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Emission estimation and prioritization of veterinary pharmaceuticals in manure slurries applied to soil

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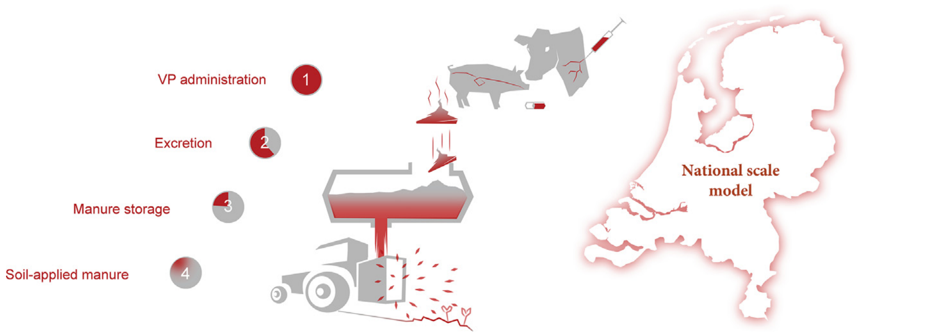
HIGHLIGHTS

- A modelling approach to quantify emissions of veterinary pharmaceuticals (VPs) to soil is provided.
- Emissions show to vary per livestock sector due to differences in VP usage and excretion.
- In addition, manure production, and storage practices influence the VP residues.
- Most commonly used VPs are frequently not the ones ending up on the soil in high concentrations.

GRAPHICAL ABSTRACT



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ABSTRACT

Veterinary pharmaceuticals (VPs) are emitted into the environment and transfer to groundwater and surface water is diffuse and complex, whereas actual information on the fate is frequently limited. For 17 VPs of potential concern in the Netherlands, we assessed sources and emission due to animal slurry applications to soil. Hence, we examined the use of VPs in four livestock sectors in the Netherlands for 2015–2018, and quantified animal excretion rates and dissipation during slurry storage. For almost all VPs, administrated quantities to the animals during the period 2015–2018 decreased. VP concentrations during a storage period of six months could decrease between 10 and 98% depending on the compound. Predicted concentrations of VPs in slurries after storage compared well with measured concentrations in the literature. Based on the storage model outcomes, we developed a residue indicator, that quantifies the potential for residues in applied slurry. This indicator agrees well with the most frequently detected VPs in the Dutch slurries, and is therefore useful to prioritize measures aiming at reducing VP emissions into the environment.

1. Introduction

Veterinary pharmaceuticals (VPs) are used worldwide to treat diseases and to protect the health of animals, where the type of used VP compounds depends on the animal sector and particular region (Berendsen et al., 2018). A major pathway by which VPs enter the environment is the excretion of urine and faeces from medicated animals and application of contaminated manure to agricultural land (Boxall et al., 2004; Crane et al., 2009). VP residues can reach and affect the quality of soil, groundwater and surface water (Kemper, 2008; Benotti et al., 2009; Lahr et al., 2018; Cycoń et al., 2019; Mooney et al., 2020; Zhang et al., 2021). Also, VP residues may end up in soil

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organisms and plants and be transferred into the food chain (Pan and Chu, 2017; El Agrebi et al., 2020).

Several comprehensive studies investigated the environmental fate and effects of veterinary medicines, from the regional or national context (e.g. Zhang et al., 2015), or a European (Kools et al., 2008) or global perspective (Sarmah et al., 2006). These studies concluded that information on VPs is available to identify environmental risks, but quantitative knowledge about administered VPs is very limited and in need of urgent attention. Similar conclusions can be derived from the European Medicines Agency guidelines (CVMP/VICH Topic GL38, 2005; European Medicines Agency [EMEA]/Committee for Medicinal Products for Veterinary Use [CVMP], 2008; EMEA, 2016). Besides application rate and frequency, the fraction of administered active substances ending up in the environment also depends on the persistence during manure storage (Lahr et al., 2017). So far, some studies (Schlüsener et al., 2006; Kuchta and Cessna, 2009; Lamshöft et al., 2010; Berendsen et al., 2018) investigated VP dissipation during storage, but often those were focused on specific substances and particular manure type. On the other hand, number of studies provided insight into VP concentrations in different manures, as summarized in the reviews (Wohde et al., 2016a; Ghirardini et al., 2020).

In the Netherlands, animal manure from intensive livestock farming is spread onto arable land and grassland in considerable amounts, on average ca. 200 kg N ha^{-1} and 70 kg P_2O_5 ha^{-1} (amounting to 30 tons slurry ha^{-1}) (CBS(1), 2021). Over 95% of manure is applied as slurry and in the case of calves and pigs manure more than 70% is applied onto agricultural land untreated (CBS(2), 2021). How much and which VPs are applied to land with the slurries depends on the origin of slurry. Even though the antibiotic use in livestock farming in the Netherlands has been reduced by more than 60% over the last decade (Veldman et al., 2020), used quantities are still significant, especially in veal farming and to a lesser extent in the pig sector (SDa, 2020). Besides antibiotics, antiparasitics and hormones are used, and end up in manure (Lahr et al., 2014; Lahr et al., 2018). The relation between VP residues measured in manure with the active substance administration rates to animals in the Netherlands is still hardly known, as only few studies (Montforts, 2006; Lahr and Van den Berg, 2009; Hoeksma et al., 2020; Wöhler et al., 2020) have elaborated this, and only for a limited number of compounds and animal types.

In this paper, we investigated the chain of processes that lead to VP concentrations in soil-applied slurry manure for a selection of VPs that were considered of potential concern and focusing on Dutch conditions. In addition, we aimed to develop a tool suitable for fast screening and prioritization of compounds, and our approach therefore did not focus on detailed modelling and sensitivity analyses. Underlying research questions were: (i) what was the use of VPs for the four most relevant livestock groups? (ii) how could we quantify the VP concentration in slurry based on substance property information, excretion rates (unmetabolized VP portion) and storage information? (iii) were predicted VP concentrations in agreement with measurements in the literature? (iv) how to translate insights of (i) and (ii) towards an indicator on the VP residue potential for stakeholders such as policy makers?

