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Pharmaceutical consumption in human and veterinary medicine in Germany: potential environmental challenges

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Pharmaceutical usage in both human and veterinary medicine contributes substantially to societal wellbeing. However, concerns regarding its environmental impacts are increasing. Despite global awareness, a substantial knowledge gap exists in Germany and several other countries regarding pharmaceutical residues, hindering comprehensive environmental risk assessments. This study aims to bridge this gap by analyzing veterinary pharmaceutical consumption in livestock farming in Germany and comparing it with human pharmaceutical usage, subsequently correlating these findings with environmental data on pharmaceutical residues to conduct a straightforward analysis of the environmental risk posed on non-target entities such as soil, water bodies, and microorganisms. Data from 129 agricultural farms in Germany were utilized to comprehensively analyze veterinary pharmaceutical usage. Extrapolation to national levels estimates a substantial quantity of active substances used, particularly antibiotics and electrolytes. Comparison with human pharmaceutical usage highlights differences in substance prevalence and usage patterns. Environmental correlations indicate a considerable presence of pharmaceutical residues in Germany, with notable distinctions between human and veterinary sources. In the environmental risk analysis, significant differences are evident between individual active substances within the same substance group. The study underscores the importance of addressing pharmaceutical residue impacts on the environment and emphasizes the necessity of comprehensive data for informed decision-making and environmental management strategies.

KEYWORDS

pharmaceutical usage, veterinary pharmaceuticals, human pharmaceuticals, pharmaceutical residues, substance monitoring, environmental impact

1 Introduction

Pharmaceuticals are undeniably integral to our daily lives. Beyond the evident benefits of disease eradication, healing, therapy, and prevention in both humans and animals, they also contribute to food safety. Globally, the pharmaceutical market has a volume of 1.33 trillion US dollars. The largest national markets are the US, with a volume of $618.281 billion, China with $110.229 billion, Japan with $65.810 billion, Germany with

$52.151 billion, and France with $40.918 billion (Federal Association of the Pharmaceutical Industry, 2023). However, concerns about the usage of pharmaceuticals have emerged as well (Zuccato et al., 2006; Barra Caracciolo et al., 2015; Maculewicz et al., 2022). Some adverse effects are widely known, such as the development of antibiotic resistance, recognized by the World Health Organization (WHO) as one of the top ten threats to global health (World Health Organization, 2019). Not only do antibiotic resistances represent a growing concern in the treatment of both humans and animals, but resistance to antiparasitic agents is on the rise as well (Charlier et al., 2022). An environmental risk has been identified in various environmental compartments, e.g., for the antiparasitic agent ivermectin (Liebig et al., 2010). In addition, the consumption of pharmaceuticals such as hormones or anti-inflammatory drugs and the resulting residues in soil and water lead to negative effects on non-target organisms in the environment (Kidd et al., 2007; Parolini, 2020). For example, when the hormonal substance 17α-ethinylestradiol enters the environment, it can cause feminization of male fish, significantly impacting fish populations (Kidd et al., 2007; Hinck et al., 2009). Similarly, in the 2000s, approximately 95% of the vulture population in Pakistan died after consuming the flesh of cows treated with diclofenac (Oaks et al., 2004). However, most of the effects on non-target organisms are still not well understood or partially unknown (Boxall et al., 2003; Hamscher and Bachour, 2018).

Despite global awareness of the issue, there exists a significant knowledge gap regarding discharges of pharmaceuticals into the environment in Germany. Accurate estimation of environmental consequences on non-target entities such as soil, water bodies, and microorganisms necessitates a comprehensive understanding of the pharmaceuticals in use, including the quantity of each active substance employed (Wöhler et al., 2020). In Germany, official data on veterinary pharmaceutical consumption are only available for antibiotics, and even this information is incomplete. Veterinarians are required to report usage data for specific animal categories only (Federal Ministry of Food and Agriculture, 2021), and the pharmaceutical industry provides only aggregated sales figures for antibiotics to veterinarians (Federal Office of Consumer Protection and Food Safety, 2021). For all other substance groups and individual compounds, consumption data are lacking. Research conducted in Germany and the European Union has primarily focused on the utilization of antibiotics in livestock purposes, with some studies only examining the frequency of use and not the quantity used (Kuipers et al., 2016; Hemme et al., 2018; Hommerich et al., 2019; Mitrenga et al., 2020; Olmos Antillón et al., 2020; Kasabova et al., 2021; van der Laan et al., 2021). In human medicine, the annual pharmaceutical report (Ludwig et al., 2022) only provides information on daily doses of medications, making it nearly impossible to calculate the absolute quantity used. Without comprehensive data on the types and quantities of pharmaceuticals used, assessing their impact on the environment is challenging. Moreover, apart from the difficulty in identifying, quantifying, and tracing the origin of environmental inputs, for most substances the effect of residues on humans, animals, and the environment have not been fully explored yet.

In response to this knowledge gap, we have collected and extrapolated veterinary pharmaceutical consumption data, specifically in the context of livestock farming, to estimate national levels. By comparing human and veterinary pharmaceutical substances, our study aims to elucidate which substances and substance groups are prevalent in different sectors. Furthermore, we correlated our findings with data on pharmaceutical residues in the German environment to establish connections between usage patterns and environmental presence to conduct a straightforward analysis of the environmental risk posed on non-target entities such as soil, water bodies, and microorganisms.

2 Materials and methods

2.1 Data

For this study, we have combined three data sources for Germany. Firstly, we utilized data from a nationwide survey[1] conducted on 129 agricultural farms (summary statistics in Supplementary Table S1), covering the entire year 2020. These farms are categorized into 50 dairy farms, 15 cattle fattening farms, 16 piglet producers, 33 pig fattening farms, 10 laying hen farms, and 5 broiler producers from nine different federal states. From their official application and dispensing receipts, we obtained medication data, providing an overview of the veterinary drugs used, including their quantities in kilograms, the active substances contained, the duration of medication, and the number and category of treated animals.

In a subsequent step, we expanded our study from the 129 surveyed farms to a national scale (168,833 farms) by estimating the total usage of veterinary drugs across Germany, categorized by animal category. To ensure accurate comparisons between different animal categories, which may vary in live weight, we computed the usage of each active substance per livestock unit using the conversion factors provided by Eurostat (2021) in Supplementary Table S2. For the extrapolation, we divided the amount of each active substance used by the livestock units in the study, and then multiplied these figures by the total number of livestock units in Germany (variable LU_DE in Supplementary Table S1), as recorded in the 2020 Agricultural Census (Federal Statistical Office of Germany, 2021a). As part of a robustness assessment in Supplementary Table S7, for each active substance, the quantity utilized per population correction unit (PCU) was computed in accordance with the methodology prescribed by the European Medicines Agency (EMA). This computation entailed dividing the active substance quantity documented in the study by the estimated live weight of the livestock cohort maintained or slaughtered within the respective year (European Medicines Agency, 2011; European Medicines Agency, 2018).

As a second dataset, we incorporated aggregated consumption data for human pharmaceuticals obtained by the German Environment Agency from the following source: IQVIA MIDAS® quarterly volume (kg) sales data for Germany, for the calendar year

1 More detailed information about the survey can be found in the paper by Abdallah et al., 2024

2020 reflecting estimates of real-world activity. The data refer to human medical use only and comprise 2,813 active substances with a total sales quantity of 38,921 t. For further consideration, active substances were categorized into groups based on the classification by Löscher and Richter (2016), including antibiotics, anti-inflammatory agents, antiparasitics, and hormones. A detailed listing of these groups of active substances can be found in Supplementary Table S8.

To establish comparability between humans and livestock, we subsequently present the administered dosage of active substance in milligrams per kilogram body weight. For this purpose, the extrapolated amounts of active substances were divided either by the total mass of livestock (Bavarian Academy for Nature Conservation and Landscape Management, 2018) or by the mass of the population of Germany (Federal Statistical Office of Germany, 2023b; Federal Statistical Office of Germany, 2023a).

As a third dataset, we utilized data on environmental findings of pharmaceutical residues. In a meta-analysis, the German Environmental Agency compiled studies worldwide between 1988 and 2020 that identified pharmaceutical residues in the environment, such as soils and waters, creating a publicly accessible database (German Environment Agency, 2022). The database includes information on the source study, the location of the findings, and the detected active substances. For further analysis, we employed 295 publications with 34,001 environmental findings specific to Germany until the year 2020. In the evaluation, we aligned the active substances used in veterinary and human medicine in 2020 with environmental findings. Detected transformation products that could be clearly attributed to an original active substance were assessed accordingly.

