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DISCUSSION

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Critical discussion of the current environmental risk assessment (ERA) of veterinary medicinal products (VMPs) in the European Union, considering changes in animal husbandry

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Abstract

Background: Veterinary medicinal products (VMPs) administered to livestock might affect the environment. Therefore, an environmental risk assessment (ERA) is conducted during the approval process of VMPs. In the European Union (EU), the ERA, which was established approximately 10 years ago, consists of two phases. In the present review, we examined the first phase. In this phase, VMPs are subjected to a decision-making process comprising 19 questions and several tables with default values published in the "Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (European Medicines Agency 2016)."

Since a proportion of livestock husbandry systems is currently shifting toward ecological husbandry and free-range production systems, there is a lower risk of VMP consumption in general, but livestock excretions possibly containing VMPs might be directly released into the environment instead of being stored and applied as manure. In the present study, the first phase of the current ERA of VMPs in the EU was critically discussed with respect to the changes in animal husbandry. The large number of default values used in the ERA were checked for topicality. In a three-step approach, firstly trends and changes in animal husbandry in Europe that might be relevant for the ERA were collected, secondly, the interactions between Phase I and animal husbandry were evaluated and thirdly, the default values used in Phase I were verified in order to identify research gaps.

Results: Several default values used in the current ERA were identified as outdated. Together with the lack of valid data (e.g., on animal husbandry systems or VMP treatments), this may have an impact on the predicted environmental concentration (PEC) as the central decision threshold of the ERA.

Conclusions: The results of the present study indicate that an update of the ERA of VMPs in the EU is required to consider the changes in animal husbandry. Several aspects related to this issue are critically discussed.

Keywords: Environmental risk assessment (ERA), Predicted environmental concentration (PEC), Animal production, Veterinary medicinal product (VMP), Environmental impact assessment (EIA)

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Background

The release of active substances or metabolites from veterinary medicinal products (VMPs) getting into the environment can impact the health of humans, animals, and other non-target organisms. Since most environmentally toxic VMPs are excreted predominantly unchanged, such as sulfonamides, tetracyclines, and avermectines [1, 2], excretions are the main path of their entry into the environment.

The most harmful veterinary drugs that enter the environment include antibiotics, antiparasitics, and hormonally active substances [3]. Only the use of antibiotics has been decreasing in Germany since the revision of the German Medicinal Products Act in 2014 (prescribed quantities 1706 t in 2011 and 670 t in 2019) and might be reduced further in the future [4]. However, a minimal level of necessary VMP treatments will likely persist to safeguard animal welfare Thus, the assessment of VMP entry pathways into the environment is necessary. Some of these VMPs are hardly degradable and accumulate in the environment, hence promoting the development of resistances or affecting non-target organisms [5, 6]. The environmental impact of VMPs ranges from immediate toxicity for environmental organisms to long-term consequences such as altering populations or restricting growth, as shown in laboratory experiments [7–11]. Additionally, the combined effects of several substances and multiple exposures from different sources may also be essential [12]. Organic fertilizers obtained from farms rearing or to a lesser extent fattening poultry or pigs can be highly contaminated [13, 14]. Tetracyclines and sulfonamides have previously been detected in high amounts (mg active substance per kg sample) in pig manure as well in soil fertilized with pig manure [15–17].

The residues of veterinary drugs are incorporated into the soil to different extents, depending on their degradation behavior and their ability to adsorb to organic and inorganic matter [18]. Higher half-lives of VMPs are always associated with higher residue concentrations. A higher adsorption tendency results in higher residues in the top soil layer. Because VMPs stay at the surface and fail to seep quickly into the deeper soil layers, those present in the top layer might enter into the surface water via runoff. Lower adsorption affinity, conversely, promotes entrance into the groundwater. Furthermore, VMPs can have negative ecotoxicological consequences for terrestrial and aquatic organisms [4].

The exposure analysis of substances plays a significant role in the environmental risk assessment (ERA) of veterinary drugs, as it is pivotal for the calculation of the theoretically expected concentrations of substances in the environment (predicted environmental concentration, PEC). The ERA of VMPs is based on their PEC in soil (PEC_{soil}), surface water ($PEC_{surface\ water}$) and ground water ($PEC_{ground\ water}$) [19]. Based on the ERA, if there are no risks identified the VMP is approvable. If there are risks identified, the applicant has to propose risk mitigation measures (RMM). If the RMM are not enough to eliminate the risks, then the environmental risks (together with other risks) will be weighed against the benefits of the VMP. If the benefits outweigh the risks, the VMP is still authorized. VMPs containing two or more active substances (fixed combination products) also undergo an evaluation process [20].

The calculation models and input values currently used by the European Medicine Agency (EMA) for the ERA of VMPs are more than 10 years old [21]. The current ERA does not allow adjustments for recent structural changes in animal husbandry and agriculture, such as the significant elevation of free-range husbandry due to increased ecological production and animal welfare standards. An increase in free-range husbandry may lead to lower VMP consumption in general, but in case of application of VMPs are more likely administered on pasture instead of in a stable. Therefore, more punctual contaminations are expected on pasture. Consequently, residues of VMPs are released into the environment in a more uncontrolled and direct manner compared with animals kept exclusively in the stable.

This study aimed to critically discuss the first part (Phase I) of the ERA of VMPs from the animal husbandry perspective. A three-step approach was used: (1) collection of trends and changes in animal husbandry in Europe that might be relevant for the ERA; (2) evaluation of interactions between Phase I of the ERA and animal husbandry and (3) verification of the default values used in Phase I and identification of research gaps.

Principles of the ERA for VMP market approval

Figure 1 shows the ERA for VMP market approval focusing only on the ERA of VMPs used in terrestrial species. The decision process is organized in a two-step approach, whereby each potential VMP undergoes Phase I first. Only if the decisions based on questions 1–19 of Phase I lead to Phase II, the potential VMP will need to be tested in more detail. The calculations reflect the models for the exposure scenarios and different default values for, e.g., each animal species. The default values are mostly shown in Tables 1, 2, 3, 4, 5, 6 of the environmental impact assessment (EIA) guideline for VMPs, in support of the Veterinary International Conference on Harmonization (VICH) guidelines GL6 and GL38 (VMP guideline) [22]. Additional file 1: Tables S1–S6 summarize all calculations and original tables that might be necessary for understanding the results of this discussion.

Categorization of livestock in the ERA

The categorization of livestock plays an essential role in the market authorization of a VMP [23].

