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

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A B S T R A C T

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.

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

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(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 6000 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 percolate 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).

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[1] 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 the supplementary information (SI).

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[2] 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 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.

[1] Also known under the synonym sulfadimidine.

[2] 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).

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.

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

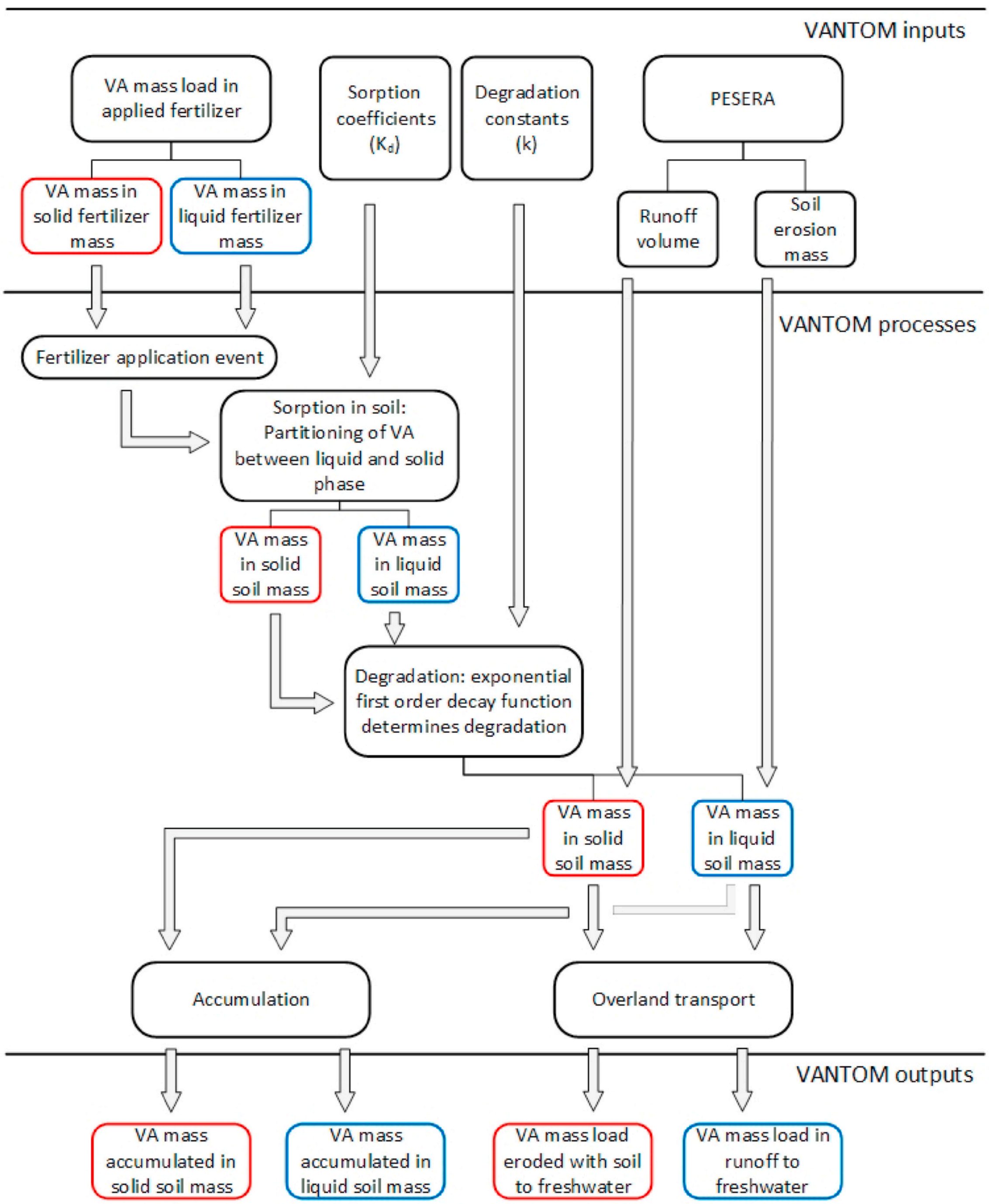

Fig. 1. Conceptual overview of the VANTOM model, distinguishing between model inputs, processes, and outputs. Veterinary antibiotic (VA) masses in solid form are labelled red, VA masses in liquid form are labelled in blue, adapted from Bailey (2015). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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 are permitted from February until August or mid-September in NL (Netherlands Enterprise Agency, 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.