2.2 Risk assessment

To ascertain the environmental risk posed by identified substances in veterinary and human medicine, we calculated Predicted Environmental Concentration (PEC) values for each substance and compare these with Predicted No Effect Concentration (PNEC) values.

According to the European Medicines Agency (2016), the Predicted Environmental Concentration in soil (PEC_{soil}) of an active substance of a veterinary medicinal product, expressed in micrograms per kilogram (µg/kg), is determined through Equation 1, where D represents the daily dose of the active substance, measured in milligrams per kilogram body weight per day (mg/(kg_{bw}*d)). Ad is the number of days the treatment is administered. BW denotes the body weight of the animal in kg_{bw}, and P is the annual turnover rate of animals per place, both variables given in European Medicines Agency (2016), Table 3. The constant 170 (kg_N)/ha refers to the European Union (EU) limit for nitrogen application on fields. Fh is the fraction of the herd that receives treatment, a value ranging between 0 and 1, given in European Medicines Agency (2016), Table 2. The value 1,500 kg/m³ is the bulk density of dry soil, the value 10,000 m²/ha represents the area of entry per hectare, while 0.05 m indicates the depth of soil penetration considered in the model. Ny is the amount of nitrogen produced per place per year, H is the housing factor, which is 1 for animals housed year-round and 0.5 for animals housed for only 6 months, both detailed in European Medicines Agency (2016), Table 3 as well. In the end, the term is converted into micrograms.

$$PEC_{soil}\left(\mu g/kg\right) = \left(\frac{D \times Ad \times BW \times P \times 170 \times Fh}{1500 \times 10000 \times 0.05 \times Ny \times H}\right) \times 1000 \quad (1)$$

For subsequent comparability, we first convert PEC_{soil} values for each active substance to $PEC_{groundwater}$ using Equation 2, with RHO_{soil} representing the bulk density of fresh soil (1,700 kg/m³). $K_{soil\text{-}water}$ is the partition coefficient between solids and water in soil (volume/volume), defined as 1 as worst case assumption due to a lack of data, and 1,000 is a conversion factor to adjust to liters (European Medicines Agency, 2016).

$$PEC_{groundwater}\left(\mu g/l\right) = \frac{\frac{PEC_{soil}}{4} \times RHO_{soil}}{K_{soil-water} \times 1000} \quad (2)$$

In a subsequent step, we convert $PEC_{groundwater}$ into $PEC_{surfacewater}$ using Equation 3 (European Medicines Agency, 2016).

$$PEC_{surfacewater}\left(\mu g/l\right) = \frac{PEC_{groundwater}}{3} \quad (3)$$

For human medicine data, we can directly calculate a $PEC_{surfacewater}$ using Equation 4 (European Medicines Agency, 2024), where A in kg/year represents the total amount of active substances consumed in humans in Germany in the year 2020. R denotes the percentage rate at which substances are eliminated through absorption, evaporation, decomposition by water, or natural degradation in disposal systems. Due to the absence of precise data for R, we follow Fass (2012) in setting this value to 0. P represents the number of inhabitants in Germany. Consequently, V in L/day is the average wastewater volume *per capita*, amounting to 200 L. The dilution factor of wastewater by surface water flow, D, is set to 10 (European Medicines Agency, 2024).

$$PEC_{surfacewater}\left(\mu g/l\right) = \frac{A \times 1,000,000,000 \times (100 - R)}{365 \times P \times V \times D \times 100} \quad (4)$$

Supplementary Table S3A gives an overview of calculated and transformed PEC values per substance.

Now that we have calculated the PEC values, we proceed to determine the PNEC values. Various metrics assess the hazard of substances: NOEC (No Observed Effect Concentration), EC10, and EC50 (the concentrations causing 10% and 50% inhibition of growth in exposed organism, respectively), and LC50 (the concentration at which 50% of the exposed organism perish). The values and sources of metrics pertaining to each specific substance can be found in Supplementary Table S3B. The PNEC value in Equation 5 standardizes these diverse metrics, rendering the values comparable across all substances. This is achieved by dividing the respective metric by a safety factor. The safety factor is set at 100 for NOEC and EC10, and 1,000 for EC50 and LC50 (European Chemicals Agency, 2008).

$$PNEC\left(\mu g/L\right) = \frac{Metric}{Safety\ factor} \quad (5)$$

For a subset of substances, the PNEC value can be calculated, thereby enabling risk assessment through the division of

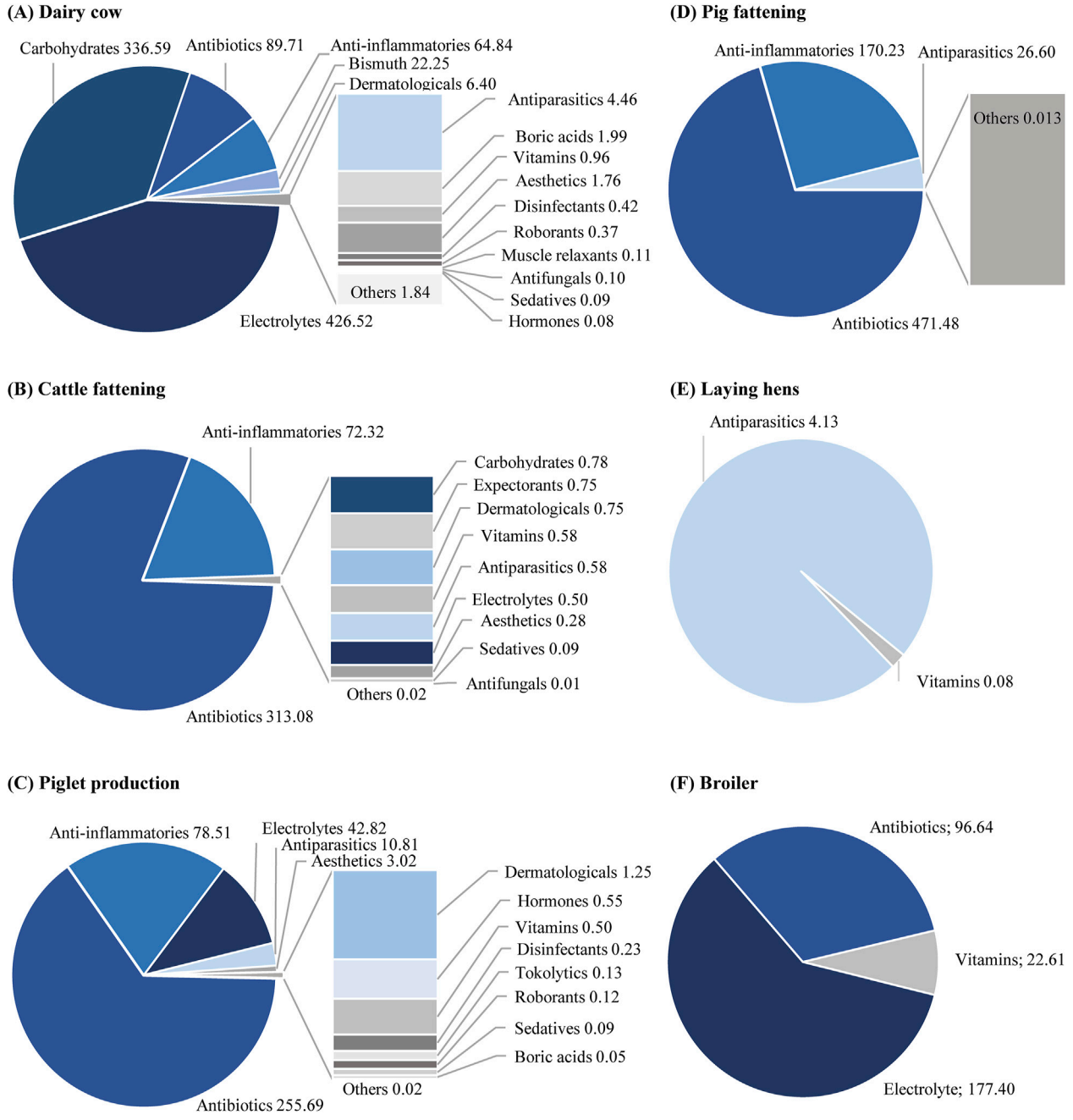

FIGURE 1
Surveyed drug consumption quantity per animal category in kg, partitioned by substance groups for the year 2020. **(A)** dairy cow, **(B)** cattle fattening, **(C)** piglet production, **(D)** pig fattening, **(E)** laying hens, **(F)** broiler.