2. Methodology

We estimated the portion of used VPs which actually ends up in the slurry manure, both before and after the storage. For this purpose, we investigated the chain of processes in four different livestock groups: dairy cows, veal calves, fattening pigs and sows. Fig. 1 schematically shows the various steps. Also, we focused on the behavior of 12 antibiotics, four antiparasitics and one hormone. We targeted VPs for this study based on three aspects. First, from reports (SDa, 2020; Veldman et al., 2020) that specify use of veterinary antibiotics in the Netherlands, the most commonly administered pharmacotherapeutic groups were selected. We identified tetracyclines, macrolides, trimethoprim/sulfonamides and penicillin groups as the most commonly administered in the veal calf sector. For dairy cows, the same groups were found to be dominant, where penicillin prevailed. For pigs (sows and fattening pigs), the same groups as in the veal calf sector, and additionally quinolones, were identified. In a second step, we screened recent Dutch studies (Lahr et al., 2014; Lahr et al., 2018; Lahr et al., 2019) with VP measured concentrations in slurry manure during or after storage to identify VPs that were persistent enough to reach soil when slurry manure is applied. Based on those inventories and taking into account the availability of VP environmental properties data from the literature, individual substances were prioritized (12) as described in Supplementary Material (SM, Section SM1). In addition to the antibiotics, six antiparasitics reported in Dutch slurry were selected, as well as one hormone (i.e. a hormone which is not naturally occurring). From these 19 VPs, a final selection was based on availability of use data, and two antiparasitics were disregarded as too few data were available. For this purpose, raw use data of VPs, for the period 2015–2018, were obtained from Dutch Farm Accountancy Data Network (FADN) and processed. The selected VPs are shown in the Table 1, and further details are given in SM (Section SM1).

Excretion rates, manure production, storage duration and dissipation parameters were estimated based on literature. Manure storage duration and frequency of manure additions affect VP concentrations in storage

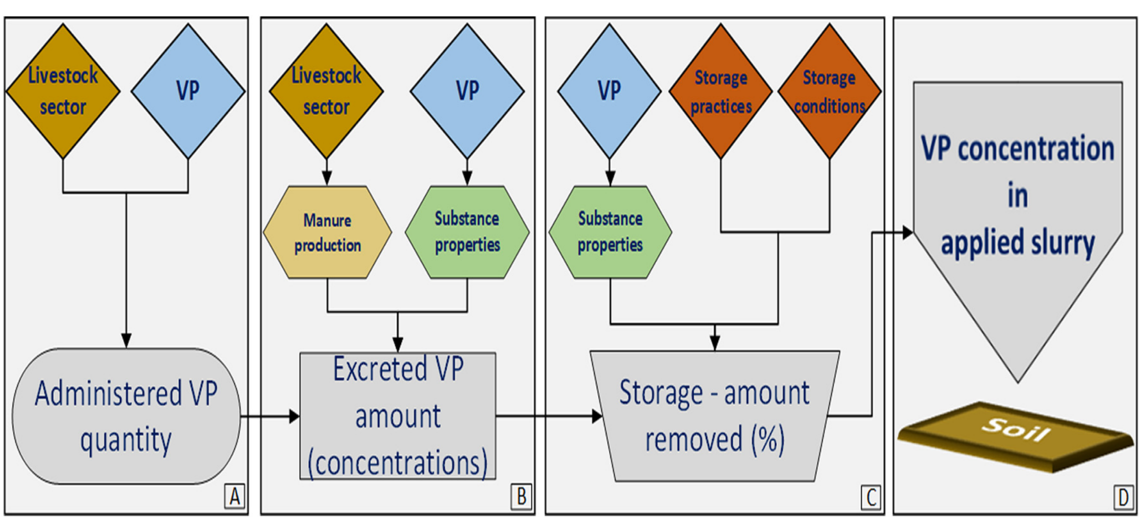

Fig. 1. Schematic representation of the process steps. (A) The administered VP amount depends upon the animal type and particular VP. (B) Portion of active substance which is excreted from animals into slurry depends on step A, quantity of produced slurry manure and VP excretion rates. (C) After excretion, VPs end up in the storage for slurry manure, where dissipation of VPs might occur. This process is influenced by storage practices, storage time, conditions and VP dissipation rates. (D) VP residues, present in the slurry after the storage period, have the potential to reach the soil when slurry is being spread on a land.

Table 1
Selected substances and their pharmacotherapeutic group, excretion rates and livestock sector.

Group	Substance	Abbreviation	Cas no.	Sector of application		Excretion rate[%]	
				Cattle[a]	Pig[b]	Cattle[a]	Pig[b]
Antibiotics							
Tetracyclines	Tetracycline	TC	60-54-8	✓[d]	×	80[g]	×
	Oxytetracycline	OTC	79-57-2	✓	✓	23[h]	60[i]
	Doxycycline	DC	564-25-0	✓	✓	90[j]	90[k]
	Chlortetracycline	CTC	57-62-5	✓	×	75[l]	×
Trimethoprim/Sulfonamides	Trimethoprim	TMP	738-70-5	✓	✓	3[c]	33.5[m]
	Sulfadoxine	SDX	2447-57-6	✓	✓	65[n]	52[c]
	Sulfadiazine	SDZ	68-35-9	✓	✓	80[c]	50[o]
	Sulfamethoxazole	SMX	723-46-6	✓	✓	30[p]	16[q]
Macrolides	Tilmicosine	TIL	108050-54-0	✓	✓	90[r]	80[r]
	Tiamulin	TIA	55297-95-5	×	✓	×	84[s]
	Tylosin	TYL	1401-69-0	✓	✓	30[t]	6[t]
Quinolones	Flumequine	FLQ	42835-25-6	✓[e]	✓[f]	5[c]	5[c]
Antiparasitics							
Avermectines	Ivermectin	IVM	70288-86-7	✓	✓	35[u]	40[v]
Benzimidazoles	Flubendazole	FLU	31430-15-6	×	✓	×	79[w]
	Fenbendazole	FBZ	43210-67-9	✓	×	35[c]	□
Pyrethroid	Permethrin	PERM	52645-53-1	✓	×	80[c]	×
Hormones							
Corticosteroid	Dexamethasone	DEX	50-02-2	✓	✓	60[c]	25[x]

[a] Valid both for dairy cows and veal calves.
[b] Valid both for sows and fattening pigs.
[c] Estimated. Details are given in the SM4.
[d] TC is only administered intrauterine and used for the treatment of afterbirth cows, hence not applicable to veal calves.
[e] Not used for dairy cows, only for veal calves.
[f] Available use data only for sow category.
[g] Feinman and Matheson, 1978.
[h] Arikan et al., 2007.
[i] Mevius et al., 1986.
[j] Shaw and Rubin, 1986.
[k] Fernández et al., 2004.
[l] Elmund et al., 1971.
[m] Zhang et al., 2015.
[n] Nielsen, 1973.
[o] Nielsen et al., 1986.
[p] Nouws et al., 1991a.
[q] Nouws et al., 1991b.
[r] World Health Organization, 1997.
[s] Dreyfuss et al., 1979.
[t] Lewicki, 2006.
[u] Liebig et al., 2010.
[v] Chiu et al., 1990.
[w] Meuldermans et al., 1982.
[x] Post et al., 2003.

and were analyzed based on previous investigation about the effects of application frequency on pesticide transport (Beltman et al., 1996) and by modifying approach developed for describing accumulation processes in soil root zone (Van der Zee et al., 2010). Predicted concentrations of VPs in calves and pigs slurry manure could be validated with data of two Dutch provinces: for Gelderland, modelling was compared with measurements from 2016 and 2017 (Lahr et al., 2018), and for North Brabant with data from 2013 (Lahr et al., 2014). To characterize the impact of VP use and substance properties on VP concentrations in a slurry manure, a VP residue indicator was developed.