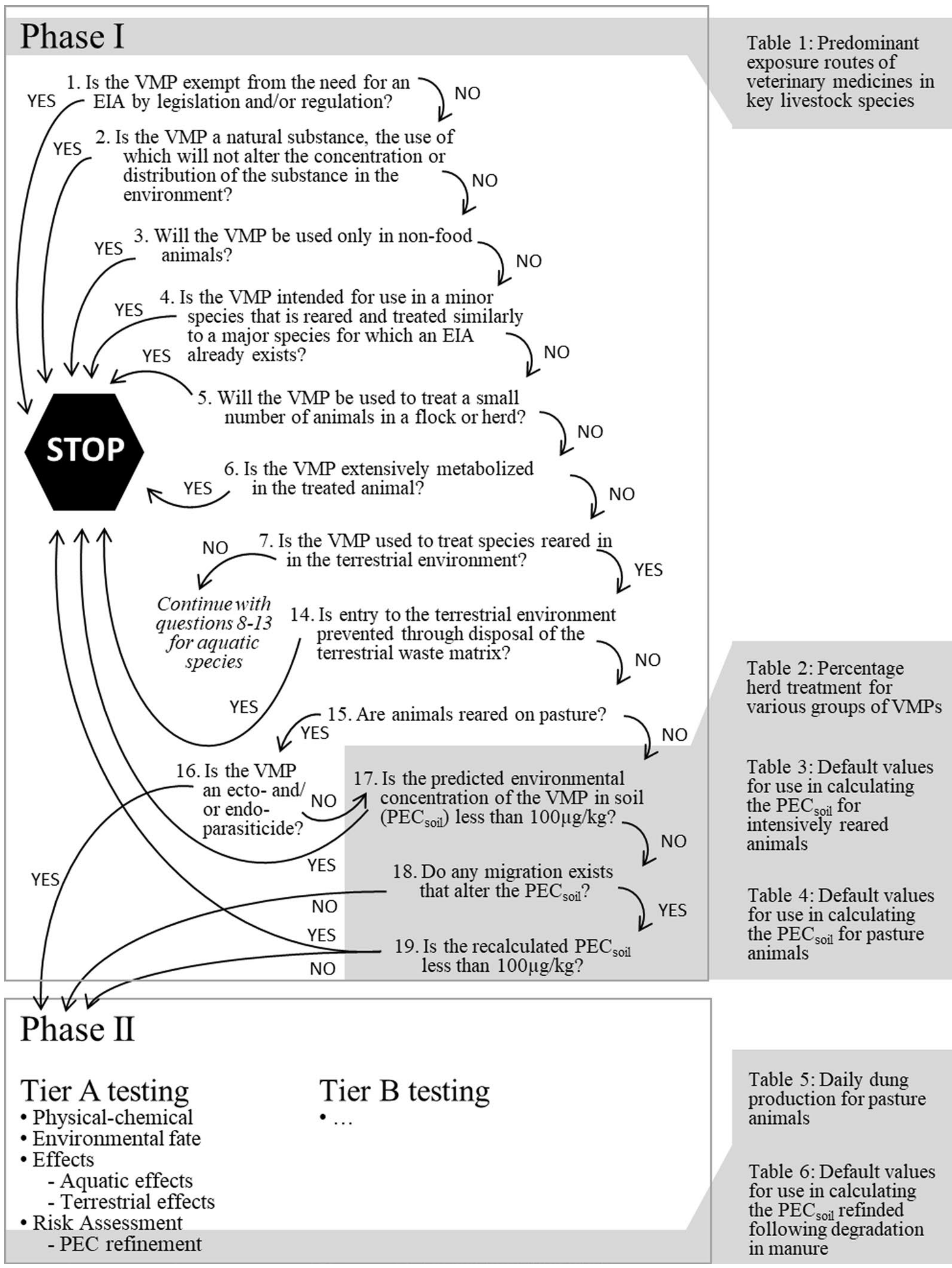

Fig. 1 Overview of the decision tree for VMP market approval according to the EMA [22] and the associated tables, which were examined to verify actuality from the perspective of animal husbandry

Because diseases and treatments appear to vary with animal age and the husbandry system [24, 25], categorization is an essential factor for risk assessment. Presently, according to VMP guidelines [22], categorization is based on age (young vs. adult) and production purpose (breeding vs. fattening). Several overlaps or gaps were encountered which could be resolved by adapting the categories appropriately. All animal types in relation to their total number in Germany and their body weights in livestock units (one livestock unit = 500 kg live weight) were analyzed as part of this study (Fig. 2). Animal types were considered independent of their categorization

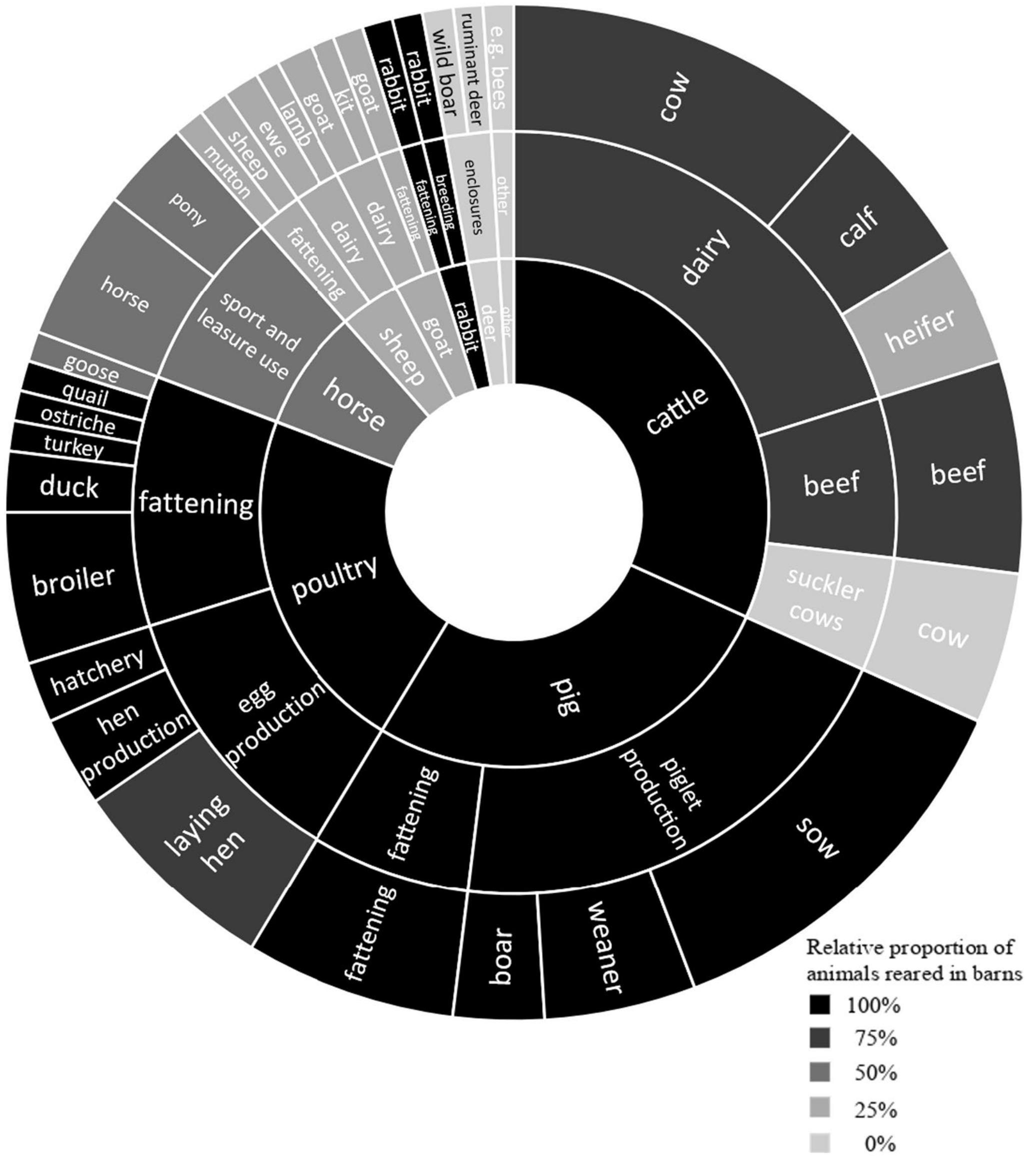

Fig. 2 Systematic categorization of animal types, with the slice size illustrating the number of animals in livestock production units based on statistical numbers in Germany. Circles represent different levels: animal species (the inner circle), production branch (the middle circle), and animal type (the outer circle). Colors indicate the proportion of animals exclusively kept in stables (black, 100%) or on pasture (light grey, 0% in stable). Data were obtained from the Statistical Office of the EU (Eurostat) [61–70], Federal Statistical Office of Germany [34, 49, 54], Federal Office for Agriculture and Food [33, 55], Federal Ministry of Food and Agriculture [56, 57], and personal communication with E. Zumnorde-Mertens at the German Equestrian Federation (FN) and with T. Roettger at the Damwild Farming Mitte-West e.V. via telephone

to major or minor species (Fig. 1, Phase I, question 4) [22]. The extensive analysis of 52 German and EU regulations (Additional file 1: Table S7) as part of this study revealed that several production animals are inconsistently categorized. An example of overlapping categories is "calves". Although "calves" are defined as cattle up to the age of 6 months, this category partly includes the category "cattle aged zero to one year" [22]. To resolve this overlap, "calves" could be defined as all newborn and young bovine up to the age of 6 months and be therefore clearly separated from the category "cattle aged six months and older". The category calves also includes veal and suckler calves, as defined in national regulations [26]. Beef cattle in the age group of 6 months and above could be summed up in one category. It would make sense to clarify the assignment of heifers, suckler cows, and calves