$PEC_{surfacewater}$ by PNEC as per Equation 6. For this purpose, the PEC values from human and veterinary medicine are summed. If the resulting value exceeds 1, the concentration of the substance in the environment is greater than the concentration deemed safe. Accordingly, risk quotients are categorized based on their significance into high (>10), moderate (≥1), low (>0.1), and insignificant (≤0.1) (Fass, 2012).

$$Risk\ Quotient = \frac{PEC_{surfacewater}}{PNEC} \quad (6)$$

3 Results

3.1 Pharmaceuticals used in livestock farming

Within the scope of this study, a comprehensive analysis was conducted on a total of 15,502 veterinary prescriptions from 129 farms. Segmented across 29 substance groups, we were able to identify 162 distinct active substances with a cumulative consumption of 2,709.95 kg. Antibiotics predominated in terms

of quantity, constituting 1,226.61 kg. The amount of antibiotics per PCU was 83.1 mg/PCU. Following are electrolytes (647.24 kg), categorized as pharmaceuticals according to EU regulations (European Union, 2022), anti-inflammatory agents (385.90 kg), and carbohydrates (337.36 kg). Antiparasitics, with a quantity of 46.57 kg, and hormones (0.63 kg) hold a quantitatively subordinate significance. More detailed figures for additional substance groups are available in Supplementary Table S4.

Figure 1 depicts, in six pie charts, the use of pharmaceutical agents per animal category in kilograms, partitioned by active substance groups.

The values for dairy cows (A) are based on 13,565 animals across 50 farms. On average, each farm issued 204 drug prescriptions in 2020. In total, substances from 26 out of 29 substance groups were employed in dairy farms, amounting to a total quantity of 957.23 kg. Electrolytes possessed the highest quantitative importance at 426.52 kg, followed by carbohydrates at 336.59 kg. Subsequently, antibiotics (89.71 kg), anti-inflammatory drugs (64.84 kg), and bismuth (22.25 kg), utilized for teat sealing, are of note. Antiparasitics and hormones were administered at 4.46 kg and 0.08 kg of active substance, respectively.

For cattle fattening (B), the values were derived from 15 farms managing a total of 5,765 animals, partly through extensive cow-calf operations on pasture and partly through intensive bull or calf fattening in barns. On average, each farm issued 70 drug prescriptions in 2020. Among the 18 utilized active substance groups in cattle fattening, totaling 389.74 kg, antibiotics with 313.08 kg and anti-inflammatory drugs with 72.32 kg were the most common. Other substance groups, such as antiparasitics (0.58 kg), electrolytes (0.50 kg), and anesthetics (0.28 kg), occurred only in minimal quantities.

For piglet production (C), the pharmaceutical data were sourced from 16 farms, typically involved in breeding sows and raising the piglets they give birth to until they reach a weight of approximately 30 kg. The pharmaceutical data were derived from 31.615,5 animals. On average, each farm issued 198 drug prescriptions in 2020. Of the 18 active substance groups utilized, totaling 393.78 kg, antibiotics (255.69 kg) and anti-inflammatory drugs (78.51 kg) occupied a central position, similar to cattle fattening farms. Electrolytes (42.82 kg), antiparasitics (10.81 kg), anesthetics with 3.02 kg, and hormones with 0.55 kg were also used in substantial quantities.

The data for pig fattening (D) come from 33 farms with 30,127.76 animals. On average, each farm issued 27 drug prescriptions in 2020. Of the 8 active substance groups employed, totaling 668.33 kg, antibiotics were by far the most utilized (471.48 kg), followed by anti-inflammatory drugs (170.23 kg) and antiparasitics (26.60 kg). Antithrombotics (0.01 kg), hyperemic agents (0.002 kg), anaesthetics (0.0005 kg) and sedatives (0.0002 kg) had a substantially lower importance and are therefore grouped and labeled as "others."

For laying hens (E), the data were derived from 10 farms with a total of 105,750 laying hens participating in the sample. On average, each farm issued 4 drug prescriptions in 2020. Besides antiparasitics (4.13 kg), this sample only recorded the use of vitamins at 0.08 kg.

The five broiler farms (F) with a total of 206,800 animals received 34 drug prescriptions on average per farm in 2020. In addition to electrolytes (177.40 kg) and antibiotics (96.64 kg), vitamins (22.61 kg) were utilized as well.

3.2 Extrapolation to nationwide numbers

For the extrapolated quantities of active substances for Germany, the sample's treated livestock units served as the basis, the target variable being the total number of livestock units in Germany. The extrapolation revealed that for 15,723,673 livestock units in Germany, approximately 1,368.33 t of active substances were utilized. Of this total, nearly 70%, equivalent to 587.58 t, comprised antibiotics, followed by 347.61 t of electrolytes mainly used in dairy cows and broilers. The amount of antibiotics per PCU was 83.3 mg/PCU for the extrapolation. Carbohydrates (187.8 t) used in dairy cows and anti-inflammatory drugs (187.48 t) were utilized in nearly equal amounts. Antiparasitics followed with a significantly lower quantity of 22.91 t. Hormones were amounting to 232 kg of active substances. More detailed information for additional substance groups is available in Supplementary Table S5.

Figure 2 displays the active substance groups of antibiotics (A), anti-inflammatory drugs (B), antiparasitics (C), and hormones (D), along with the individual active substances within them. The bars indicate the consumption quantity in tons, and the colors indicate the animal category for which the substances were used. In the upper part of Figure 2, the antibiotic group (A) is further broken down. Penicillins, totaling 266.49 t, and tetracyclines, amounting to 146.47 t, constituted 70% of the overall antibiotic quantity. Penicillins are primarily used in pig fattening, while tetracyclines are predominantly employed in cattle farming. However, both subgroups of antibiotics also have significant importance in other animal categories, except for laying hens. In broiler production, polypeptide antibiotics and aminoglycosides play a major role. Polyene antibiotics are exclusively used in dairy cows for ketosis prophylaxis (VETIDATA, 2024). Highest priority critically important antimicrobials (HPCIA), such as fluoroquinolones (1.56 t) and third (0.87 t) and fourth (0.20 t) generation cephalosporins, are used in limited quantities. Fluoroquinolones and fourth-generation cephalosporins are primarily used in dairy cows, while third-generation cephalosporins are mainly employed in piglet production.

As shown in the upper-right part of the figure on anti-inflammatory drugs (B), these were only used in cows and pigs in our sample. Quantitatively, only NSAIDs were significant with 187.01 t. Glucocorticoids amounted to 0.46 t, and antihistamines were at 4.9 kg, used exclusively in cows.

Antiparasitics (C) are depicted in the bottom-left diagram and were used in all categories except for broilers. Benzimidazoles (14.55 t), constituted the largest group and were primarily used in pig fattening, piglet production, and laying hens. In our sample, no other antiparasitics were used in laying hens. Piperazine (4.67 t) was exclusively used in pig fattening. Triazine derivatives (1.54 t) rank third and were predominantly used in piglet production and dairy cows. Macrocyclic lactones and pyrethroids were mainly used in dairy cows. Salicylanilides and anticoccidials were used exclusively in dairy cows, and organophosphates were used in pigs only.

In the graph at the bottom-right, hormones (D) exhibit a small quantity, totaling only 232 kg, as they are administered in very small doses. Among the sex hormones, progestins were the most prominent (210 kg) and were used in sows and dairy cows.