2.1. Usage of VPs

In the Netherlands, the federation of the Dutch veterinary pharmaceutical industry (FIDIN) provides annual sales information for all antimicrobial veterinary medicinal products. However, these data do not distinguish between animal species, but only give the total sales for all animals, whereas actual administration can differ from the amounts sold, due to stockpiling and cross-border use (Veldman et al., 2020). On the other hand, MARAN (Veldman et al., 2020) and SDa (2020) reports provide an overview of the used quantity of veterinary antibiotic groups in different livestock sectors on an annual basis. Still, used amounts of individual VPs in the Dutch livestock sector are not publicly disclosed. To improve estimates, we obtained additional information about the annual use of individual VPs at the farm level in the Netherlands, originating from the Dutch FADN system as collected by Wageningen Economic Research. This dataset contained purchase data of antimicrobial VPs, data about antiparasitics and hormones, and was based on 350 to 380 farms, depending on the survey-year and livestock sector. We considered VP quantities purchased at each farm as being used (irrespective of whether they are actually used). The details are given in the SM (Section SM2).

The FADN dataset did not cover the veal calf sector, where administered quantities of most antibiotics are structurally larger than for dairy cows (Veldman et al., 2020). Therefore, we decided to estimate the usage of individual VPs in veal calves by assuming constant ratios in defined daily doses (SDa, 2020; Veldman et al., 2020) between dairy cows and veal calves, for each antibiotic group. Then, for the selected individual antibiotics (Table 1), the (previously calculated) usage data of dairy cows were transposed into usage data for veal calves. The transformation factors (F_c), estimated VP usage, and details are given in the SM (Section SM3).

For antiparasitics and the hormone, such a conversion approach was unfeasible as their use in veal calves was not available. Therefore, for these substances we estimated use in veal calves by combining the FADN dataset with VP prescriptions (Dutch Veterinary Medicines Information Bank, 2021), as detailed in the SM (Section SM3).

2.2. Excretion of VPs

Of VPs administrated to animals, a significant percentage of VPs may be excreted via urine and faeces in its original form (unmetabolized) (Boxall et al., 2004; Kim et al., 2010). Several studies (Sarmah et al., 2006; Masse et al., 2014; Zhang et al., 2015) provided ranges of VP excretion rates that vary per livestock sector and active substance. However, the majority of these studies focused on antibiotics while data about antiparasitics and hormones are scarce. Literature on VP excretion rates to manure (see Tables 1 and S7), was searched, preferably for experimental data, and for individual VPs and animal type. We averaged if several values were reported, and in view of our focus on slurry manure, if rates for faeces and urine were found. When no data were available, an estimation was based on values reported for animal sector in general or structurally similar compounds (see Table 1 and SM4). From the portion of VP excreted and from the yearly production of slurry manure for a single animal (CBS, 2019), we calculated the initial concentration of VPs in the slurry manure, according to

$$C_{in} = \frac{U \times ER}{P \times 100} \tag{1}$$

where C_{in} represents the concentration in slurry manure prior to storage ([mg/ton]), U corresponds to VP yearly administered amount ([mg/animal per year]), ER is excretion rate ([%]) and P is the annual produced slurry manure ([ton/animal per year]).

2.3. Manure storage – dissipation model

Upon excretion, VPs end up in manure storage where they may dissipate by different processes (e.g. degradation/transformation, volatilization), that depend on environmental circumstances and physical-chemical properties of the VPs. Nationally regulated, manure slurry is stored for about 6 months (Lagerwerf et al., 2019; RVO, 2021) in the winter (from September to February). Half-lives (DT50) of antibiotics in stored manure have been experimentally determined for Dutch manure types (Berendsen et al., 2018), and half-lives for 11 antibiotics in slurry manure from this study were used. For the remaining six VPs values were taken from the literature as given in SM5.

Besides DT50 values and storage times, factors such as storage conditions (e.g. temperature) and manure handling may influence the VP concentration (Montforts, 2006). For dissipation kinetics, a first order rate law was assumed (Spaepen et al., 1997; Wang and Yates, 2008; Ray et al., 2017). We modelled dissipation by assuming that slurries are added to the storage basin stepwise. The frequency of manure additions may vary in practice, where continuous addition is one of the limiting cases (of high frequency) and where the unrealistic situation of instantaneous addition of the full yearly quantity is the other limit. The periodic addition of manure to the storage depot imply that dissipation always follows the same 1st order pattern, but the available time for dissipation differs between earlier and later additions. Moreover, each time when new manure is added, dilution of VP already present in the storage occurs. Referring for details of the original derivations to the earlier two papers (Beltman et al., 1996; Van der Zee et al., 2010), the governing modified expressions are

$$C_{f,tb} = \frac{C_{in}(t=0)}{n} \times \frac{\exp(-\mu \times \Delta t) \times \left[1 - (\exp(-\mu \times \Delta t))^{n}\right]}{1 - \exp(-\mu \times \Delta t)} \tag{2}$$

$$C_{f,ta} = \frac{C_{in}(t=0)}{n} \times \frac{1 - \left[\exp(-\mu \times \Delta t)\right]^{n}}{1 - \exp(-\mu \times \Delta t)} \tag{3}$$

where $C_{f,tb}$ and $C_{f,ta}$ represent the final VP concentration in slurry manure at the end of storage period ([mg/ton]), C_{in} ($t = 0$) is the initial concentration ([mg/ton]) prior to storage from Eq. (1), n denotes how many times manure has been added into the storage ([−]) during the entire storage period, μ is the dissipation constant ([day^{-1}]) and equals $\mu = \frac{\ln(2)}{DT50}$, and Δt is the application interval ([day]). The extra term compared with the original equation (Beltman et al., 1996; Van der Zee et al., 2010), accounts for the mentioned dilution effect. Whereas Eq. (2) gives the concentration just before new manure is placed into the storage (t_b), Eq. (3) gives the concentration immediately after new manure is brought into storage (t_a). Accordingly, they represent the minimum and maximum concentrations of the sawtooth concentration pattern in time (Beltman et al., 1996; Van der Zee et al., 2010).