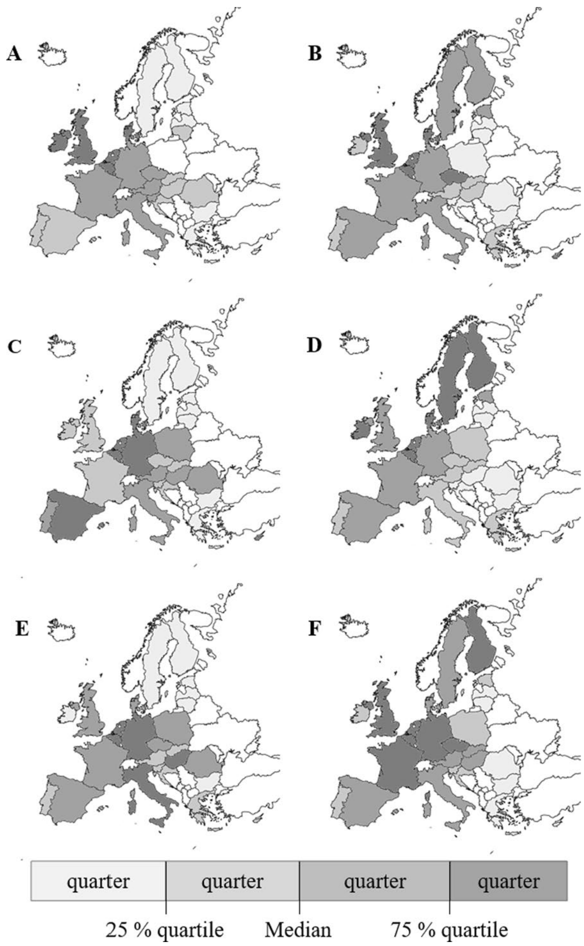

Fig. 3 Farm animal density (**A**, **C, E**) and average herd size (**B**, **D**, **F**) in Europe. Densities of cattle (**A**), pigs (**C**), and poultry (**E**) calculated by dividing the number of each animal species in each country by the geographical area of the respective country (km^2). All 28 EU states (including Great Britain) were considered. Average herd size of cattle (**B**), pigs (**D**), and poultry (**F**) calculated by dividing the number of each animal species in each country by the number of farms in the respective country [31, 61–71]

from suckler cow husbandry to the categorization of beef cattle and delete the term "beef", because all these animals will not get intramammary treatments or be dried off with a VMP, for example. Among dairy animal types, the category "mother including pup" does not match the current husbandry systems because of the separation of the pup from its mother immediately after birth; therefore, a new category "pups from birth onward" would be appropriate. Consequently, all pup categories should start at weaning.

Changes in animal husbandry and relevance for the ERA

Figure 2 also shows the proportion of animals reared on pasture, which is addressed in Phase I assessment in question 15 of the VMP guideline (Fig. 1).

Cattle

The animal type "dairy cow", as listed in original Tables 3, 4, 5, 6 of the VMP guideline, should clearly include or exclude heifer and suckler cows, whereby the category "calves" includes calves for dairy replacement as well as for veal or beef production. Calves raised in suckler cow production systems are currently neglected, but they represent a considerable proportion of the whole calf production. Suckler cow production systems are mainly established on pasture. The category "other cows" represent mainly suckler cows or rare breeds, which are all predominantly kept on pasture. In Germany approximately 650,000 cows belong to that category, representing up to 14% of all cows in comparison to more than 4 million dairy cows in Germany [61]. The proportion of suckler cows with 14% is too high to neglect their husbandry system.

Heifers are also partly raised on pasture. The housing factor is 1 for animals housed throughout the year in the stable and 0.5 for animals housed indoors for only 6 months and on pasture for the rest of the year. It fails to mirror some current husbandry systems including those with permanent access to stable and pasture, and daily access to pasture for a few hours. Thus, we suggest that an additional factor (pasture-to-stable ratio; Table 3) should be considered, which reflects the exposure routes shared between manure and direct entries on the pasture.

Pigs

Pig production occurs mainly in enclosed stables and almost never on pasture [21], and given the risk of African swine fever infection, this practice will likely continue in the future. Boars are increasingly used for fattening because of the obligation for pain relief during castration in Germany and in other European countries [27, 28]. Boars differ from other fattening pigs in N retention and excretion, which results from of differences in their growth and feed conversion [29, 30]. Thus, either boars should be categorized as an additional animal type, besides females and barrows, or the default values for "nitrogen produced per place and year" should be changed to a slightly higher value (1 kg N $year^{-1}$) for all fattening pigs. The differentiation between breeding systems of boars and sows could be skipped, as breeding facilities keep only a small number of boars, and the

Table 1 Predominant exposure routes of veterinary medicines in terrestrial key livestock species

Species	Slurry application			Grazing animals			Loss at application/exposure outdoors			Direct entry into water[a]		
	VMP[b]	IM[c]	A[d]	VMP[b]	IM[c]	A[d]	VMP[b]	IM[c]	A[d]	VMP[b]	IM[c]	A[d]
Cattle	x	x	x	x	x	x	x		x	x	x	x
Pigs	x	x	x								x	
Horses and ponies	x	x	x	x	x	x					x	x
Sheep and goats		x		x	x	x	x	x	x	x	x[e]	x
Poultry	x	x	x			x			x		x	x

Checkmarks illustrate that the exposure route is considered to be relevant in husbandry systems for this species

[a] Direct entry into water can be through direct excretion, loss from the fleece/hide, or direct entry of the veterinary medicine

[b] Original VMP guideline Table 1 [22]

[c] IM: initial model of Montforts [21]

[d] Authors' suggestion for an update

[e] Applicable only to sheep

Table 2 Proportion of herd or flock treatments for various groups of VMPs of the EMA guideline, with suggestions for an update

Product group	Herd treatment (%)	Recommended actions	Reference(s)[a]
Anthelmintics	100	Data collection and update required	[96]
Products for the treatment of diarrhea in calves, lambs, and pigs (excluding products administered in feed and water)	30	–	
Coccidiostats	100	Data collection and update required	[97]
Ectoparasiticides	100	Data collection and update required	[98]
Intramammary preparations:			
For drying-off	100	Change "100%" to "75%" herd treatment; data collection and update required	[99–101]
In lactating animals	25	Data collection and update required	[80–83]
Antibiotics (feed and water medication)	100	Change "feed and water" to "feed or water"; data collection and update required	[102]
Antibiotics injectable:			
All pig treatments	50	Data collection and update required	
respiratory infections in cattle	50	Data collection and update required	
Foot rot in sheep	100	Change "foot rot in sheep" to "footbath"; data collection and update required	[103–105]
		Add: pain medication, the proportion of herd treatment is dependent on the indication (50% for castration or 100% for disbudding in genetic non-hornless herds)	[94, 106]
Teat dip and sprays	100		
All products for poultry	100		
All products for fish	100		

[a] Activities or strategies that lead to suggested change of the level of herd treatment

number of farms harboring numerous boars for breeding purposes is also low. Therefore, the category "breeding boar" could be neglected. Accordingly, the category "sow" could be defined as "breeding pig", which includes sows with suckling litter as well as a few boars for breeding.