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 Fig. 1 for a conceptual overview of VANTOM inputs, processes and outputs and Figure S2 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 SI.

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 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):

$$\frac{VA_s}{M_s} = K_d \times \frac{VA_l}{M_l} \tag{1}$$

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 SI). 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 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):

Table 1
Veterinary antibiotic's sorption coefficients (K_d) and half-lives (DT_{50}) representative for soil conditions of the study area and used as VANTOM inputs (for more information see SI), 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][a]
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

[a] PNEC values were taken from Bergmann et al. (2011).

$$VA_{rest}[v,c] = VA[v,c] \times e^{-k \times T} \tag{2}$$

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 SI. 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 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 (SI). VA loads moved through overland transport of liquid and solid soil mass loads are proportional to these and defined as:

$$VA_{rem}[v] = \frac{d_r[v]}{d_p} \times VA_{rest}[v,p] \tag{3}$$

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.

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 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.[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.

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). The SI presents further details of the uncertainty analysis.

3. Results

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. Fig. 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

[3] 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.

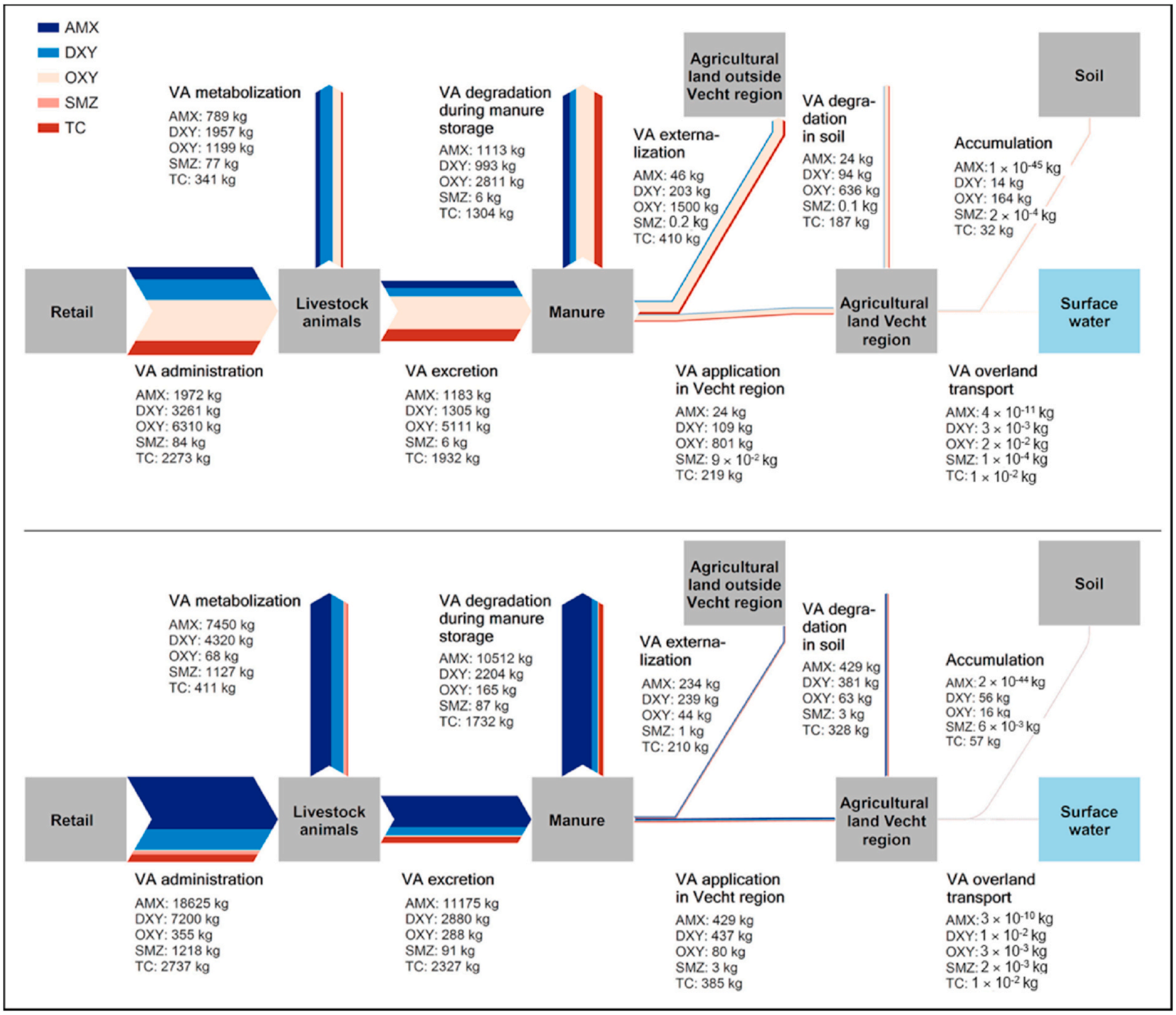

Fig. 2. Annual veterinary antibiotic (VA) mass flows from administration to surface water emission in the Dutch (top) and German (bottom) part of the Vecht river catchment for the substances amoxicillin (AMX), doxycycline (DXY), oxytetracycline (OXY), sulfamethazine (SMZ) and tetracycline (TC).