2.4. VP residue indicator

Besides the fraction of VPs ending up in soil-applied slurries, also the national coverage (e.g. the number of farms involved) affect the environmental urgency. Hence, a VP residue indicator (*R*), was developed that informs on the VP residue potential in the Netherlands for dairy cows and pigs. This indicator is confined to these two animal sectors as for veal calves administered VP quantities were unavailable. The indicator is based on the VP excretion rate (ER), concentration change during storage (C_f/C_{in}), but also on the percentage of farms where individual VP was reported administered (F_u). Thus, F_u characterizes how widespread a certain substance was used and therefore its influence on VPs appearance in Dutch soil-applied slurry. The VP residue indicator, *R* ([−]), is given by:

$$R = \frac{ER}{100} \times \frac{C_f(t_a)}{C_{in}} \times \frac{F_u}{100} \tag{4}$$

All three terms in (Eq. (4)) are dimensionless and range from zero to one. R equal to *zero* implies that this VP residue will not be found in the soil-applied slurry, whereas for R equal to *one* on all farms all administered amounts are fully excreted, and also no dissipation in storage occurs.

3. Results and discussion

3.1. Usage and excretion of selected VPs

The number of investigated farms varied each year, and ranged from 230 to 260 for dairy cows, for sows from 50 to 60, and for fattening pigs from 50 to 70. In case of dairy cow farms, the representative sample covered around 1.5% of farms in the Netherlands, whereas for pigs this was around 4% (Lahr et al., 2019). For over 95% of the farms in the dataset, at least one substance of our interest was reported as purchased in that respecting year. Since each farm location was identified at the province level, we could observe that the biggest variety of purchased VPs corresponded with the provinces with the highest farm density: see SM (Section SM2).

The dataset revealed that four out of 17 selected VPs were exclusively used to treat dairy cows, three only in the pig sector (fattening pigs or sows), and 10 VPs were used in all involved livestock sectors. As purchase data for veal calves were unavailable but estimated, we assumed that all VPs applied for dairy cows (except Tetracycline) were also used for veal calves. This claim was for investigated VPs based on the prescription data (Dutch Veterinary Medicines Information Bank, 2021). Selected substances and their main characteristics are given in Table 1.

The VPs purchased on most of the dairy cow farms during the analyzed period were OTC (87%), TMP (86%), SDX (68%) and DEX (61%). In the case of sow farms, these were TMP (80%), OTC (74%) and FLU (64%). For fattening pigs the dominant ones were OTC (62%), TYL (52%) and DC (51%). The complete overview of average F_u-values and standard deviations for the period 2015–2018 is shown in Fig. 2.

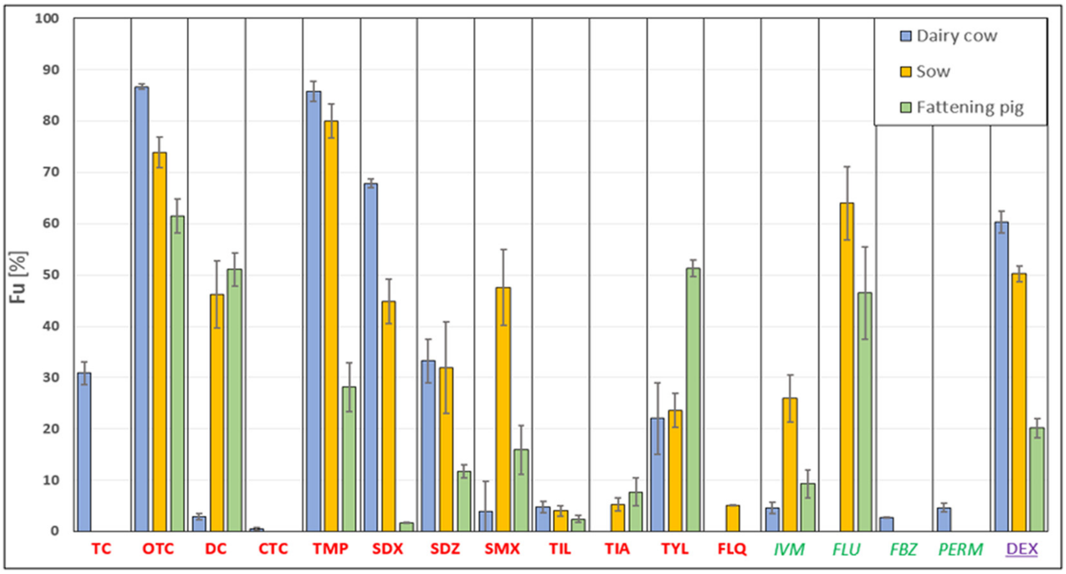

Fig. 2. Part (F_u in %) of analyzed farms on which VP was administered (refers to the percentage of farms on which particular VP is reported as being purchased) for three livestock sectors (airy cow, sow and fattening pig). F_u values are averaged for the period 2015–2018, and error bars denote standard deviations. Antibiotic names are in bold red, antiparasitics are in italic green, and hormone is in underline purple.

As Fig. 2 reveals, the primarily purchased VPs on the dairy cow farms were antibiotics, and antiparasitics only on less than 5%. This is rather different for pigs, where the antibiotics prevailed, but two of the investigated antiparasitics (IVM, FLU) were applied on a substantial number of farms. The hormone (DEX) was administered on more than half of dairy cow and sow farms, and on about 20% of the fattening pig farms. Worth mentioning was the considerable use of TMP, originated from its combined application with the antibiotics from the sulfonamide group. Based on the prescription data (Dutch Veterinary Medicines Information Bank, 2021), the aforesaid mixture contained around 20% of TMP while the rest was reserved for, in this study, SDX, SDZ or SMX. Additional observations about Fig. 2 are given in the SM (Section SM6).

Regarding administered quantities (*U in [mg per animal per year]*), based on average values for the period 2015–2018, in a dairy cow sector the VPs FBZ, CTC and the mixture TMP/SDX were prevalent (Fig. 3). For sows, the main VPs were DC and TMP/SMX (Fig. S2-B), and for the fattening pigs DC and TYL (Fig. S2-C). Fig. 3 gives an overview on the distribution of use data in dairy cow sector for the period 2015–2018 with respect to VPs reported