Poultry

In the case of poultry, the current categorization can be maintained because it follows the established categorization by species. However, because of the increasing number of laying hens on pasture [31, 32] or in husbandry systems with access to pasture, the exposure routes seems to be mixed between manure production within a stable and direct entries on the pasture as described for cows. Therefore, we recommend using the suggested additional factor pasture-to-stable ratio (Table 3). This accounts for a non-neglectable amount of animals, including animals of free-range husbandry systems with a proportion of 18.4% in Germany and 15.3% in the EU in 2019 [33, 34]. Additionally, ecological husbandry requires access to free-range poultry, which accounts for 11.5% of all laying hens held in Germany and 5.1% of those in the EU [33–35], so the estimated proportion of laying hens housed predominantly free-range consisting of the sum of free-range and ecological husbandry is about 25%. Additionally, other birds such as geese, quails, and ostriches are frequently reared free-range, with access to surface water in some cases. This is not addressed in the current ERA. Overall, we propose that the original VMP guideline Table 1 [22] should be amended with checkmarks.

A more detailed description of these husbandry systems is necessary because the number of free-range husbandry systems is increasing and the separation between indoor and outdoor husbandry systems does not reflect the entry of VMPs into the environment. Furthermore, some husbandry systems for pigs and poultry, designated as “outdoor”, do not provide any route for the direct entry of VMPs into the environment because the outdoor yards are covered with concrete floor. Similarly, the term “intensively reared” is mainly associated with animals kept in stables, but also applies to outdoor systems. In the ERA, differentiation should be made between solid floor and unpaved surface. Currently, the calculation of $PEC_{soil\ initial}$ for animals reared free-range relies only on stocking density (Eq. 2, VMP guideline, [22]). Dung dropping behavior should be researched and considered for free-range husbandry, such as rank patches [36, 37]. It might be worthwhile to distinguish between terrestrial and aquatic birds, to account for access to water. Some species such as ducks are almost completely reared outdoors, with access to water, which suggests that the direct VMP entry into water is possible (original VMP guideline Table 1 [22]).

Horses

The majority of horses (> 90%) are raised for sport and leisure activities so that their owners can avoid the additional effort involved in documentation, which is required for maintaining the food production status of equine species in Germany. The status of being a VMP-treated food-producing or non-food-producing animal (question 3, [22]) seems to be irrelevant for an ERA because companion animals also dump their droppings on pastures or pasture-like surfaces, especially in residential areas [38]. Horses are included in the ERA, although they are almost exclusively categorized as non-food species in Germany. Since substantial amounts of VMPs are also administered to companion animals [39, 40] as well as other non-food species, and to the best of our knowledge, data on the proportion of feces disposed of via residential trash are warranted [41, 42]. A justification for the exclusion of non-food species from the ERA is missing, thus opposing a risk-oriented approach.

Small ruminants

Dairy goats are increasingly being reared intensively in some production systems [43–45], so that they might be added to Tables 3 and 6 of the VMP guideline. Trends for indoor husbandry seen for dairy goats seem to be similar for dairy sheep [46–48]. Besides small ruminants, deer should be added as another category as they are increasingly being used in intensive outdoor husbandry systems. Direct entry of VMPs into water most likely also applies to small ruminants and equine in case of external application [49], but is unclear for systemic treatments since information about defecation behavior in water is missing. To maintain consistency in the wording used in Table 1, we suggest using the plural for goats as for all other animal types. Analogous to the additions to the original VMP guideline Table 3 (intensively reared animals), we suggest adding the categories “boars”, “dairy goats”, and “dairy sheep” to the original VMP guideline Table 6 and to fill the rows with values (table not shown).

Other species

The category “others” in Fig. 2 includes insect species such as bees, black soldier flies or mealworms. On the basis of the current use of insects as (novel) food for humans or feed for livestock, these new production animal species might be intensively reared on specialized farms [50–52]. Because of the completely different pathways and husbandry systems [53], the environmental impact assessment for insects should be developed completely decoupled from that for the existing terrestrial livestock branches and aquatic production systems.

Exposure routes Table 1, which is based on the original VMP guideline Table 1 [22], shows the predominant exposure routes of veterinary medicines in key livestock species and compares the original EMA data with Montforts [21].

The original VMP guideline Table 2 [22] describes the proportion of herd or flock treatment for various groups of VMPs. To differentiate between the route of exposure and the husbandry system, the column headings of the original VMP guideline Table 2 [22] should be revised as shown in Table 1. Considering the route of application, the term “slurry” might be replaced by a more general term that includes all excretions used as organic fertilizer. This includes all kinds of feces with or without bedding material such as poultry litter or solid manure of hoofed and clawed animals since they represent all husbandry systems in which excretions can be collected on concrete (without direct environmental entry), stored, and uniformly applied as organic fertilizer. The term “grazing animals” refers to a husbandry system in which animal feces directly enter the environment without any storage. This occurs regardless of the surface type, predominantly on pasture but especially in free-range poultry and small ruminant husbandry systems, where grass might be lacking [58]. All environmental entries, besides the excretions of animals, are included in the two remaining categories “loss at application/exposure outdoors” and “direct entry into water”.

Data collection

The ERA for market approval should strike a balance between benefit and effort, as described by Montforts [21]. However, a higher number of categories requires the analysis of an equally higher number of scenarios and the preparation of more detailed information. Animal numbers are recorded in different ways in Germany and the EU. Not all animal species are subject to the same reporting requirements within the German federal states. The German federal states report to the Federal Statistical Office destatis, which forwards the data to the statistical office of the European Union called Eurostat. Due to different recording periods as well as minimum recording limits with regard to animal numbers per farm, there may be considerable differences in the data here. Data collection periods and limits should be harmonized as a matter of urgency in order to minimize these discrepancies (Haupt et al., unpublished manuscript).

Animal husbandry: regional differentiation between European countries

Over years the question arose if differences in livestock production systems exist among European countries as it is known from the exposure assessment of plant protection [59, 60] that should be reflected in a future ERA of VMP. Neither animal density nor average herd size showed a consistent pattern that could allow the construction of model regions within the EU. Additionally, within Germany (as an example), regions displayed a high intra-diversity. Overall, a detailed comparison was not possible because of the lack of standardized and systematic data. Thus, data from 2013 were used in this study to estimate the animal density (number of animals per km^2) and average herd size (number of animals per farm) for each country (Fig. 3). Hence, we advise against the differentiation of Europe into territorial areas as in Regulation (EC) No. 1107/2009 [59] when reviewing the VMP exposure scenarios.

Proportion of herd treatment for various VMP groups

Generally, for most groups of VMPs, it is assumed that the entire herd is treated [22]. However, for most VMPs, particularly anthelmintics, individual treatments are preferable [72]. Reducing the use of VMPs such as by applying selective deworming strategies is gaining importance and increasingly being implemented in livestock production systems. Monitoring antibiotic treatments and resistance [73] as well as a more detailed diagnosis before the treatment have increased awareness and decreased the proportion of animals treated with antibiotics [74, 75]. A good scientific practice is to treat each animal individually and abstain from entire (100%) herd treatments. Nonetheless, some oral VMPs are still commonly administered with feedstuff or drinking water to the entire herd or respective flock in some cases [76–78]. The selective administration of VMPs via feed or water, especially in pig and poultry production systems, requires complex and expensive solutions such as switch points in pipe systems to limit VMP application to each compartment [79]. Besides the primary goal of improving animal health, it would be favorable to further reduce the unnecessary application of VMPs by promoting these technical solutions and individual treatments in general. The shift from oral administration to individual application will likely be reflected in VMP groups and the proportion of herd treatment.