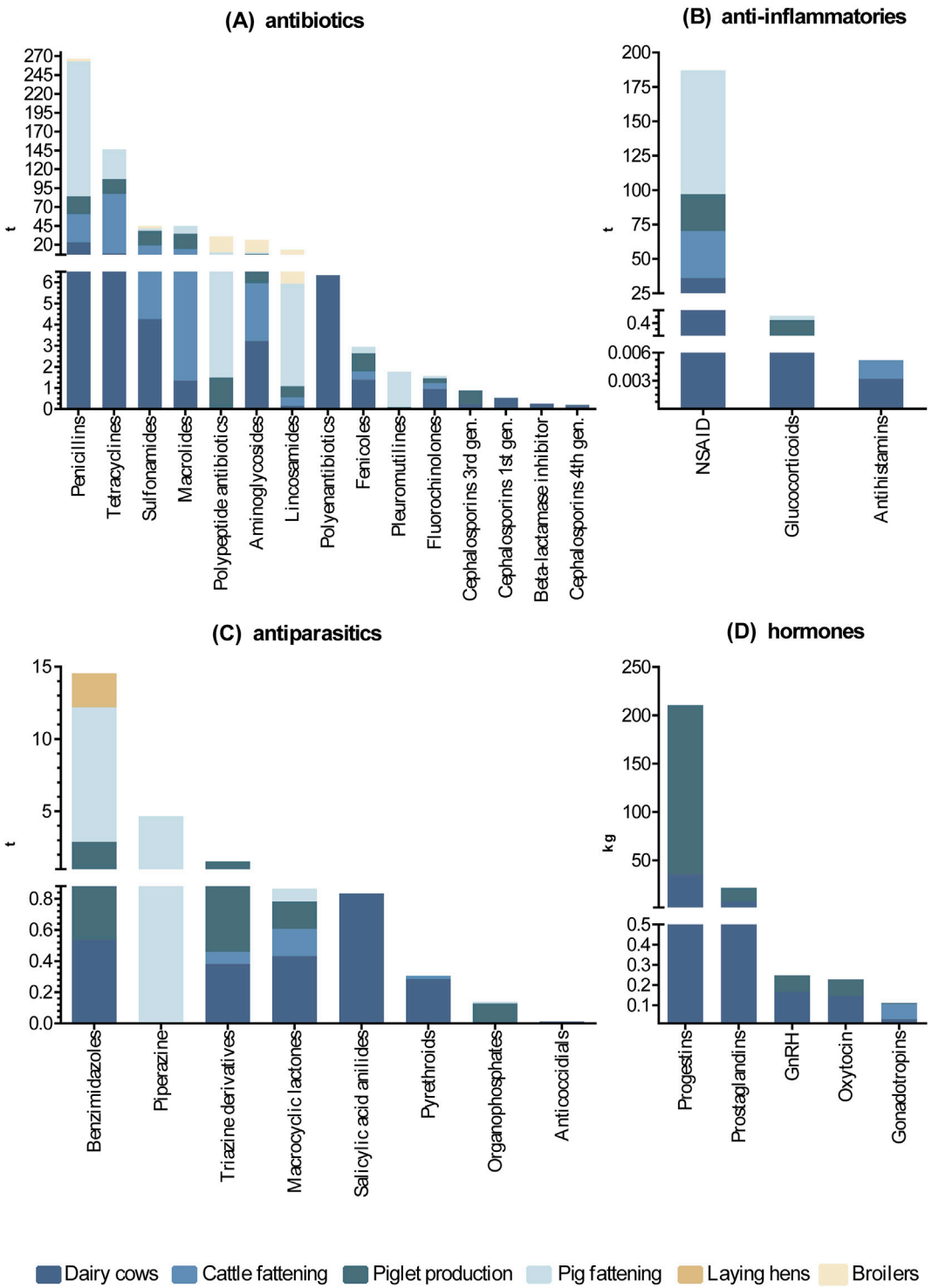

FIGURE 2
Extrapolated consumption quantities of active substances in the substance groups of **(A)** antibiotics, **(B)** anti-inflammatories, **(C)** antiparasitics, and **(D)** hormones for Germany in 2020, partitioned by animal category.

Prostaglandins and their analogues were much less frequently used, totaling 20 kg. Finally, GnRH (0.25 kg), as well as oxytocin (0.23 kg) and gonadotropins (0.11 kg) were applicated in lower kilogram amounts. In our survey, sows were treated with equine chorionic gonadotropin (eCG) as well, however, no quantity of active substance in kilograms could be determined as there was insufficient information provided by the manufacturer regarding the concentration of the active substance in the preparation.

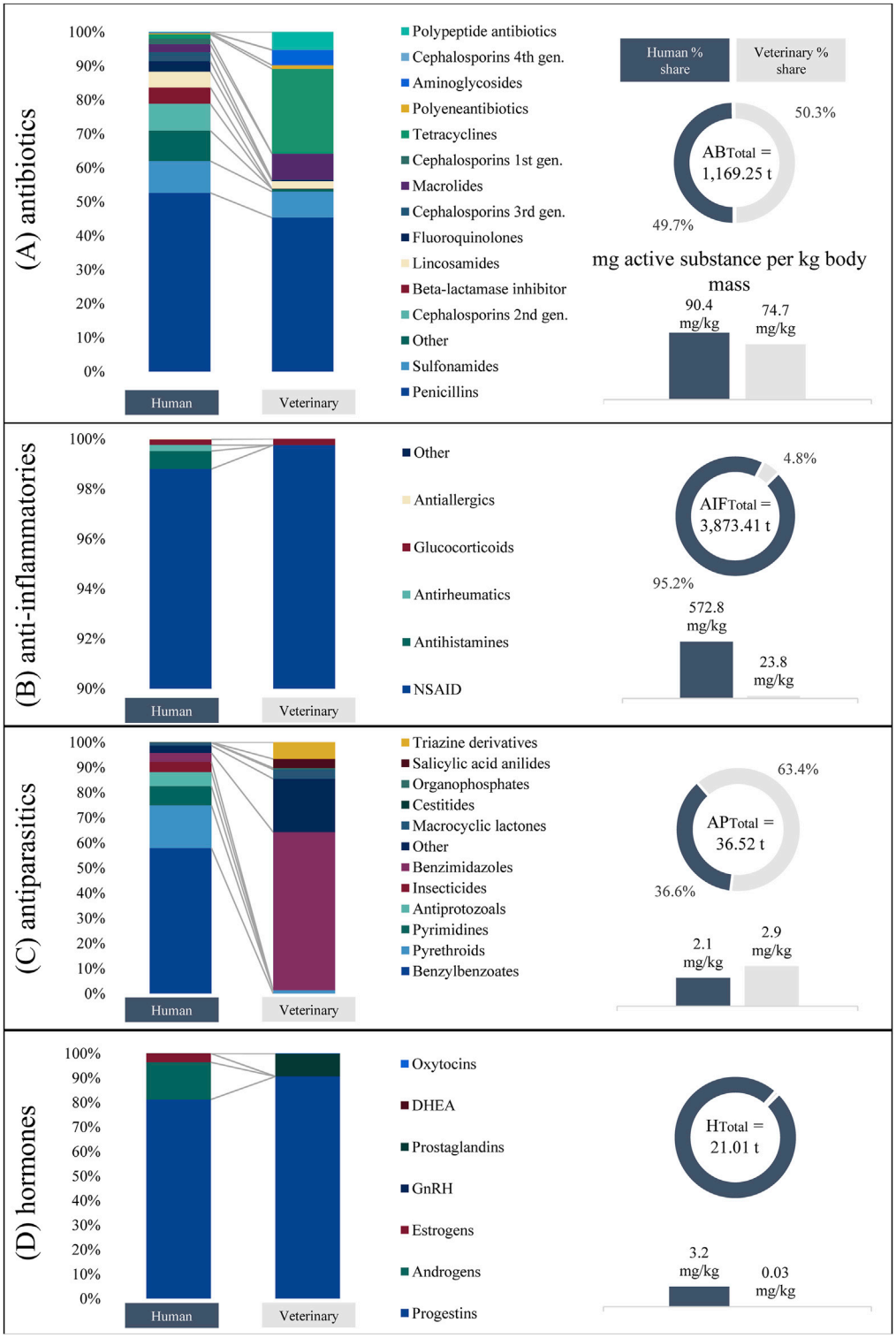

FIGURE 3
Comparison of the use of veterinary and human pharmaceuticals, categorized by active substance groups of **(A)** antibiotics, **(B)** anti-inflammatories, **(C)** antiparasitics, and **(D)** hormones for Germany in 2020. Illustrated in the bar charts on the left is the comparison of the consumed active substances. Shown in the top right is the consumption share of the total quantity and in the bottom right, the amount of active substances used per kilogram of body mass. Based on author analysis using human health data from the following source: IQVIA MIDAS® quarterly volume (kg) sales data for Germany for calendar year 2020, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved.

3.3 Comparison of human and veterinary pharmaceutical use

Utilizing consumption data derived from human medicine, we were able to delineate the comprehensive utilization of pharmaceuticals across human and veterinary medicine in Germany. Figure 3 comprises four segments, representing the substance groups of antibiotics (A), anti-inflammatory drugs (B), antiparasitics (C), and hormones (D). Within these classifications, as adapted from Schröder et al. (2020), the bar charts on the left illustrate the relative consumption of individual substances within each substance group. The left bar signifies pharmaceutical usage in human medicine, while the right bar conveys extrapolated values for veterinary medicine. The right segment further provides insights into the proportion of the overall drug quantity attributed to human *versus* veterinary medicines. Lastly, the estimated application of these drug categories per kilogram in humans and animals is outlined. For an assessment of the average utilized drug quantity per person or animal, the indicated milligram value necessitates multiplication by the respective body mass.