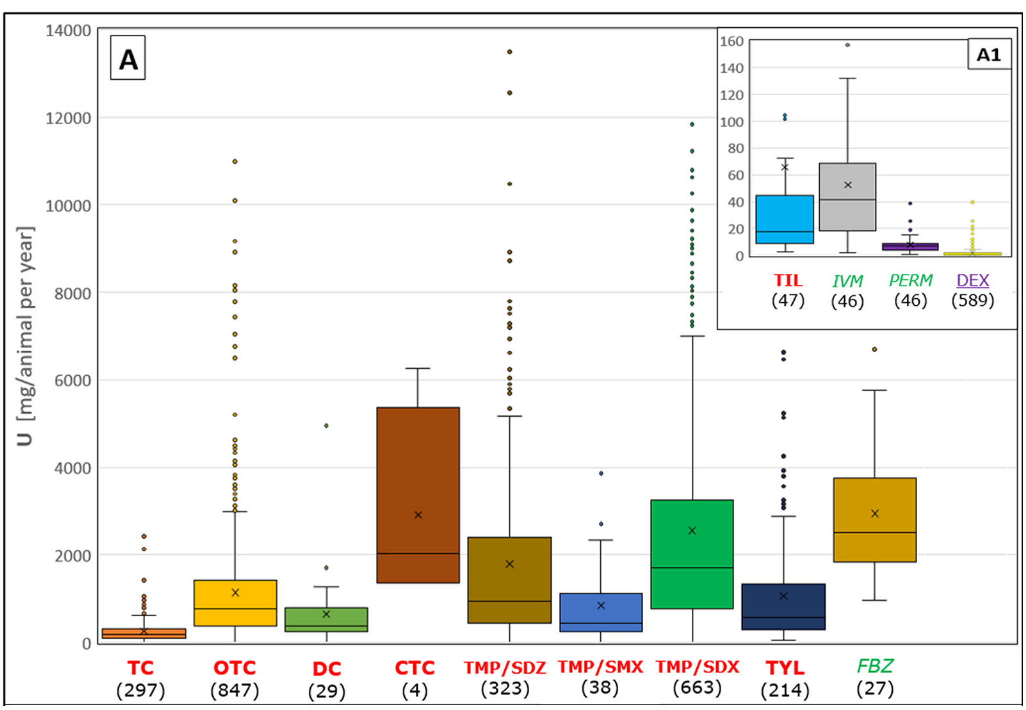

Fig. 3. Distribution of VP use data for the period 2015–2018, illustrated with *Box and Whisker Plot.* Numbers in legend indicate sample size. (A) VP use in dairy cow sector; inset (A1) shows VPs with administered quantities below 160 mg/animal per year. Antibiotic names are in bold red, antiparasitics are in italic green, and hormone is in underline purple. VP use in sow and fattening pig sectors is shown in Fig. S2-B/C, where details about *Box and Whisker Plot* and sample size are also given.

in the Table 1. The situation for the other two sectors is illustrated in the SM (Section SM6).

The administered amounts over the years revealed a clear trend of reduction in use of TMP/SDZ, TYL, and FBZ for dairy cows (Fig. S3-A), DC, TMP/SDZ, and TMP/SDX for sows (Fig. S3-B), and TMP/SDZ for fattening pigs (Fig. S3-C). Administration of VPs OTC, PERM and DEX remained pretty constant in dairy cows (Fig. S3-A/A1), as well as for DEX in fattening pigs (Fig. S3-C1). For other VPs no clear patterns were seen. However, the overall distribution for the entire analyzed period (2015–2018) showed that almost all administered quantities in 2018 were lower than in 2015. For antibiotics this is consistent with the official Dutch reports (SDa, 2020; Veldman et al., 2020). Exceptions and details are indicated in the SM (Section SM7).

Used quantities of antibiotics in the veal calf sector were estimated based on the conversion factors (Table S5) and use data of dairy cows (Fig. 3). Some bias may occur as for example FLQ is not used for dairy cows, while in calves it is used to treat respiratory and digestion tract infections. The use of the mixture TMP/SDX may be lower in veal calves than dairy cows (being preferentially used for lactating animals). Research by Lahr et al. (2019) can be interpreted likewise. Derived usage for veal calves and details are shown in the Table S5.

3.2. VP concentration in the slurry manure

Concentrations of VPs in the slurry, prior to and after the storage, were calculated based on the average annual VP use per animal for the period 2015–2018 (Fig. 3 and S2, and Table S5). For the same period and considering four investigated animal sectors, also the average annual quantities of produced slurry manure in the Netherlands were estimated (CBS, 2019). Fig. 4 provides an overview on the predicted VPs concentrations using the DT50 values in the storage as specified in SM (Section SM5). The concentrations concerned those prior to storage, Cin (mg/ton) and after 6 month of storage, Cf (mg/ton), for dairy cows/veal calves and sows/pigs, respectively.