In dairy cow husbandry, the commonly used dry-off treatments containing antibiotics are increasingly being questioned and replaced by antibiotic-free products or management strategies [80–84]. For intramammary preparations containing antibiotics, it is currently assumed that the entire herd is treated, but in fact, not the entire herd will be dried off; for example, heifers with no previous lactation, cows who had an abortion during the lactation period, cows who are continuously milked and cows without a dry-off period that will be sold to the slaughter. Assuming a replacement rate of 25–40% [85–87] and as shown in the model of Montforts [21], we suggest reducing the value for herd treatment of intramammary preparations in the original VMP guideline Table 2 [22] to 75%. Even if heifers are excluded

Table 3 List of suggested amendments (black) to the original (gray or crossed out) values in the VMP guideline Table 3 [22], modified with recent data considering the N-reduced feeding strategies

Animal type	Number of animals raised per place per year	Average body weight (kg)	Nitrogen produced per year per place (kg N y^{-1})			Housing factor	Pasture-to-stable ratio
			VMP-GL[a]	Chamber of Agriculture NRW[b]	Authors' suggestion for updated values		
Calf (0–6 months)	2	150	10	22	16	1	< 1
Dairy cow	1	550	60	91	75.5	0.5	< 1
Cattle (> 0.5 y)	1	300	28	70	49	0.5	1
Weaner pig (to 25 kg)	6.9	13.2	2.25	3.8	3.0	1	1
Fattening pig (25–125 kg)	3	65	7.5	12.2	9.9	1	1
Sow (with litter)	1	280	26	27.3	26.7	1	1
Boar (25–125 kg)	1	65	–	22.1[c]	22.1[c]	1	1
Broiler	9	1	0.23	0.39	0.3	1	1
Laying hen	1	1.6	0.35	0.76	0.56	1	< 1
Replacement layer	2.6	0.8	0.24	0.27	0.26	1	1
Broiler breeder	1	1.7	0.69		0.69	1	1
Turkey	2.7	6.5	0.9	1.34	1.12	1	1
Duck	7	1.6	0.41	0.61	0.51	1	< 1
Horse	1	400	35	53.6	44.3	0.5	< 1
Dairy goat	1	40	–	15.2[d]	15.2	1	< 1
Dairy sheep	1	70[e]	–	20.1[f]	20.1	1	< 1
Rabbit	8	1.4	0.352	0.7	0.53	1	1

[a] VMP guideline [22]

[b] Data were obtained from the Chamber of Agriculture of North Rhine-Westphalia [29] unless indicated otherwise

[c] Data were taken from [108–111]

[d] Data were taken from [112]

[e] Data were taken from Liesegang et al. 2007 [113]

[f] Data were obtained from the Chamber of Agriculture of Lower Saxony [114]

from the category "cow", their number most likely mirrors the number of cows for slaughter, where treatment will be avoided to decrease the input cost and withdrawal times. However, intramammary preparations containing antibiotics are not included in the national German antibiotic monitoring. They are either used for treatment of mastitis or drying-off, whereby following good practice antibiotics should only be used to treat an actual infection. The unacceptable connivances of antibiotic applications are enhanced by monetary factors, as antibiotic preparations are cheaper than preparations of antibiotic-free sealants. Consequently, intramammary preparations are often administered prophylactically and for financial reasons, which should be strictly reduced in the future. Thus, a proportion of antibiotic dry-off herd treatment can be partly substituted by sealants in the future. It is also predicted that the number of herd treatments with certain product groups, such as anthelmintics, coccidiostats, and antibiotics, will decrease within the next few years because of the recent regulatory changes [88]. Thus, we suggest collecting data on the use of the respective groups during the next few years and evaluating the proportion of herd treatments based on reliable data in the future (Table 2). Another relevant factor is that the performance of dairy cows partly depends on the number of milkings per day (Table 6), influencing the frequency of administration of teat dips and sprays at milking. Automatic milking systems enable more than 2.5–3 milkings per day [89]. Considering the proportion of dairy herds with automatic milking systems, together with some other dairy farms capable of 2–3 milkings per day, we suggest increasing the number of milkings per day as a default value of PEC_{soil} for dairy cattle teat dips or sprays (Eq. 3, [22]) from 2 to 2.5.

Foot rot in sheep is a common disease in which the entire herd is usually treated. It is possible to treat foot rot by injectable antibiotics or footbath. Since injectable antibiotics are already covered by original VMP guideline

Table 4 Recalculation of the average body weight of several animal types

Animal type	Linear growth	Transition	Fully grown	Birth weight (kg)	Weaning weight (kg)	Age at the end of the linear gain phase (d)	Weight at the end of the linear gain phase (kg)	Age at the fully grown stage (d)	Weight at the fully grown stage (kg)	Average body weight (kg)[a]	Authors correction and other comments that explain dissenting suggestions for default values in Table 3 (body weight, kg)	References
Calf (0–6 months)	x	–	–	50	50	365	300	–	–	> 175	Production ends earlier, but 140 seems to be a little low	[115]
Dairy cow	–	x	x	50	50	365–450	300–350	750–1250	500–800	> 550	425 seems to be low	[115, 116]
Cattle (> 0.5 y)	–	x	x	50	50	180–300	250–380	–	–	> 415	New category; production ends earlier (330)	[117]
Weaner pig (up to 25 kg)	x	–	–	1.4	6.5–8.0	13–15	7–13	–	–	13.2 (15.8)	Birth weight was neglected; therefore, 12.5 seems to be low	[118–120]
Fattening pig (25–125 kg)	x	–	–	1.4	6.5–8.0	70–160	25–125	–	–	75	Production ends earlier; therefore, 65 is realistic	[119–121]
Sow (with litter)	–	x	x	1.4	6.5–8.0	180–200	1–130	600–1000	320–380	> 280 (> 310)	240 seems to be low	[120, 122]
Boar (25–125 kg)	x	–	–	1.4	6.5–8.0	200–220	1–170	500–800	380–420	75	Production ends earlier; therefore, 65 is realistic	[120, 122]
Broiler	x	x	–	0.04–0.05	–	28	1–1.2	63–84	3.1–4.1	1.6	Production ends earlier; therefore, 1.0 is realistic	[123, 124]
Laying hen	–	x	x	0.04–0.05	–	120–140	1.1–1.2	210–560	1.6–2.5	> 1.5	Corrected for underestimation; 1.6 is realistic	[124, 125]

Table 4 (continued)

Animal type	Linear growth	Transition	Fully grown	Birth weight (kg)	Weaning weight (kg)	Age at the end of the linear gain phase (d)	Weight at the end of the linear gain phase (kg)	Age at the fully grown stage (d)	Weight at the fully grown stage (kg)	Average body weight (kg)[a]	Authors correction and other comments that explain dissenting suggestions for default values in Table 3 (body weight, kg)	References
Replacement layer	x	–	–	0.04–0.05	–	120–140	1.1–1.2	210–560	1.6–1.8	> 0.6	Corrected for underestimation; 0.8 is realistic	[124, 125]
Broiler breeder	x	x	x	0.04–0.05	–	189–200	2.5–2.75	280–420	3.5–3.75	> 1.4	Corrected for underestimation; 1.7 is realistic	[126, 127]
Turkey	x	x	x	0.06	–	48–50	2.2	91–126	6–9.5	> 4.8	Corrected for underestimation; 6.5 is realistic	[127]
Duck	x	x	–	0.04–0.08	–	14–49	0.5	70–140	3.1–3.8	1.9	Production ends earlier; therefore, 1.6 is realistic	[128]
Horse	x	x	x	48	180–200	250–330	200–250	480–720	400–700	> 375	Corrected for underestimation; 400 is realistic	[129, 130]
Dairy goat	x	x	x	4.7	8–14	85–90	10	270–390	30–60	> 33	New category	[131–133]
Dairy sheep	x	x	x	4.4	20–25	60	23.7	230–370	50–60	> 33	New category	[134]
Rabbit	x	x	–	< 0.5	0.6–0.7	30	0.8	100–300	3.5–4	2.3	Production ends earlier; therefore, 1.4 is realistic	[135, 136]