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 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.

3.2. 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 SI 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 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.

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 8000. This implies that for the catchment as a whole, water

Table 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).

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, Fig. 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 SI.

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 3600 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 S5. 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.

4. Discussion

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

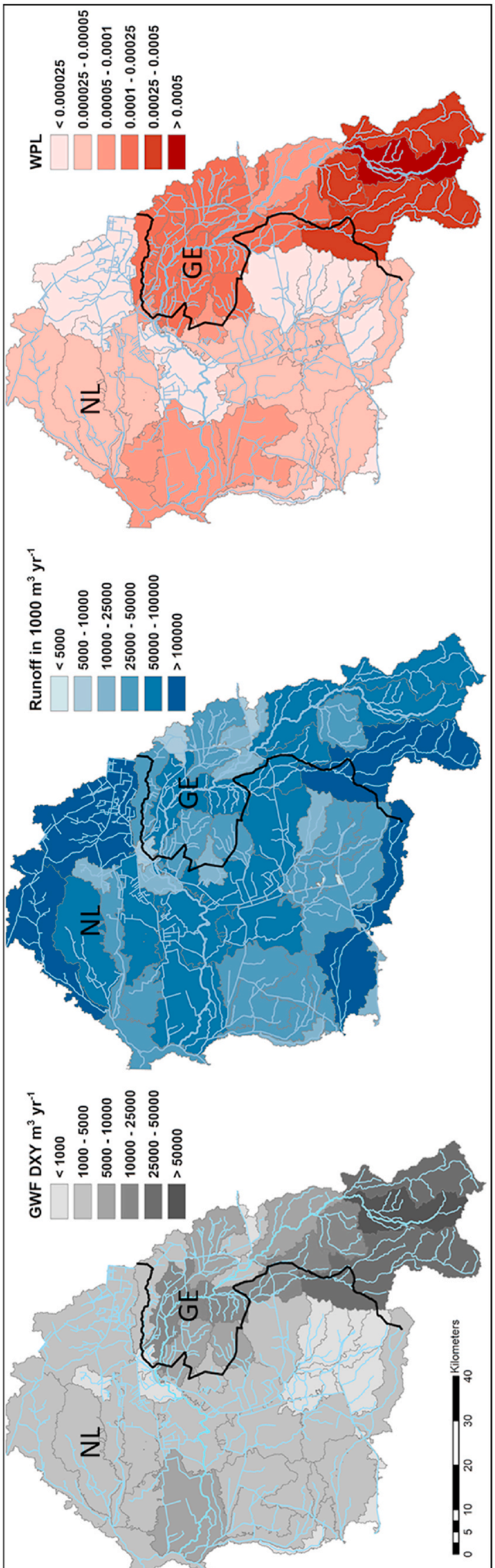

Fig. 3. GWFs of the most critical substance doxycycline (DXY) (left), available runoff (middle) and water pollutant level (right) per sub-catchment in the Vecht catchment.

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, above-mentioned 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 integrated modelling approaches that cover the entire pharmaceutical lifecycle. We recommend such analysis to be conducted in the future.

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%–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.

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.

Declaration of contribution

Lara Wöhler: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft. **Pieter Brouwer**: Conceptualization, Formal analysis, Investigation, Methodology, Software, Writing – review & editing, **Denie Augustijn**: Methodology, Supervision, Writing – review & editing, **Arjen Hoekstra**: Conceptualization, Funding acquisition, **Rick Hogeboom**: Supervision, Writing – review & editing, **Brian Irvine**: Data curation, Resources, Software, Writing – review & editing, **Volker Lämmchen**: Data curation, Software, Writing – review & editing, **Gunnar Niebaum**: Methodology, Software, Writing – review & editing, **Maarten Krol**: Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2021.117746.

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