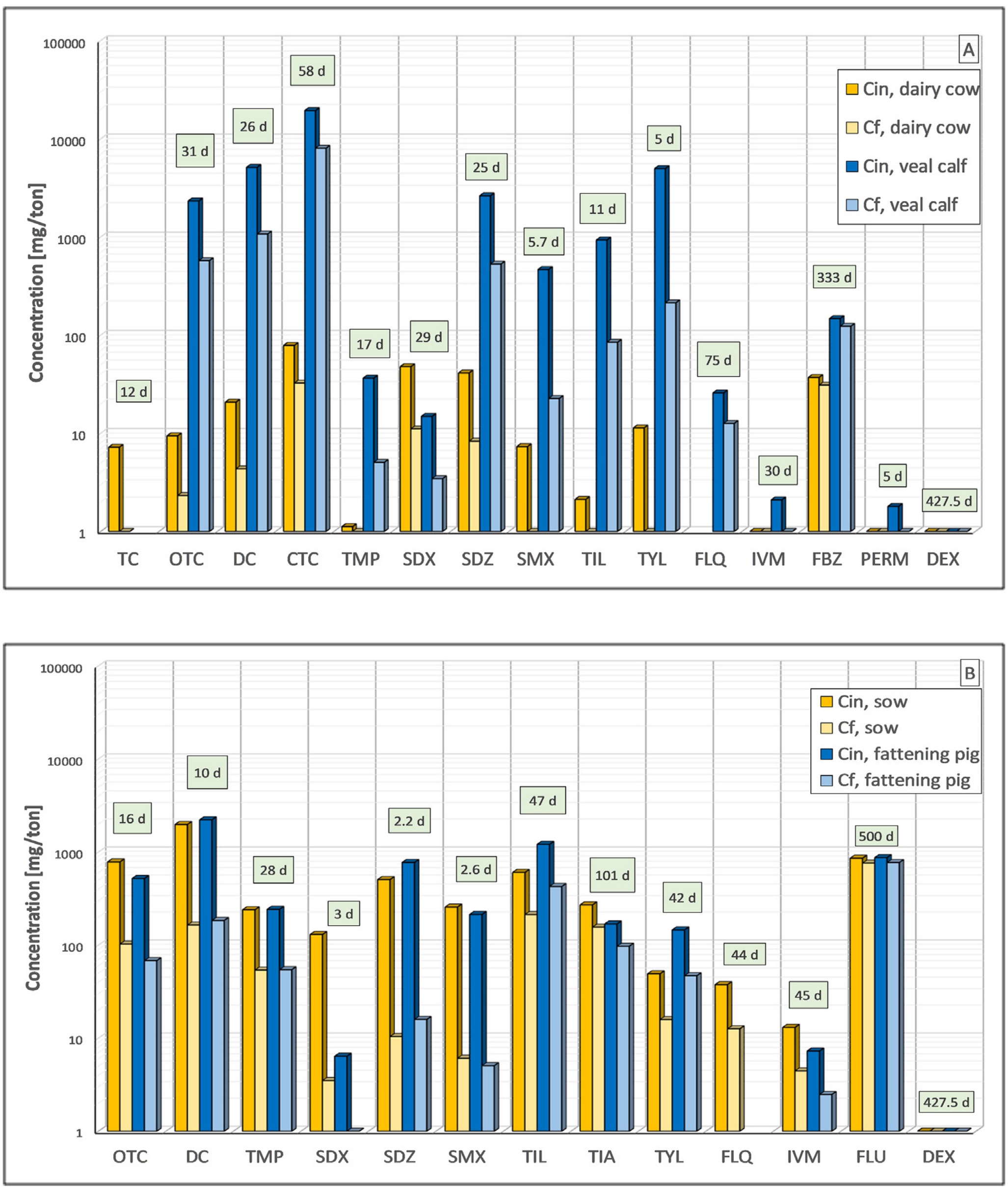

Fig. 4. Concentrations of VPs in slurry manure prior to storage (Cin) and after 6 months of storage (Cf) (log *scale*), including substance half-live in the storage (DT50 in *days*) displayed in the green text box. (A) In cattle sector for 15 different VPs. (B) In pig sector for 13 VPs. Cin is calculated with Eq. (1) and Cf with Eq. (3). Quantities of produced slurry manure (P) were estimated as 28 (dairy cow), 3.5 (veal calf), 4.5 (sow) and 1 (fattening pig) ton/animal per year.

As Fig. 4A divulges, initial concentrations in dairy cow slurry were below 80 mg/ton for all investigated antibiotics, and for the hormone and antiparasitics (except FBZ) smaller than 1 mg/ton. The initial concentrations in veal calf slurry were significantly larger due to higher use (Table S5) and a lower manure production. Concentrations after storage greatly depended on substance DT50, which was assumed to be equal for the two cattle categories and therefore had the same dissipation pattern. During the storage period of six months, FBZ and DEX concentrations reduced less than 20%, and SMX, TIL, TYL and PERM over 90%. For other analyzed VPs, this was between 50% and 85%. In the pig sector (Fig. 4B), reduction between sows and fattening pig slurry was similar, with the exception of SDX, TIL and TYL, where again DT50 was the same for both animal types with respect to individual VP. For pigs, all investigated tetracyclines and sulfonamides concentrations reduced for more than 87%, while FLU and DEX less than 15%. Remaining VPs had concentration reductions between 42% and 78%.

The results indicate that the lowest VP-total mass ends up on the soil if dairy cow slurry coming from storage is applied: 12 out of 14 investigated VPs used in dairy cows had calculated concentrations lower than 10 mg/ton. This finding, and general distribution of VP concentrations within four investigated slurries, seems comparable with studies done in other countries (Zhao et al., 2010; Ghirardini et al., 2020; Li et al., 2021). Some VP groups with predicted high concentrations in the slurries (e.g. tetracyclines), after being applied on the soils are found in the upper soil layers due to their low mobility and sorptive behavior (Gros et al., 2019). The group of sulfonamides, even though extensively used, showed small concentrations when applied in manure slurry to soil. That this group cannot be disregarded is caused by their high mobility in soil, that favors their leaching to groundwater (Aust et al., 2010; Kivits et al., 2018). Furthermore, particular focus should be on the behavior of FLU, as our results indicated its high concentration in pig slurries, and it is known that this VP can be detected at various soil depths (Gros et al., 2019). In general, VP concentrations in soil and groundwater are influenced, among others, by additional adsorption, degradation, and transport processes, which was out of the scope of this study.

To calculate VP concentrations at the end of the storage period, we used Eq. (3) and made an assumption that manure has been added to the storage every day during a six months period ($n = 180, \Delta t = 1d$). The sensitivity of the stored manure concentration to the DT50 is illustrated in Fig. S4 which shows concentration decline during storage for VPs with a DT50 varied from 5 to 333 d. As Fig. S4 reveals, if different VPs enter the storage with the same initial concentrations and at the same moment, by further following identical manure addition patterns (n, Δt), the influence of DT50 on final concentration is considerable, i.e. after six months the ratio of concentrations between a substance with a DT50 of 333d and the one of 5d is almost 22. On the other hand, with periodic applications (Fig. S5), the VP concentration present in the storage at a particular moment ($T_{storage}$) can vary depending on the frequency of manure additions up to that point. Nevertheless, animals produce manure each day and even if that manure is not immediately added to the storage, we can assume that VPs start their dissipation process after being excreted. Thus, the simplification of daily manure additions and de-emphasizing the sawtooth pattern seems reasonable. Note that besides stored slurry, dairy cows excrete manure directly on the land during pasture season excluding dissipation in storage. This pathway represents about 10% of the total produced manure by dairy cows (CBS, 2019), consequently these soil-applied amounts are less significant. As residues of VPs in manure from grazing animals could affect dung fauna (e.g. IVM) (Lahr et al., 2019), further investigation of that pathway may be required.

3.3. Results validation

Berendsen et al. (2015) investigated concentrations found in animal faeces at 20 randomly selected pig and calve farms in the Netherlands in 2014. The faeces were taken from the animal gut from animals selected in the slaughter phase. VPs investigated both in our study and in the mentioned research were OTC, DC, SDX, SDZ and TIL for the cattle sector. In general, quantities found in the calve faeces were considerably lower (except for OTC) than our predicted prior-storage concentrations in slurry manure. In the case of pigs our estimations for OTC, DC and TYL were within the measured range, whereas for SDZ and TIA our predictions were above measured values. Table 2 provides an overview on the predicted and measured VPs concentrations. The differences might be caused by a lower usage of particular VPs in 2014 (not included in our study period) compared to the one from 2015 to 2018, but this is less probable since for the antibiotics we observed a reduction trend in usage over the years. A more plausible explanation is the VP elimination route through urine, which was incorporated in our predicted concentrations via ER, yet not considered in the aforementioned study (Berendsen et al., 2015). In addition, samples in Berendsen et al. (2015) were taken from the slaughterhouse, implying that last VP administration might have been weeks before, and therefore concentrations were expected to be lower than our predicted initial concentrations.

Predicted VP concentrations in slurry manure after storage, for veal calves and pigs, were compared with the measurements done in 2017 in slurry manure in the province of Gelderland (Lahr et al., 2018). We assumed that concentrations in that study resulted from VP use in 2016 and 2017, hence we used average administered quantities of VPs over those years in the Netherlands (Fig. S3), and considered only those found in the slurry at farms which actually reported those VPs as used, as detailed in Lahr et al. (2018). This maximized the chance that measured VP amounts were a consequence of actual usage. The measured and calculated concentrations in slurry are shown in Fig. 5. In another study, Lahr et al. (2014) provided VP quantities found in 2013 in fattening pigs slurries in storage tanks of processing installations in the province of North Brabant, and also shown in Fig. 5. As no VP use data of 2013 were available, these points in Fig. 5 used national use data from 2015 instead of 2013, which made the comparison more an impression. In all cases, we also estimated the

Table 2
Comparison between VP concentrations measured in faeces (Berendsen et al., 2015) and predicted prior to storage VP concentrations in slurry manure.