[a] Average body weight in parentheses reflects the definition of the animal type "mother with offspring until weaning"

Table 5 Suggestion for updating the original VMP guideline Tables 4 and 5 [22] containing default values for pasture animals

Animal type	Stocking density (animals ha^{-1})	Maximum body weight (kg_{bw})	Daily dung production (kg_{wwt} d^{-1})	Daily dung production ($kg_{\text{dry matter}}$ d^{-1})[c]
Dairy cow	3.5	800	36	9
Beef cattle	9.5	330	13	3.25
Laying hen	230[a]	2.5	0.07[b]	0.008–0.020
Pony	5	250	10	2.5
Horse	3	600	25	6.25
Sheep (adult ewe)	15	80	2	0.6
Lamb	25	36	0.9	0.27
Goat	15	60	1.6	0.48
Red deer (stag)	15	110	2.8	n.a

[a] Ecologically housed laying hens [143]. Maximal 170 kg nitrogen produced per year and hectare, which corresponds to 230 laying hens per hectare

[b] Data were taken from [144]

[c] Data were taken from [145]

Table 2, we recommend changing "foot rot in sheep" to general "footbath" since increasing the appearance of digital dermatitis in bovine species leads to the usage of footbaths with comparable active agents in all ruminant species [90–93]. Currently, footbaths are applied only at the herd level.

The suggested changes for the original VMP guideline Table 2 [22] are included. Based on the increasing implementation of reduction strategies, as described in the listed literature [80–83, 94–106] and unpublished personal observations, in many cases, the proportion of herd treatment is expected to be lower than the current default values in the guideline [22]. This gives certainty that, regarding herd treatment, the exposure of the environment would currently not be underestimated. If reliable data on the percentage of herd treatment are collected within the next few years, lowering some default values could be considered where major changes have occurred because of new legislation or treatment guidance.

The ERA of many treatments of "a small number of animals" ends at Phase I (question 5 [22]), except for injectable antibiotics (used in pigs, to treat respiratory disease in cattle and to treat foot rot in sheep) as well as hormones, which have a zootechnical use [22]. Since antibiotics are increasingly being applied as individual treatments, and anesthetics, sedatives, and injectable nonsteroidal anti-inflammatory drugs are increasingly being used for herd treatments [107], the listed product groups selected for further assessment should reflect the environmental toxicity besides their changing relevance in animal production. In some production processes such as castration, pain medication is currently applied as an individual treatment or to half of the herd (50% herd treatment), which would require the addition in Table 2. This requires monitoring the data of all VMP groups, whereby this information is already available on the individual farm level.

Animal type-related default values

Husbandry system

Table 3 shows the original VMP guideline Table 3 [22], with our proposed amendments. We suggest replacing the term "body weight" in the original VMP guideline Table 3 [22] with the term "average body weight" from Montforts [21] to enable the reader to easily understand the concept of higher values of maximum body weight and the differences therein. The average body weight is calculated over the production period [21] and is defined as the sum of the weight at housing-in (start of the production period or birth) and the weight at removal (end of the production period or slaughtering) divided by 2. The pasture-to-stable ratio is an authors' suggestion to represent existing differences in husbandry systems not included in the housing factor. The value of pasture-to-stable ratio is 1 if animals have no access to pasture, or < 1 if animals have access to pasture.

Body weight

The concept of average and maximum body weight was exemplarily visualized by the growth curve of a dairy cow (Fig. 4). Figure 4 provides a theoretical explanation of the default value calculation for both weights during various periods of growth (left) and shows how trends in animal production influence these weights (right). For example, breeders' associations confirmed that the body weights of production animals have increased in recent years, which increased the maximum body weight as well as the average body weight in many cases. On the basis of the systematically drawn approach, weights were recalculated as shown in

Table 6 Factors included in the $PEC_{soil\ initial}$ calculation and their relationship with the result (positive correlation, negative correlation, constant factor, and factor neglected in the respective equation), the summarized trends in animal husbandry, and the expected effect on $PEC_{soil\ initial}$

Factors	Equations for $PEC_{soil\ initial}$ calculation, according to EMA [22] and as shown in Additional file 1: Table S1[a]			Changes in animal husbandry in the last decade	Expected effect on $PEC_{soil\ initial}$[b]
	Intensively reared animals	Pasture animals	Dairy cattle teat dips or sprays		
Numerator					
Daily dose of the active ingredient (a.i.)	/	/	–	Low dose[c]	↓
Number of days of treatment	/	/	–	One shot[c]	↓
Average body weight	/	–	–	Increased for some animal types	↑
Maximum body weight	–	/	–	Increased for some animal types	↑
Animal turnover rate per place per year	/	–	–	Decreases or remains constant	↓
Stocking density	–	/	–	Decreases or remains constant	↓
EU nitrogen spreading limit	°	–	–	Remains constant	°
Fraction of herd treatment	/	/	–	Decreases for many product groups	↓
Volume of dip used each milking	–	–	/	Decreases or disappears completely (antibiotics), while other remain constant[d]	↓
Number of milkings per day	–	–	/	Increases slightly[e]	↑
Number of days a dairy cow is in lactation	–	–	°	Remains constant	°
Concentration of the a.i. in the product	–	–	/	No or unknown evidence for changes	°
Fraction of dip entering dirty water	–	–	/	Remains constant	°
Denominator					
Bulk density of dry soil	°	°	°	Remains constant	°
Depth of penetration into soil	°	°	°	Remains constant	°
N produced per year per place	\	–	–	Increased for some animal types	↓
Housing factor	\	–	–	Remains constant	°
Spreading rate for dirty water	–	–	°	Remains constant	°
Volume of water used to wash the milking parlor	–	–	°	Remains constant	°

[a] /, Positive correlation; \, negative correlation; °, constant factor; –, factor neglected in the respective equation

[b] ↑, Increase; ↓, decrease; °, constant

[c] Data indicating these changes [147–149]

[d] Data indicating these changes [150, 151]

[e] Data indicating these changes [152, 153]

Table 4. Following a consistent definition of the animal type "mother with offspring until weaning", the recalculation of average body weight should be based on weaning weights instead of birth weights, as shown in pigs (Table 4).

N-excretion

N-reduced feeding is used on an increasing number of farms in Europe, as indicated by the number of funded projects and as shown by studies on feeding strategies for reducing N [137–139]. The regulatory requirement to limit N entries via organic fertilizer [140] leads to several strategies for optimizing N efficiency in animal production systems and for reducing N excretion using rations with lower total N. The implementation of resource-efficient feeding strategies will continue over the next few years, which will likely result in a lower amount of produced N in the future.

