as result of strict regulations for their work
Societal barriers	• There are many (environmental) problems, people are overwhelmed • Scepticism about changes • Peoples willingness to change • Doubt on credibility for self-regulation by sectors
Other barriers	• Potential bias as only actors who are interested participate in the discussion • Measures can come with trade-offs • Discrepancy between what consumers demand and what agriculture can supply

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born on 7th March 1991 in Osnabrück, Germany

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Enschede, 4th of March 2022

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The SENSE Research School has been accredited by the Royal Netherlands Academy of Arts and Sciences (KNAW)

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AKADEMIE VAN WETENSCHAPPEN

The SENSE Research School declares that **Lara Wöhler** has successfully fulfilled all requirements of the educational PhD programme of SENSE with a work load of 57.8 EC, including the following activities:

SENSE PhD Courses

- Environmental research in context (2017)
- Research in context activity: 'Communicating MEDUWA project outcomes to a broader audience' (2017-2021)

Other PhD and Advanced MSc Courses

- Innovation and Sustainability Transition, The Arctic University of Norway (2018)
- Water Footprint Assessment, University of Twente (2017)
- Geographical Information Systems, Universität Osnabrück (2018)
- Taste of Teaching Bootcamp, University of Twente (2018)
- Academic Publishing Bootcamp, University of Twente (2017)
- Dutch for beginners, University of Twente (2017)
- Dutch Language Course follow up 1, University of Twente (2018)
- Dutch Language Course follow up 2, University of Twente (2018)
- Professional Dutch, University of Twente (2018-2019)
- High Proficiency Dutch, University of Twente (2019)

Management and Didactic Skills Training

- Supervising two MSc students with thesis (2019-2020)
- Supervising two BSc students with thesis (2020-2021)
- Teaching in the MSc courses 'Water Footprint Assessment' (2018-2021) and 'Water Quality' (2019-2021)

Oral Presentations

- *The water footprint concept: State of the art, research outlook and opportunities for education.* 4th Water Agency Conference, 5 October 2018, Rogaška Slatina, Slovenia.
- *Alternative societal solutions to pharmaceuticals in the aquatic environment.* AGU, 10 December 2021 (online)

SENSE coordinator PhD education

Dr. ir. Peter Vermeulen