In the case of antibiotics (A), it is evident that in both human and veterinary medicine, penicillin was the most extensively used antimicrobial, followed by sulfonamides for human and tetracyclines for veterinary use. In livestock farming, tetracyclines and macrolide antibiotics were employed more frequently than in human medicine. However, in human medicine, second-generation cephalosporins and HPCIA, i.e., cephalosporines of the third and fourth generations, as well as fluoroquinolones, were more prevalent. The consumption of approximately 1,169 t of antibiotics was divided roughly equally between human and veterinary medicine. Regarding the quantity used per kilogram, human medicine surpassed veterinary medicine with 90.4 mg/kg compared to 74.7 mg/kg body mass.

Concerning anti-inflammatory drugs (B), it is evident that in both human and veterinary medicine, NSAIDs were utilized in more than 90% of cases. The consumption of approximately 3,873 t of anti-inflammatory drugs was predominantly attributed to human medicine, accounting for 95.2%. Additionally, the calculated quantity of active substance per kilogram in human medicine, at 572.8 mg/kg, was substantially higher than the corresponding value in veterinary medicine, which stood at 23.8 mg/kg.

A diverse pattern is evident in the bar chart for antiparasitics (C). While scabicides agents and antiprotozoals dominated in human medicine consumption, they were scarcely applied in veterinary medicine. In contrast, benzimidazoles prevailed in veterinary medicine, while they played a minor role in human medicine. The consumption of 36.5 t of antiparasitics in Germany was attributed to approximately 63.4% in veterinary medicine. Additionally, the quantities of active substances used per kilogram were at a similar level, with 2.1 mg/kg in human medicine and 2.9 mg/kg in veterinary medicine.

In the lower part of the figure, hormones (D) are depicted. Both in human and veterinary medicine, progestins were predominantly used. In human medicine, androgens were additionally utilized, while in veterinary medicine, prostaglandins were employed. Of the approximately 21 t of hormones consumed, 98.9% were attributed to human medicine. Moreover, the consumption in human medicine, at 3.2 mg/kg, was a hundred times higher than in veterinary medicine, which stands at 0.03 mg/kg.

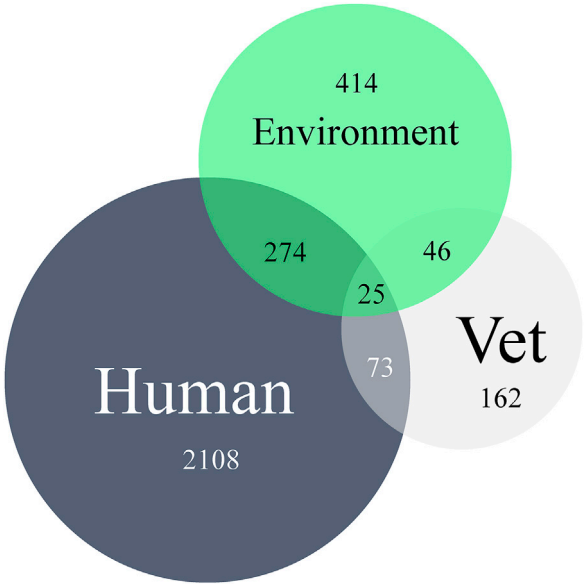

FIGURE 4
Number of active substances and derivatives found in the environment and their association with human and/or veterinary pharmaceuticals used in 2020. Based on author analysis using human health data from the following source:IQVIA MIDAS® quarterly volume (kg) sales data for Germany for calendar year 2020, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved.

3.4 Environmental findings

From the previous results, it is now evident which active substances from which substance groups were used in the field of human medicine and in livestock farming within our study. As depicted in the Venn diagram in Figure 4, a total of 2,108 different active substances were identified in the human domain, and 162 different active substances in the field of livestock farming veterinary medicine. 73 active substances were utilized in both domains; illustratively, amoxicillin and acetylsalicylic acid can be mentioned.

We correlated this information with environmental findings of active substances and derivatives. In total, 414 active substances and derivatives were identified in the environment in Germany by the end of the year 2020 (German Environment Agency, 2022). Most environmental detections originate from surface waters (rivers and streams) and from the effluents and influents of wastewater treatment plants. Only about 30% of detections in Germany come from soil samples (Graumnitz and Jungmann, 2021).

Comparing the active substances used in our study in 2020 with those found in the environment up to 2020, approximately 66% (or 274 substances) can be attributed to human medicine, while about 11% (or 46 substances) originate from the veterinary medicine domain. 25 active substances, constituting 6% of all identified substances, were used in both domains, including penicillin G and metamizole. A total of 119 environmental findings did not

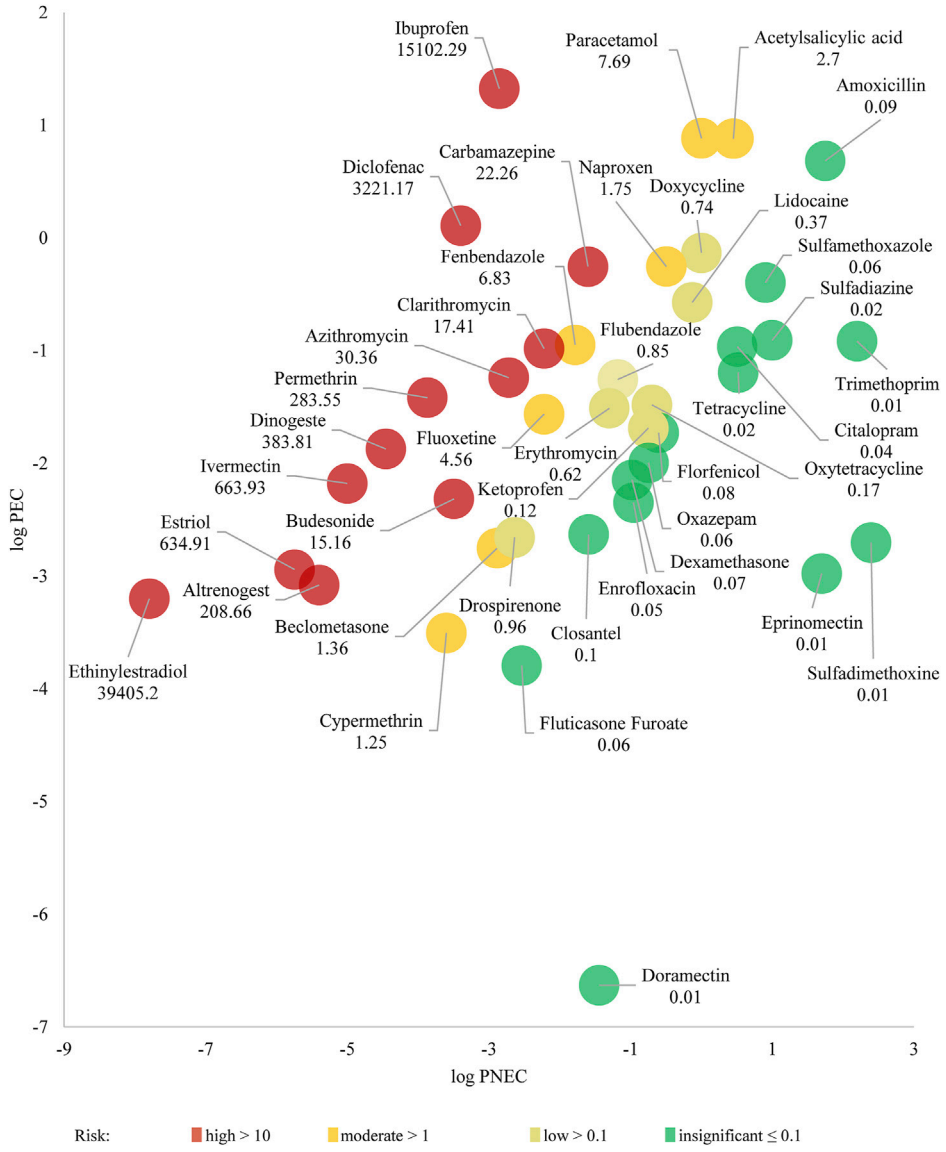

FIGURE 5
Environmental impact assessment based on PEC and PNEC values. Based on author analysis using human health data from the following source: IQVIA MIDAS® quarterly volume (kg) sales data for Germany for calendar year 2020, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved.

correspond to data on human pharmaceuticals used in 2020 or appear in the study conducted on agricultural farms. For 1834 active substances from human medicine and 116 active substances from our veterinary medicine sample, no environmental match could be identified.