Thus, we suggest calculating an average of the existing value of "nitrogen produced in one year per place" used in the EMA [22] and of recent calculations from the Chamber of Agriculture of North Rhine-Westphalia [29]. Using the average of the existing and new values might enable the continuation of the trend and reflect developments under practical conditions. As discussed above, N excretion is a result of the level of intake, defined by the N content of feed and the total amount of feed consumed, as well as metabolism. Intake is highly dependent on the performance level, i.e., the higher the production level, the higher the amount of N produced per place per year [29]. When this factor is used in the calculation of $PEC_{soil\ initial}$ for animals reared in stables (Eq. 2, [22]) as a denominator, higher performance enables higher doses of VMPs with the same threshold for PEC_{soil}. According to recent developments in animal breeding and animal welfare, high performance is very critically discussed and sometimes associated with higher incidence of the so-called production diseases [141, 142]. This is why we recommend adopting the variable "nitrogen excretion per year and place" very carefully while keeping in mind that current high performance will likely be limited to a certain extent in the future. This leads to a lower dilution effect of the VMP as a function of PEC_{soil}.

Default values for pasture animals

Table 5 of the original VMP guideline [22] describes the daily dung production for pasture animals. Since [22] the body weight is shown twice with only little additional information, it seems suitable to combine the two original tables into one as shown in Table 5. To enhance the understanding of the default values, it would be preferable to add the term "average body weight" to the original VMP guideline Tables 3 and 6 and the term "maximum body weight" to the original VMP guideline Tables 4 and 5 (Table 5). Additionally, a row with values for laying hens was added because laying hens are also partly kept free-range with direct entries of VMPs to the soil. Likely, daily dung production increases relative to body weight, but data are rare.

For all newly suggested animal types, data regarding storage time and N production during storage are rare, and further research is necessary for recommending realistic default values. Since the water content of dung varies, especially when animals got treatments (e.g., diarrhea), daily dung production should have been indicated as dry matter instead of wet weight.

Effects of changes in animal husbandry on PEC calculation

Default values show a linear relationship with the result of PEC_{soil} calculation (Eqs. 1–3, VMP guideline, [22]). This suggests the higher the value of the numerator, the higher the calculated PEC value, and vice versa. Conversely, the higher the dominator, the lower the calculated PEC value. Positive and negative correlations between the calculated PEC and default values are indicated in Table 6.

Only a few factors will lead to an increase in the calculated PEC values after an update, as suggested above. These factors include body weight, number of daily milkings, and housing factor. As suggested, we specified consequently the default value "body weight" in either average or maximum body weight for the PEC_{soil} calculations as in Table 6. Animal body weight varies substantially between breeds, whereas housing factor differs with the type of pasture management. To calculate body weight and housing factor, we recommend collecting reliable data on the number, breed, and representative growth curves of animals as well as their pasture management and housing systems. Generalization for all animals of the same type regardless of the production system and management as done for the housing factor, the newly suggested pasture-to-stable ratio (Table 3) or stocking density seems to be only a rough estimate (Fig. 2), but it is currently the most suitable alternative for modeling VMP entries in the environment.

Changes in animal husbandry reflect the recent effort to enhance animal health, fitness, longevity, and other animal welfare indicators, which will likely continue in the future. In synergy with many of the changes in animal husbandry, the result of the assumed updated PEC calculation may lead to lower PEC values in the future (Table 6). This is reflected by all factors included in the PEC calculation that lead to a decline of calculated PEC values after an update, as suggested (Table 6). The penetration depth of manure in soil after application must be taken into account in order to estimate how active substances contained in manure might affect the soil and its organisms. The deeper the manure is incorporated, the more likely it is for active substances to migrate into deeper layers of soil or even into groundwater. In the past, organic fertilizers were mainly applied on croplands in the depth of 20 to 30 cm with a plow, but nowadays they are applied more superficially (3–15 cm) with modern technologies. Slurry and poultry manure penetrated into soil by 3 to 8 cm, fermentation residues from biogas plants by 3 to 15 cm and manure from hoofed livestock by 8 to 15 cm [146].

Different application scenarios of VMPs, especially with low-dose VMPs, lead to the expectation that some VMPs might never exceed the threshold of 100 µg kg^{-1} for $PEC_{soil\ initial}$, although the substance might be highly toxic for the environment [38]. Especially some antibiotics, such as gentamicin, tilmicosin, tulathromycin, and long-acting oxytetracycline [38], are administered at a relatively low dose but may exert high impact on the environment [154–160]. By revising the questions in the decision tree, it can be discussed if and how toxicity can be included in Phase I of the current ERA for VMPs.

Other potentially relevant factors during an ERA

Informal records showing the use of off-label topical antibiotics in production systems indicate that a self-mixed combination of a tyrothricin-containing human medical product and baby powder is applied prophylactically to piglets during castration [94]. In the case of some minor species and seldomly appearing diseases, rededication is necessary and is possible in Germany because of the missing VMP alternatives and the imperative to treat an animal according to the animal protection law [73, 161, 162]. The so-called off-label uses are increasingly restricted and required a valid justification and a detailed documented diagnosis. Unfortunately, only limited data are available on off-label use. If these data had been available, a systematic analysis might have identified common scenarios of off-label use. For now, only case data can be used; however, documentations from farms indicate that blind spots exist, which will not be covered during the approval of VMPs. The off-label use of topical VMPs must be investigated in more detail in future research. We recommend keeping off-label use in mind due to the risk of additional, currently neglected, environmental entries or establish a regulation of off-label use as implemented for aquaculture recently [73]. It can be discussed if the approval process, particularly Phase I, should include a question about the potential fields of off-label use to further address their environmental impact and to enable a retrospective analysis of common off-label cases.

Currently, excretion via feces and urine are included in the model used for environmental entries via manure, but N loads of waste milk are neglected [21]. Milk constitutes a substantial pathway of N excretion, as shown in table S8. Additionally, intramammary preparations are released via milk. Waste milk is recommended to be disposed into manure since feeding is prohibited and leads to an increase in antibiotic resistance [19]. Additionally, it is also necessary to address the disposal of waste water, which occurs in the pipe systems past a treatment administered orally via water, especially in poultry and pig production systems, and which should be released to make sure feed and drinking water are VMP free and to begin with withdrawel times not too early. The disposal of waste milk and waste water as well as the emission of resistance against antibiotics and anthelmintics via air or slurry represent pathways currently not included in the ERA models. It is important to further develop the existing models for addressing the exposure routes in the future in a more detailed manner.

Some animal types are often exposed to a higher risk of infection, for example, poultry kept for breeding because of higher performance for egg production and sows or cows categorized as "mothers including offspring" because of gravidity or lactation [163, 164]. These animals are treated several times with VMPs in their lifetime. Higher risk of infection results in a higher prevalence of treatments, which is likely mirrored in the spread of resistance [24]. The current ERA does not address these risks.

Perspective

Animal welfare, consumer safety, and environmental protection in animal husbandry are increasingly implemented in standards of production chains and demanded by consumers as well as policy-makers. Quantities of most VMPs, especially administered antibiotics, are predominantly declining because of regulations, higher monitoring efforts, and industry-specific standards. However, monitoring measures should be expanded to other groups of VMPs (e.g., antiparasitics, hormones, and pain medications) and include different usages (e.g., drying-off and mastitis treatments in dairy cows, and mastitis, metritis, and agalactia treatment in sows). This will enable a more reliable estimation of the proportion of herd treatments. Monitoring will provide incentives to further improve animal health and reduce environmental entries in general.

Further harmonization of the farm animal categorization and time schedule for recording of animal numbers in the EU would considerably simplify the empirical data on livestock populations across the EU, which would enable us to compare statistics and make valid statements. Another challenge highlighted in the present study is the lack of data, particularly in the field of free-range husbandry. Valid data are urgently needed to be able to make more detailed statements about uncontrolled excretions in free-range husbandry scenarios and the associated environmental exposure. Generally, more information about husbandry systems and animal numbers is needed not only for modeling ERA of VMPs, but also for monitoring epizootic or zoonotic diseases (Haupt et al., unpublished manuscript).