Calves				Pigs			
VP	Number of farms[a]	Measured range [mg/ton]	Predicted concentration[b] [mg/ton]	VP	Number of farms[a]	Measured range [mg/ton]	Predicted concentration[b,c] [mg/ton]
OTC	17	4–21,000	ca. 2300	OTC	8	4–1500	ca. 750
DC	11	5–177	ca. 5100	DC	9	2–4500[d]	ca. 2000
SDX	1	1–5	ca. 15	SDZ	6	1–216	ca. 500
SDZ	12	1–81	ca. 2600	TYL	6	2–516[e]	ca. 50
TIL	8	1–218	ca. 900	TIA	2	1–4	ca. 250

ca. Circa (= about).
[a] Number of farms measured range is based on.
[b] From Fig. 4.
[c] Assumed concentration in sow slurry.
[d] At one farm the reported maximum was 95,000. We considered this as an outlier.
[e] At one farm the reported maximum was 7700. We considered this as an outlier.

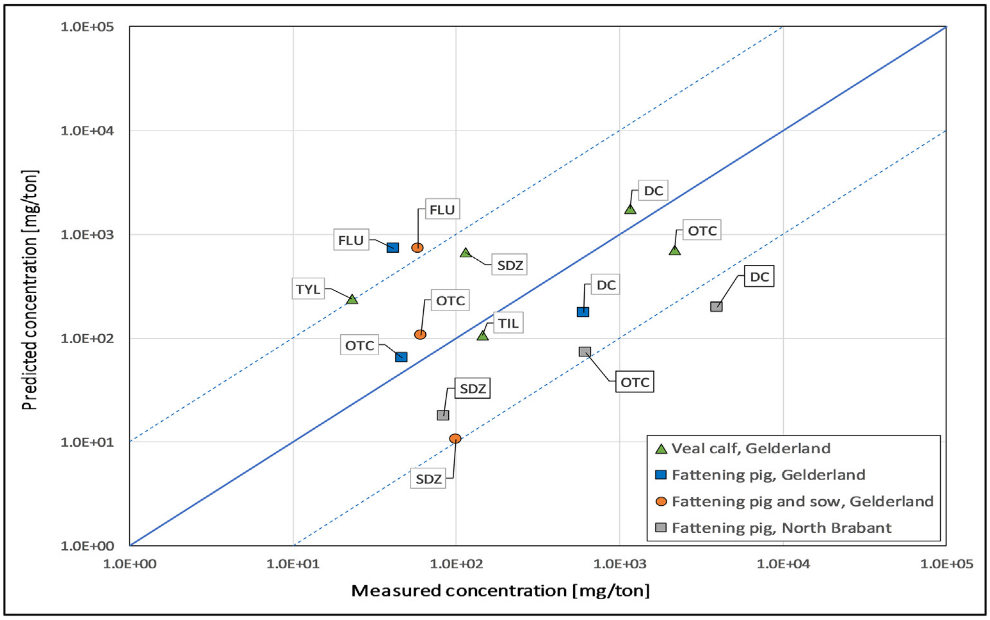

Fig. 5. Predicted and measured (fresh weight) concentrations in slurry manure. The solid line marks the ratio of 1:1, dotted lines differ a factor 10 from 1:1. Four cases* concern: in Gelderland measurements and estimations for 2016/2017, in North Brabant combined measurements for 2013 and estimations for 2015. When the concentration of a particular VP was measured in more than one farm of the same type, an average concentration was taken. **For the case when measurements were done in a combined slurry (fattening pigs and sows), estimates from both sectors were aggregated according to the portion of produced slurry (80% sow, 20% fattening pig).*

quantities of produced slurry manure with respect to animal type and relevant year (CBS, 2019).

From totally 14 combinations of measured and predicted concentrations, 11 were within the 10-fold deviation from the ideal ratio of 1:1. Outside this range were only FLU (Gelderland) and DC (North Brabant). For FLU, our predicted concentration was around 15 times larger than measured, both for fattening pigs and the combined case. This could possibly be explained by the fact that DT50 of FLU was roughly estimated, as detailed in SM5. For DC, the predicted concentration at North Brabant was around 20 times lower than the measured one, even though the agreement for fattening pigs in Gelderland was good. We attribute this to our approximation of use in North Brabant. In view of the trends mentioned before, the use of DC in 2013 was likely higher than in 2015, which was possibly amplified at particular farms from where the slurry originated. As also for other two VPs in North Brabant our predictions were lower than measured quantities, this reasoning seems plausible. As two cases (TYL-veal calf, SDZ-fattening pig and sow) were based on single measurements, their reliability is in need of improvement.

As Fig. 5 reveals, our estimates of VP usage in the veal calf sector resulted in predicted VP concentrations in the after-storage slurry that corresponded fairly well to measurements. In general, our predictions for hormone and antiparasitics (except FBZ) suggested that concentrations in the veal calf slurries after the storage were below the detection limits (Lahr et al., 2018), which for IVM was shown to be not always the case (Wohde et al., 2016b; Lahr et al., 2019). The possibly underestimated IVM administered to veal calves and its toxicity for manure organisms (Liebig et al., 2010), warrants closer examination.

Besides considering national VP usage, for veal calves in Gelderland (2016/2017) we also calculated after-storage concentrations with use data aggregated from the dairy cow farms located only in the Gelderland province. Despite the accuracy lost by regional aggregation, this gave a good (TYL, SDZ, OTC) or reasonable (DC) agreement with the national analysis (Fig. S6).

3.4. Residue indicator

We calculated R (Eq. (4)) for all VPs for dairy cows, sows and fattening pigs (Table S9). Based on R, and with respect to predicted after-storage concentrations (Fig. 4), we performed a ranking in all three livestock categories, as shown in Table 3.

VPs with highest potential (highest R) of being present in the after-storage slurries at dairy cow farms in the Netherlands were DEX, SDX, SDZ and OTC. However, since their predicted concentrations in these slurries were very low to low (Fig. 4A), these VPs might have escaped measurement in view of detection limits (Lahr et al., 2018). On the other hand,

Table 3
VP ranking based on residue indicator (R indicated in parentheses), with respect to predicted after-storage concentration for the period 2015–2018.