The majority of various active substances in the environment were derived from the group of antibiotics, such as sulfonamides (sulfamethoxazole, sulfadiazine, sulfadimidine) (human sector 42, veterinary sector 29, both sectors 11). Following antibiotics, active substances from the group of anti-inflammatory agents emerged, with diclofenac and ibuprofen taking precedence (human 44, vet 6, both 6) and being the most represented individual active substances in the database as well. Subsequently, clotrimazole, sulfamethoxazole and carbamazepine ensued as important individual substances. Following antibiotics and anti-inflammatory agents, active substances from the group of antidepressiva (human 19, vet 0, both 0), antiypertensiva (human 15, vet 0, both 0) and hormones (human 10, veterinary 0, both 0) emerge, such as estradiol. Antiparasitics (human 2, vet 2, both 0) did not rank among the top ten identified groups of active substances.

3.5 Risk calculation

For 41 substances used in livestock farming and human medicine, we were able to calculate Predicted No Effect Concentration (PNEC) values, thereby enabling the assessment of environmental risk. Figure 5 illustrates the logarithmically scaled Predicted Environmental Concentration ($PEC_{surfacewater}$) values on

the ordinate against the logarithmically scaled PNEC values on the abscissa. Each circle in the diagram represents a substance, with its risk quotient value determining the color of the circle. At first glance, a trend from the bottom left to the top right becomes evident, indicating that high $PEC_{surfacewater}$ values are associated with high PNEC values. A horizontal comparison of substances reveals that those with a similar amount used, hence a similar high $PEC_{surfacewater}$ value, such as altrenogest (left) and eprinomectin (right), can have very different PNEC values, resulting in a wide range of risk quotient values from 39,405.20 (ethinylestradiol) to 0.000007 (doramectin). The vertical comparison clearly demonstrates that for substances of similar environmental hazard levels, the quantity used significantly influences the risk, driving it upwards [compare, for example, carbamazepine (top) with doramectin (bottom)]. According to our calculations, the substances posing the greatest risk are ethinylestradiol, ibuprofen and diclofenac with values between 39,405.20 and 3,221.17, followed by ivermectin, estriol, dinogest, permethrin, and altrenogest with still high values around 663.93 and 208.65. Ethinylestradiol has the highest risk quotient with 39,405.20, indicating that the concentration of the active substance in the environment is approximately forty thousand times higher than the concentration deemed to be safe. Substances like paracetamol, fluoxetine and acetylsalicylic acid present moderate risk, whereas substances like doxycycline, lidocaine and flubendazole have a low risk. Antibiotics like amoxicillin, tetracycline, and antiparasitics such as eprinomectin and doramectin pose insignificant risk. Therefore, the risk assessment depends on the individual substance, as no clear pattern emerges within substance groups, with, e.g., antibiotics represented almost across all risk categories.

Among the 12 active substances with the highest risk, 9 are exclusively used in human medicine according to our surveys. These include the anti-inflammatory drugs ibuprofen, diclofenac, and budesonide; the antibiotics clarithromycin and azithromycin; the hormonal substances dienogest, estriol, and ethinylestradiol; and the antiepileptic carbamazepine. The antiparasitics permethrin and ivermectin, which are also listed among the 12 highest-risk substances, are used in both human and veterinary medicine. The hormonal substance altrenogest is solely used in veterinary medicine.

4 Discussion

The first dataset of our study contains data on the use of veterinary pharmaceuticals on farms, encompassing the main categories of animals kept in Germany: cattle, pigs, and poultry. To the best of our knowledge, it is the first survey of all substance classes used in livestock farming in Germany that is not restricted to antibiotics. The pharmaceutical consumption of other livestock, like sheep and goats, as well as companion animals was not considered. When official data on animals kept or slaughtered in Germany in 2020 are considered, the animal categories included in our survey represent approximately 90% of all animals (Federal Statistical Office of Germany, 2021a; Federal Statistical Office of Germany, 2021b; Central Association of Zoological Specialist Companies, 2023; Fédération Equestre Nationale, 2023). Additionally, our sample of farms is based on voluntary participants due to the absence of legal reporting requirements. The farms participating in our study are distributed across 9 of the 16 federal states in Germany, with a notable aggregation in both the northwest and southern regions, mirroring the national distribution. Our data show that approximately 90 percent of the farms are located in these regions, compared to about 80 percent reported in the 2020 Agricultural Census. The representation of farms from Eastern Germany is marginally lower in our study. Consequently, we anticipated a slight underestimation of the quantity of pharmaceuticals used, reflected in the extrapolation from a sample to the entire population.

Regarding antibiotics, there exist official statistics that can be compared with our study. The sales figures of antibiotics to veterinarians in 2020 (Federal Office of Consumer Protection and Food Safety, 2021) and the antibiotic quantities from this survey show a very similar distribution for some groups, with penicillins and tetracyclines ranking first and second, respectively (see Supplementary Table S6). Additionally, the annual indicator published by the EU for antibiotic use per PCU slightly exceeds that of this survey, with 83.8 mg/PCU (European Medicines Agency, 2021) compared to 83.1 mg/PCU (see Supplementary Table S7) and 83,3 mg/PCU for the extrapolation. Although the extrapolation is derived from a sample of only 129 out of 168,833 farms, it is deemed plausible due to the comparable PCU values. Overall, Germany's antibiotic usage is slightly below the European average of 89 mg/PCU. Poland leads with 187.9 mg/PCU in 2020, followed by Italy (181.8 mg/PCU), Portugal (175.8 mg/PCU), Hungary (169.9 mg/PCU), and Spain (154.3 mg/PCU). In terms of total quantities used, Spain tops the list with 1,244.5 tonnes, followed by Poland with 853.2 tonnes. The countries with the lowest antibiotic consumption are Norway with 2.3 mg/PCU, Iceland with 3.8 mg/PCU, and Sweden with 11.1 mg/PCU (European Medicines Agency, 2021). For other substance groups, there are no official comparison values in veterinary medicine. Furthermore, there are hardly any studies available that go beyond antibiotic use and address other substance groups (Sawant et al., 2005; Kuipers et al., 2016; Hemme et al., 2018; Hommerich et al., 2019; Olmos Antillón et al., 2020; Kasabova et al., 2021). Regarding hormone use, van der Laan et al. (2021) demonstrate in their study with 760 Dutch farms a similar distribution of hormonal agents used in dairy cows. Although our data are based on a sample rather than a full census, they provide initial important insights into pharmaceutical use in livestock in Germany.

Differences in the number of pharmaceutical prescriptions or the amount of active substances used are evident across various animal categories. For instance, in dairy cows or breeding sows, the focus often lies on individual animal treatment, whereas in group-housed fattening pigs or laying hens, treatment is administered to subgroups or the entire group. In the case of antiparasitics, the leading substances in terms of quantity are typically administered orally or as pour-on preparations, necessitating higher concentrations than injections (Otranto et al., 2005). Some groups of active substances are not used in all animal species, either due to the absence of approved drugs for the respective animal category or because the disease profile does not occur in a specific husbandry system or animal category. In this study, no antiparasitic agents are used in broilers, although most broilers are infected with Eimeria species (Andreopoulou et al., 2022). Farmers

often combat these parasites using substances approved as feed additives, which are available without veterinary prescription and do not require explicit documentation (European Union, 2003; Dalloul and Lillehoj, 2006). All these reasons could account for the occasionally substantial differences in drug utilization among animal categories.

In comparing active substances used in human and veterinary medicine, it becomes apparent that a similar quantity of antibiotic agents is employed, although the distribution among substances varies. Penicillins, as first-line antibiotics, hold significant importance in both human and veterinary medicine. Alongside penicillins, tetracyclines are predominantly utilized in veterinary medicine, particularly in pig and cattle fattening (Federal Ministry of Food and Agriculture, 2019). Since entire groups are typically treated metaphylactically in these cases, the quantities of active substances used are markedly higher. Tetracyclines are less prominent in human medicine, where there is generally greater variability among substances compared to veterinary medicine. One reason for this is that newly approved antibiotics are used exclusively in human medicine. Furthermore, in Germany, legal regulations in veterinary medicine restrict the use of HPCIAs or subject their use to specific conditions (Federal Ministry of Food and Agriculture, 2009). This regulatory framework likely explains the substantially lower use of third-generation cephalosporins and fluoroquinolones in livestock compared to human medicine. In contrast, antibiotics such as aminoglycosides and macrolides, classified by the WHO as Critically Important Antimicrobials (CIAs) (World Health Organization, 2024), are used significantly more in livestock than in human medicine. This disparity may stem from the absence of stringent regulations governing the use of CIAs in veterinary medicine compared to HPCIAs.