The collected data can provide a basis for updating the VMP guideline tables. The basis of this research was German data. To update the default values and to draw more general conclusions, information from other EU member states will need to be considered. Besides the discussion of default values, a validation of the exposure model is recommended to ensure that the results of the models are generally protective and do not underestimate the concentration of VMPs in the environment. Updating the default values will also help to avoid possible overestimates, which would lead to constant discussion about the default values, calculations or ERA results in case of rejected VMPs. Nevertheless, it will be challenging to include possible relevant exposure routes in the models in the future, e.g., for insects used as food- and feed-producing species. This may reduce the acceptance of environmental risks because of the lack of models for the unique way of exposure, e.g., isoflurane entries via air,

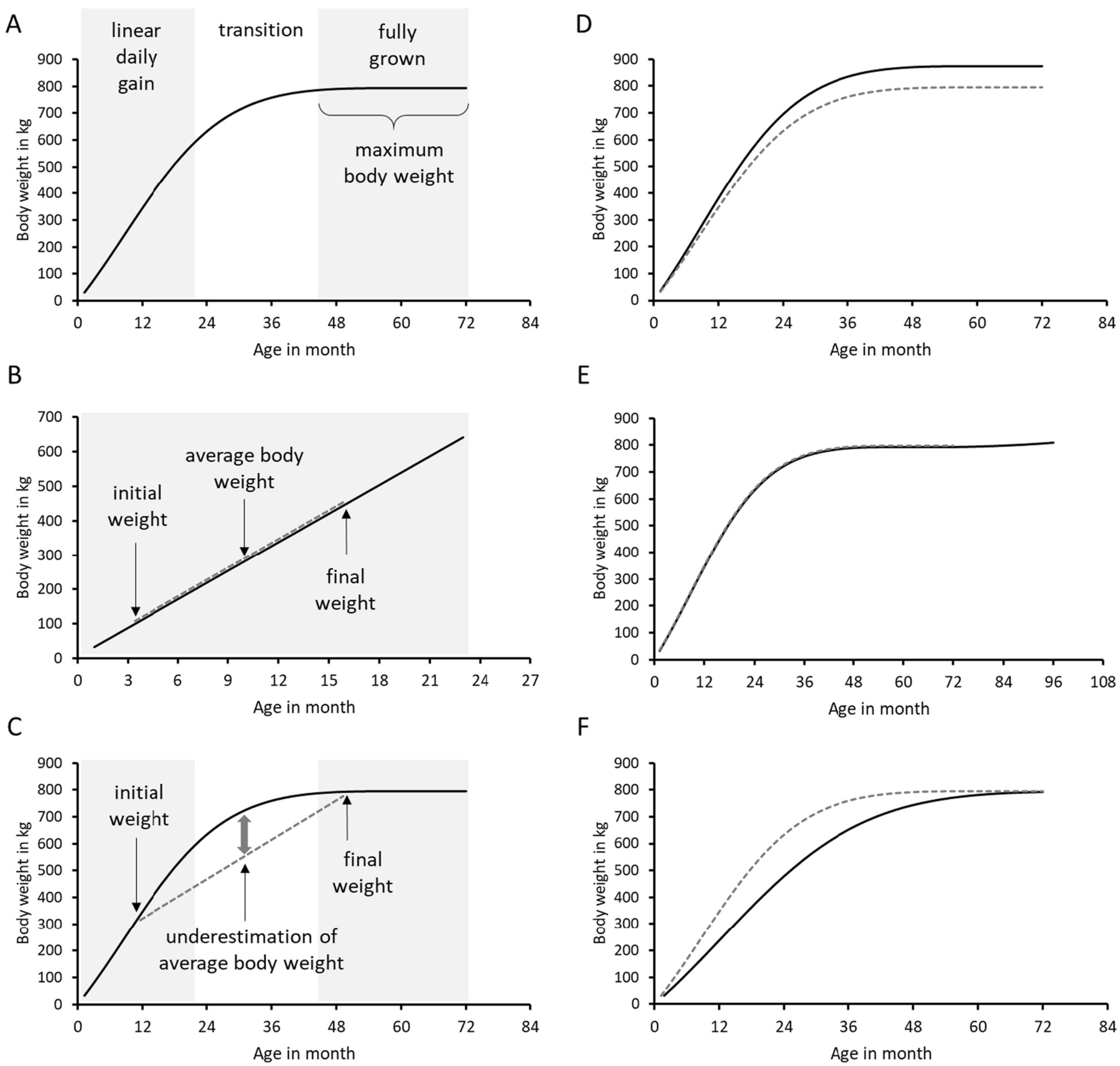

Fig. 4 Exemplary growth curves of dairy cows. **A** Growth rate of cows. The initial linear daily gain is followed by a transition, ultimately reaching a plateau, where cows are fully grown, with zero growth rate and a weight that equals their final adult body weight. **B** Estimation of the average body weight during the linear daily gain phase. **C** Underestimation of the average body weight. This occurs when the transition time is included in the calculation of the average body weight. **D**–**F** Changes (black) compared with the standard growth curve (gray, dashed) in animal production are mirrored as changes in the growth curve: a taller shape of the animals increases the maximum body weight (**D**); a higher functional longevity increases the proportion of time at fully grown (**E**); and a lower growth rate enhances the proportion of time at linear growth (**F**)

or the retroactive reevaluation of existing authorizations with all the difficulties.

To accurately determine the suggested new factor for access to pasture (pasture-to-stable ratio; Table 3), more data on housing conditions are needed from all European countries.

Environmental risks can be substantially reduced if good agricultural practice is applied. For example, pasture care by harrowing the dropped dung prevents local peak entries. Further implementation of good scientific practice requires research, which will facilitate the development of recommendations and the transfer of scientific knowledge.

In conclusion, the model of the ERA of VMPs in the EU is still important and suitable for the intended purpose. However, due to changes in livestock husbandry, an update for the ERA is required. It seems to be possible to reduce the questions of Phase I assessment and revise the default values and relevant factors to mirror recent changes. Certain areas of the ERA need to be revised as they are currently too vague. It would be useful to make these areas more specific. One approach could be to reduce the number of questions in the decision tree and to adapt the default values to current changes. Considering the One Health aspect, farmers, veterinarians and environmental scientists should be involved in a revision of the model.

Abbreviations

EIA: Environmental impact assessment; EMA: European Medicine Agency; ERA: Environmental risk assessment; EU: European Union; PEC: Predicted environmental concentration; RMM: Risk mitigation measure; VICH: Veterinary International Conference on Harmonization VMPs: Veterinary medicinal products.

Supplementary Information

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Additional file 1: Table S1. Equation for calculation of $PEC_{soil\ initial}$ according to the European Medicine Agency [22]. **Table S2.** Percentage herd treatment for various groups of VMPs, according to EMA [22]. **Table S3.** Default values used in the calculation of PEC_{soil} for intensively reared animals, according to EMA [22]. **Table S4.** Default values used for calculating PEC_{soil} for pasture animals, according to EMA [22]. **Table S5.** Daily dung production data of pasture animals, according to EMA [22]. **Table S6.** Default values used for calculating the $PEC_{soil\ refined}$ following degradation in manure, according to EMA [22]. **Table S7.** Overview of various regulations and directives of the European Union (EU) and Germany (as a representative European country) researched in this study in regards to the classification of farm animal species and framework for husbandry and management. **Table S8.** Overview of various feeding studies on N consumption and excretion in dairy cows.

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Authors' contributions

JSW and CH were involved in the funding acquisition. CH, RH, and JSW conceptualized the data search. RH and JSW drafted the manuscript. JSW, RH, MG and RB created the figures. SMS, JJH, CH, and JSW reviewed the manuscript with major contribution and JSW edited the draft. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets and records used in the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Federal Environment Agency.

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