Predicted concentration [mg/ton] - classes	Dairy cow	Sow	Fattening pig
High (>100)	/	1. FLU (0.448)	1. FLU (0.325)
	/	2. OTC (0.058)	2. DC (0.038)
	/	3. DC (0.035)	3. TIL (0.007)
Medium (>10–100)	1. FBZ (0.008)	1. TMP (0.06)	1. OTC (0.048)
	2. CTC (0.002)	2. TYL (0.005)	2. TIA (0.037)
	/	3. SDZ (0.003)	3. TMP (0.021)
Low (>1–10)	1. SDX (0.102)	1. IVM (0.035)	1. IVM (0.013)
	2. SDZ (0.054)	2. SDX (0.006)	2. SMX (0.001)
	3. OTC (0.049)	3. SMX (0.002)	/
Very low (≤1)	1. DEX (0.314)	1. DEX (0.109)	1. DEX (0.044)
	2. TC (0.024)	/	2. SDX (0.0002)
	3. TIL (0.004)	/	/

ranking VPs based on R for sow farms indicated that FLU, DEX, OTC, TMP, DC and IVM were most probable to occur in slurry. For fattening pig slurry, the most probable to occur were FLU, OTC, DEX and DC. To arrive at F_u (to calculate R) for the veal calf sector, we used observations by Lahr et al. (2018). That study revealed that four out of five investigated veal calf farms reported administration of OTC, DC and TIL and three out of five reported SDZ and IVM. This small sample resulted in F_u of 80% for OTC, DC and TIL, and 60% for SDZ and IVM, and we obtained R-values of 0.15 (DC), 0.1 (SDZ), 0.07 (TIL), 0.05 (OTC) and 0.05 (IVM). In addition, for those VPs (except IVM) our predicted concentrations in the after-storage veal calf slurry were in the range medium to high (Fig. 4A).

In summary, based on the residue indicators, we predicted that OTC was the most frequently soil-applied VP in the Netherlands, as it came out as prioritized in all investigated slurries, followed by DEX, DC, SDZ, FLU and IVM. These findings are coherent with the reported frequencies of detection in the earlier Dutch studies which targeted VPs in the slurry manure (Lahr et al., 2019), except for DEX, that was not considered in those earlier studies. According to our predictions, DEX seems to have a high potential to be widely present in all investigated slurries (Table 3), although used DT50 and ER are subject to uncertainty (Table S7). In addition, for antibiotics our results seem comparable with studies done in other countries, as summarized by Wohde et al. (2016a) and Ghirardini et al. (2020), which also highlighted OTC, DC and SDZ as one of the most frequently detected VPs. Those studies indicated wide occurrence of CTC, whereas this was not expected in the Netherlands as only few farms reported administration of this VP.

Note that R is only indicating the potential risk with respect to produced manure. For the actual risk the spatial distribution of the applied manure should be also taken into account. This depends on the manure produced on farms, the available area of agricultural land, the manure transport from farm to farm, manure processing and export, and the admissible nitrogen and phosphorus applications rates being regulated by the EU Nitrates Directive. This aspect will be addressed in a next paper.

3.5. Uncertainties

For the steps in Fig. 1, some assumptions have been made. To calculate VP concentration changes during storage, we disregarded if storage conditions as temperature varied from place to place. Implicitly, this variation may have been accounted for, as literature data on storage dissipation mostly concerned different Dutch manure types. For some VPs (e.g. DEX), such an implicit correction was not done. To obtain Fig. 4, we used average yearly administered VP quantities despite that slurries at individual farms may deviate from those average values. Similar reasoning could also apply to the VP measured quantities, as they are known to deviate per farm (Lahr et al., 2014, 2018).

Based on the estimated concentrations in manure, the conversion between administered VP quantities in dairy cows to veal calves using factors given in Table S5 performed quite well. For at least one antibiotic from each group, predicted concentrations compared to measurements with a deviation<10-fold. In cases, where this conversion would not work, that was clearly mentioned (e.g. SDX and FLQ). However, our conversion of use data for the hormone and antiparasitics could not be validated, and there were indications that for the latter we underestimated the usage in the veal calf sector (e.g. IVM). Most reasonable explanation is that some of the medicines containing antiparasitic drugs are not recommended for use in animals producing milk for human consumption. Therefore, the assumption that veal calves receive the same number of doses annually as dairy cows is probably not valid for all antiparasitics and an individual approach is required. To completely explore this issue, an insight into the dairy cow farms that reported those VPs as used is necessary, but also a deeper investigation on prescription data and withdrawal periods (in milk and meat). All of that was out of the scope in this paper.

Another important hypothesis related to the assumed VP excretion rates. In general very little is known about these parameters and their variations between animal types. Knowledge about VP excretion in specific animal (e.g. veal calf) is mostly based on the studies done more than 20 years ago, hence a lot of VPs are not even considered. Frequently, focus is either on excretion through urine, or faeces, whereas data related to both fractions are extremely limited. In addition, we focused only on the excretion of unmetabolized portion of VPs, whereas in reality some metabolites may be of greater interest (e.g. when metabolite is more toxic than the parent compound).

4. Conclusion

Given the uncertainty associated with the input data, which also differed between livestock sectors, our modelling approach showed estimated VPs emissions in manure and prioritization in VPs, which were in reasonable agreement with monitoring results of VPs. For dairy cow, sow and fattening pig sector, VP usage was investigated at the national scale, while using national datasets on farmer uses. For veal calves VP usage was approximated based on the administered VP quantities in dairy cows. Based on more than 40 different literature sources, we observed that available data on VP excretion and dissipation in manure show a large spreading, if available at all. This lack of accurate information is an important source of uncertainty in predicting VP emission to soil. Our results also showed that emissions of VPs to the environment varied per livestock sector due to differences in VP usage and excretion, and manure production. This aspect might be very relevant for identifying regions of potential risk and for spatial prioritization. Our modelling results showed further that the most commonly administered VPs are frequently not the ones ending up on the soil in high concentrations. Also, a VP residue indicator was developed to prioritize the potential for VP residues in soil-applied slurry manure at a national level. This indicator is based on VP excretion potential, VP behavior in the storage and number of farms where VP is reported as administered. Since influence of VP quantities administered to animals is indirectly excluded, this indicator requires less information and could be used as a first tier assessment to identify if compounds could pose a risk to the environment. This is especially convenient as there are nearly 350 active substances used as VPs (data from 2017) in the Netherlands, whereas only a small portion of them is studied in detail.

Disclaimer

The used data originate from the Dutch FADN system as collected by Wageningen Economic Research. The Centre of Economic Information (CEI) has provided access to these data. Results shown are and remain entirely the responsibility of the authors; neither do they represent Wageningen Economic Research / CEI views nor constitute official statistics.

CRediT authorship contribution statement

Nikola Rakonjac: Conceptualization, Methodology, Visualization, Writing – original draft. **Sjoerd van der Zee**: Conceptualization, Methodology, Writing - review & editing. **Louise Wipfler**: Methodology, Writing - review & editing. **Erwin Roex**: Methodology, Writing - review & editing. **Hans Kros**: Resources, 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

Contains additional details about substance selection, use data(set), excretion rates, storage modelling/dissipation, results validation and residue indicator. Supplementary data to this article can be found online at doi:10.1016/j.scitotenv.2022.152938.

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