The importance of another group of active substances, anti-inflammatory agents, also varies markedly between human and veterinary medicine. In human medicine, for instance, tablets or gels containing anti-inflammatory agents such as ibuprofen, paracetamol, acetylsalicylic acid, and diclofenac are frequently purchased over the counter in pharmacies without a prescription (Sarganas et al., 2015). All of the mentioned substances belong to the group of NSAIDs and ranked among the top 7 anti-inflammatory agents used in human medicine in our study. In veterinary medicine, the situation differs as drugs or active substances cannot be obtained without a prescription for livestock (VETIDATA, 2024). Moreover, ibuprofen and diclofenac are not approved for use in animals due to their potential for adverse effects (Scherkl and Frey, 1987; Federal Institute for Drugs and Medical Devices, 2024). While there are approved drugs for animals containing acetylsalicylic acid and paracetamol, the latter appears to play a minor role according to our findings. We can only speculate that anti-inflammatory agents, like meloxicam, are more frequently used in companion animals compared to livestock, as companion animals generally live longer and are often regarded as family members with different medical expectations. On the other hand, companion animals account for only about 10% of the animal population in Germany (Federal Statistical Office of Germany, 2021a; Federal Statistical Office of Germany, 2021b; Central Association of Zoological Specialist Companies, 2023; Fédération Equestre Nationale, 2023) and, due to their lower body weight, require smaller individual doses. Therefore, conclusions on the change in the distribution between human and veterinary medicine by including companion animals cannot be drawn, as published data on consumption in companion animals does not exist.

The differences in the use of antiparasitic substance groups between human and veterinary medicine reflect the treatment goals in both fields. In livestock, animals are often kept in close quarters in contact with their excretions. Depending on hygiene management, endo- and ectoparasites can be easily transmitted (Roepstorff and Nansen, 1994). Animals with access to pastures are even more exposed to parasitic pressure (Vanderstichel et al., 2012). Therefore, antiparasitics are used in livestock for reasons of animal welfare and food safety. The objectives of antiparasitic treatment in animals include preventing disease transmission to the animal itself, such as vector borne diseases, and also controlling the zoonotic potential of transmission from pets to humans (Baneth et al., 2016). In human medicine, the primary goal is to combat parasites directly affecting humans, such as mites (Sunderkötter et al., 2019). This is reflected in the most commonly used substances as well, such as benzyl benzoate and pyrethroids, which are used against ectoparasites.

The objectives of hormone use differ between human and veterinary medicine as well. Progestins are corpus luteum hormones and primarily used in human medicine for contraception. Nearly 70% of German women prefer hormonal contraception, with hormonal preparations being taken for up to 36 weeks per year in some cases (Balakrishnan et al., 2023). In veterinary medicine, the focus lies less on contraception and more on treatment of fertility problems or on synchronizing the sexual cycle in female animals for the issue of herd management. Progestins are therefore primarily used in sows for estrus synchronization over approximately 18 days (Wang et al., 2018; Federal Institute for Drugs and Medical Devices, 2024). Besides contraception, human medicine encompasses a variety of other indications for hormone use, such as prostate cancer and menopausal symptoms (Sweeney et al., 2015; Armeni et al., 2021), which are not relevant in livestock medicine. In Germany, hormonal substances are prohibited in all fattening animals (Federal Ministry of Food and Agriculture, 2009), and since 1996, certain hormonal growth promoters have been banned for use in all livestock throughout the EU as well (European Union, 1996). In our study, hormone use, like the use of all pharmaceuticals, could be likely underestimated. In addition to the overlooked hormonal treatment of animals, technically, the amount of active substance could not be calculated for drugs containing the natural hormone eCG, which is used in sows to influence the weaning-to-first-service interval and litter size (Sechin et al., 1999). In our study, eCG accounted for less than 5% of all hormone preparations used, which is why the underestimation remains within acceptable limits. The partial ban on hormonal substances in livestock animals on the one hand and the extensive use of hormones as contraceptives in humans on the other hand can explain the immense difference in the quantities used.

Following the markedly different applications of pharmaceuticals in animals and humans, there are differences and similarities in contamination through pharmaceutical residues found in the environment. Those refer to the remnants, byproducts, and fragments of pharmaceutical substances. Unlike intact pharmaceuticals, residues encompass metabolized or

unchanged forms of these substances and persist in the environment after initial use. According to Fick et al. (2009) surface, ground, and drinking water can be contaminated during the production process. Subsequently, pharmaceutical residues are typically excreted and introduced into surface water through sewage systems. While sewage treatment plants can remove some substances, others such as ethinylestradiol, diclofenac, propranolol, macrolide antibiotics, fluoxetine, tamoxifen, and carbamazepine are poorly removed and are thus partially discharged into water bodies (Comber et al., 2018). Additionally, wastewater is sometimes used for irrigation, and roughly 15% of sewage sludge is utilized as fertilizer. In agriculture, residues enter fields and aquatic systems through manure and dung (Hamscher and Mohring, 2012). Consequently, residues are particularly detected in soil (Monteiro and Boxall, 2009) and water samples (Hirsch et al., 1999; Kolpin et al., 2002). Improper disposal of medications also contributes to increased environmental contamination (Barnes et al., 2004; Ruhoy and Daughton, 2007; Comeau et al., 2008; Götz et al., 2015).

As the volume of consumption and the diversity of active substances in human medicine are generally much higher than in veterinary medicine, we expect to find more environmental occurrences originating from human medicine. Furthermore, given the significantly higher use of hormones and anti-inflammatory drugs in human medicine, it is likely that most of these detected preparations primarily originate from the human medical sector. However, many substances cannot be clearly attributed to just one sector. Approximately half of the veterinary medicinal substances found in the environment are used as human pharmaceuticals as well. This is not surprising, as drug development is costly, leading to only few medications being developed exclusively for the smaller veterinary market, with many being used additionally for animal treatment alongside humans. Additionally, the residues of substances found in the environment (database of the German Environmental Agency) could be connected to molecules that were not reported in the IQVIA MIDAS® data for the year 2020, or in the data from veterinary medicine in our survey. These could be substances used for the treatment of companion or other animals, which we did not survey, or substances that were used prior to 2020 (Spielmeyer et al., 2020). Additionally, the list of substances found in the environment includes metabolites and transformation products, which naturally are not found among the active substances used. Furthermore, there is a possibility that substances exist in the environment that are either currently undetectable or have not yet been investigated. More studies are needed to analyze samples from water bodies and soils to address this gap.

In environmental findings, various antibacterial and anti-inflammatory substances are most commonly encountered. Among individual active substances, diclofenac, ibuprofen, clotrimazole, sulfamethoxazole and carbamazepine, were most frequently detected in Germany. Globally, the pattern is similar, with diclofenac being the most commonly detected, followed by ibuprofen, carbamazepine, sulfamethoxazole, and naproxen (aus der Beek et al., 2016; Graumnitz and Jungmann, 2021; German Environment Agency, 2022). The environmental findings database is based on scientific publications. Given the longstanding public focus on antibiotic residues and diclofenac, there is a bias in the number of substance detections due to a higher number of research projects in these areas. Further comprehensive investigations are needed for an accurate description of residual quantities of all active substances that are relevant for measurements in the environment.

After pharmaceutical substances are found in the environment, a simple environmental risk assessment is conducted. The impact of pharmaceutical residues on both ecosystems and human health has been extensively documented, particularly concerning specific active substances or substance groups. Some substances, such as penicillins or cephalosporins, degrade rapidly in the environment, while substances like tetracyclines or fluoroquinolones tend to accumulate (Kumar et al., 2019). For example, tetracyclines accumulate in the upper soil layers over years but are scarcely leached into groundwater. In contrast, sulfonamides penetrate deeper soil layers and enter water bodies (Blackwell et al., 2007; Spielmeyer et al., 2020). The individual concentrations of pharmaceutical substances or their metabolites found in the environment are often too low to exert a direct toxic effect (Straub, 2016). However, there is evidence suggesting that chronic effects may occur and that mixtures of pharmaceuticals can have much stronger effects than individual substances (Geiger et al., 2016). Furthermore, knowledge about the effects of transformation products of pharmaceuticals is still very limited (Maculewicz et al., 2022). In addition to direct and indirect environmental impacts, antibiotic resistance genes released into the environment can affect human health as well (Larsson and Flach, 2022). The public is well aware that the use of antibiotics in both human and veterinary medicine contributes to the emergence of antibiotic resistance (Wellington et al., 2013; Bártíková et al., 2016). Additionally, the use of antiparasitic agents fosters resistance development as well, limiting their effectiveness (Charlier et al., 2022). Moreover, aquatic invertebrates face lethal poisoning upon exposure to antiparasitic agents like moxidectin during the application of manure and dung (Mesa et al., 2018). Parolini (2020) demonstrates that freshwater invertebrates are exposed to a mixture of various anti-inflammatory agents, which are toxic to them as well. Another example of the ecological impact of anti-inflammatory agents is the near-extinction of vulture populations in Pakistan due to the treatment of cows with diclofenac (Oaks et al., 2004). Even in Europe, scavenging vultures continue to succumb to residues in cattle meat (Herrero-Villar et al., 2021). When hormones enter the environment, estrogen, for instance, significantly influences fish reproduction in Canada, posing a threat to their existence (Kidd et al., 2007). Residues of oxazepam, an anxiolytic used in human medicine, demonstrably alter the behavior of perch, carrying ecological and evolutionary consequences (Brodin et al., 2013). Even banned substances like methamphetamine, whose residues reach water bodies, induce addiction and alter habitat preferences in brown trout (Horký et al., 2021). All these examples demonstrate that pharmaceuticals not only affect the target organism, but they pose a risk to the environment and the ecosystem as well.

The risk analysis indicates that not only the quantity of active substances used, as measured by the PEC value, is relevant for potential environmental hazards. While active substances such as ibuprofen and diclofenac, which are used in large quantities, are associated with a high calculated risk, substances like altrenogest,

ivermectin, or ethinylestradiol, which are deployed in significantly smaller amounts, also exhibit some of the highest values in the risk analysis. This is due to the low PNEC values of these substances. Conversely, trimethoprim, despite being used in large quantities, poses no environmental risk due to its significantly higher PNEC values. The examination of antibiotics also reveals that it is not a substance group *per se* that poses a danger to the environment, but that rather the active substances must be considered individually or within a subgroup. Thus, antibiotics are found across all three risk categories. Besides the quantities used, documented in this study, factors like the behavior of substances during manure storage in livestock farming are important. For instance, tylosin, penicillin, and nicarbazin persist in manure for a few days, whereas ivermectin, chlortetracycline, and amprolium can remain for months (Sommer et al., 1992; Loke et al., 2000; Gavalchin and Katz, 2020). Once in the environment, chemical properties such as water solubility, volatility, and sorption, as well as environmental factors like pH, play crucial roles (Boxall et al., 2003). However, this study focuses on providing an overview of quantities used and does not include these considerations.

With four substances, the group of hormones is the most represented among the 12 substances with the highest risk. This predominance is likely attributable to the high reactivity of these substances, even at minimal doses. Gunnarsson et al. (2019) demonstrated that hormones, due to their low PNEC values, frequently exhibited high risk quotients. Consequently, extended environmental compatibility studies are mandated during the approval process for hormonal substances (European Medicines Agency, 2024). For ethinylestradiol, identified as the substance with the highest risk in this study, Desbiolles et al. (2018) also determined a high risk, and numerous studies document its effects on non-target organisms. For instance, ethinylestradiol impacts the reproduction and energy metabolism of mussels (Almeida et al., 2020), the hemoglobin balance of amphibians (Garmshausen et al., 2015), and the reproductive system and fertility of fish (Aris et al., 2014).

Following hormonal substances, anti-inflammatory substances constitute the second most frequent group among the 12 high-risk substances, with three substances. Unlike hormonal substances, this is not primarily due to a very low PNEC value, but rather to a high PEC value, indicating substantial usage quantities. In 2020, hormonal substances were used at a rate of 3.2 mg/kg body weight, while anti-inflammatory substances were used at 572.8 mg/kg body weight in human medicine. Commonly used substances include ibuprofen and diclofenac, which are available over-the-counter in Germany. Ashfaq et al. (2017) also demonstrated a high risk value for these substances in their risk analysis for Pakistan. Ibuprofen can have toxic effects on organisms in aquatic ecosystems (Parolini and Binelli, 2012), generating radicals that lead to oxidative stress in tissues, such as those of zebrafish (Sánchez-Aceves et al., 2021). In addition to its already mentioned impact on vulture populations in Asia (Oaks et al., 2004) diclofenac also has negative effects on other organisms, such as its toxic impact on water fleas and zebra mussels (Parolini et al., 2011; Du et al., 2016).

Among the 12 highest-risk substances, the group of antiparasitics is the third most represented, with the substances permethrin and ivermectin. In Germany, antiparasitics are used in significantly smaller quantities compared to antibiotics or anti-inflammatory substances, with only 36.52 tonnes used annually. However, due to their properties, they pose an increased environmental risk. Permethrin is used worldwide and primarily induces oxidative stress, resulting in neurotoxic, immunotoxic, cardiotoxic, and hepatotoxic effects on both humans and animals (Wang et al., 2016). Ivermectin can have adverse effects on soil, negatively impacting the survival and reproduction of predatory mites and earthworms (Römbke et al., 2010).

Among the 12 highest-risk substances are the antibiotics clarithromycin and azithromycin, both of which belong to the macrolide group. These substances are not approved for animals. Accordingly, these substances were not used on farm animals in our survey (VETIDATA, 2024). Macrolides can affect functions such as growth, food intake, and energy metabolism in non-target organisms (Rhee et al., 2013). For example, azithromycin inhibits the feeding behavior of zooplankton and nutrient accumulation in Daphnia magna (Li et al., 2020). Desbiolles et al. (2018) also reported a high risk for these two macrolides. Additionally, they identified an increased risk for amoxicillin and trimethoprim, findings which we were unable to corroborate.

Lastly, the antiepileptic substance carbamazepine is also among the 12 highest-risk substances. Carbamazepines can exert various toxic effects, such as neurotoxicity and hepatotoxicity, on non-target organisms (Baali and Cosio, 2022). However, toxicological studies typically use much higher concentrations than those expected in the environment, so individual substances found in the environment rarely have acute effects. Nevertheless, the combined effects of mixtures of substances, such as carbamazepines and other compounds, can be potentiated (Juhel et al., 2017). Earl et al. (2024) determined a risk quotient greater than 1 for carbamazepine, indicating a probable threat to human health. In contrast, Desbiolles et al. (2018) did not identify any risk associated with carbamazepines.

Our calculation of the risk quotient assumes a worst-case scenario. It presupposes that 100% of active substances used is released into the environment, and that 100% of the residues deposited on soils are transported into the groundwater. For example, in the case of ivermectin, substances such as monosaccharide-, aglycone derivatives, and 24-hydroxymethyl metabolites are additionally excreted (Fink and Porra, 1994), each possibly having different environmental impacts than the original active substance. Moreover, the behavior of the active substance in the environment and its ability to degrade are not considered. Penicillins such as amoxicillin are rapidly degraded in the environment, whereas tetracyclines tend to accumulate in soil (Kumar et al., 2019). Therefore, there are numerous factors influencing the behavior of a substance in the environment that could not be considered here, partly due to a lack of data. Additionally, the development of antibiotic-resistant pathogens is among the ten greatest threats to human health. Neither the potential for emerging resistances nor the enhanced efficacy of active substance mixtures (Geiger et al., 2016) are incorporated into risk assessments. The risk quotient only accounts for the direct toxic effects on non-target organisms in the environment. Overall, PNEC values could be calculated for only a fraction of the substances used in Germany. Pharmaceutical companies are required to provide detailed information for an environmental impact assessment only under certain conditions during the authorization process (European Medicines Agency, 2006; European Medicines Agency, 2016; European Medicines Agency, 2024). Consequently, only few values are available for calculation (Giunchi et al., 2023). Nevertheless, this risk analysis

provides an initial overall impression of environmentally relevant substances from veterinary and human medicine.

5 Conclusion

In our study, we quantified the use of pharmaceuticals in Germany and compared the utilized groups of active substances between human and veterinary medicine. Substantial differences were observed in both the substances administered and the treatment strategies. These differences exist not only among different animal categories but between animals and humans as well. We demonstrate that there are several pathways for pharmaceuticals to enter the environment and many substances already being found in the environment. However, the risk posed by individual substances in the environment can only be assessed to a limited extent, while its complexity has not yet been conclusively clarified and requires further research efforts.

As demonstrated, there are no reliable official data on pharmaceutical consumption in veterinary medicine in Germany. It is therefore necessary to discuss the obligation of pharmaceutical industry to disclose production numbers and the central digital recording of consumption data. In addition, more research is needed to assess which entries occur and to analyze the specific pathways and persistence of individual substances in the environment. This can help comprehensively evaluate the direct and indirect risks of individual substances and combinations of pharmaceuticals to the environment and, consequently, to humans.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

MA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing–original draft, Writing–review and editing, Supervision. JB: Formal Analysis, Methodology, Software, Validation, Visualization, Writing–original draft, Writing–review and editing, Data curation. FT: Conceptualization, Funding acquisition, Writing–review and editing. AH: Project administration, Resources, Validation, Writing–review and editing, Conceptualization. MH: Conceptualization, Funding acquisition, Supervision, Validation, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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