Health Care Without Harm

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VETERINARY MEDICINE IN EUROPEAN FOOD PRODUCTION: PERSPECTIVES ON THE ENVIRONMENT, PUBLIC HEALTH, AND ANIMAL WELFARE

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INTRODUCTION

Medicines are essential tools in the treatment of diseases in humans and in animals. However, some of them are frequently misused in food-producing animals to compensate for poor hygiene and sustain irresponsible farming practices that favour profits over the environment, human health, and animal welfare.

Veterinary medicines, such as antibiotics and antiparasitics, can enter terrestrial and aquatic environments throughout their life cycle. They can accumulate in plants and non-target animals, have adverse effects on ecosystems and contaminate water and food, including drinking water. Antimicrobial residues in the environment can also contribute to the development and spread of antimicrobial resistance (AMR).

This report assesses trends in veterinary medicinal use, identifies impacts of veterinary medicines on the environment, public health, animal welfare issues, and highlights provisions in the upcoming EU regulatory framework that will require changes in veterinary medicinal use in the context of the EU Farm to Fork Strategy.

It demonstrates that there is a need for a systemic change in the way food is produced in Europe and makes recommendations for the food production sector to move towards a health-oriented system that allows for responsible veterinary medicinal use.

Research carried out for this report is the result of a first formal collaboration between Health Care Without Harm (HCWH) Europe and Pesticide Action Network (PAN) Germany, two organisations that advocate for stronger rules to tackle pharmaceutical pollution from a healthcare and food production perspective, respectively.

This partnership mirrors the 'One Health' approach, which recognises that the health of humans, animals, and the environment are interconnected and that a cross-disciplinary, collaborative effort is needed to ensure health for people, animals, and the environment.

Medicines are frequently misused to sustain farming practices that favour profits over the environment, human health, and animal welfare.

Nearly 90% of antimicrobial products used in European farm animals are typically used for group treatment.

VETERINARY MEDICINE USE IN EUROPEAN FOOD PRODUCTION

The primary veterinary medicines used in food-producing animals include antibiotics to treat bacterial infections, antiparasitics to treat parasite infestation, vaccines against certain diseases, and hormones to stimulate certain body functions. This section provides an overview of medicines used in livestock farming and aquafarming, with a focus on antibiotics and antiparasitics.

LIVESTOCK FARMING

Due to insufficient data available in the EU, it is challenging to give a comprehensive overview of the amount or types of drugs used in livestock farming, as well as the active substances they contain. Only sales data for antimicrobials are collected and published, but this does not include information on use by animal species.[1] In addition, the frequency of therapies is only recorded in some European countries and some production sectors. In Germany, for example, the governmental database 'Hi-Tier' only contains data on drugs used for animal fattening.[2]

While diseases in humans are treated individually, veterinary medicines are largely applied prophylactically or metaphylactically to food-producing animals, through feed or water supplements. Nearly 90% of antimicrobial products used in European farm animals are typically used for group treatment.[3] Veterinary medicines are therefore not only used on sick animals but also on healthy animals to avoid outbreaks of disease.

Prophylaxis

Preventive treatment: treating individuals or groups of animals, with no sign of infection or infectious disease, to prevent the occurrence of infections or infectious diseases.

Metaphylaxis

Control treatment: treating a group of animals to prevent the spread of an infection or infectious disease within a group following diagnosis in individuals or part of the group.

Antibiotics

Sales patterns for antimicrobial agents vary widely between European countries based on production sectors and husbandry practices, but overall antibiotics are the ones sold in the highest volume. In 2020, penicillins (31.1%), tetracyclines (26.7%), and sulfonamides (9.9%), which are all antibiotics, were the largest categories of antimicrobials sold in Europe.[4]

In livestock production, antibiotics are used for prevention or treatment of diseases caused by bacterial infections such as diarrhoea, pneumonia, tuberculosis, and certain skin diseases. Although all antibiotics approved for the treatment in animals are subject to prescription, group treatment implies a high use of antibiotics that contribute to antimicrobial resistance (AMR). This is of particular concern when antibiotics used in animal production are also of great importance for curing serious bacterial infections in human medicine.

Antibiotics used in both human and veterinary medicine and considered the highest priority among the critically important antimicrobials by the World Health Organisation (WHO) include cephalosporins (3rd, 4th and 5th generation), glycopeptides, macrolides, ketolides, polymyxins, and quinolones.[5]

Two examples of crucially important antibiotics that are misused in food production:

Colistin (a polymyxin) is often used to treat and prevent diarrhoea in piglets caused by stress after early weaning.[6,7] Colistin is also used as a last-resort antibiotic in human medicine to treat life-threatening infections caused by carbapenem-resistant *Enterobacteriaceae*. Within Europe, colistin is currently used much more in food-producing animals than in humans.[8]

Fluoroquinolones are used to treat colibacillosis in poultry.[9] They are also used to treat infections with *Campylobacter* species in humans, the most common foodborne infection in the EU, often caused by contaminated poultry meat.[10] Resistant *Campylobacter* germs that enter the food chain can no longer be treated with fluoroquinolones.[11]

Ionophores

Ionophores are used in poultry and cattle to treat intestinal parasitic diseases and bacterial infections. Despite their antibiotic effect, they are not classified as antibiotics in the EU because they are not considered medically important due to their toxicity to the human organism. This means that they do not require a prescription for use in animals.

Products of animal origin treated with ionophores can therefore be declared as 'reared without antibiotics' in the EU.[12] Whilst sales of medically important antimicrobials for humans in veterinary medicine have decreased in Europe, a high increase of sales of ionophores has been observed in some countries, such as the United Kingdom.[13]

Antiparasitics

Livestock worldwide are susceptible to infestation from diverse parasitic fauna. Parasites are usually treated with antiparasitics and, like antibiotics, they are used either for treatment or for prevention.

Internal parasites (endoparasites) such as stomach, intestinal, and lung roundworms are among the most significant infectious agents of grazing animals. Most medicines used in cattle, sheep, and horses to treat endoparasites are applied by feed additives and contain active ingredients such as ivermectin, doramectin, and fenbendazole.[14]

Flies, lice, mites, and ticks are among the most concerning external parasites (ectoparasites) of grazing animals.[15] Several species of ectoparasites are also vectors of zoonotic pathogens that are transmissible to humans.[16] Ectoparasiticides for infestation treatment are mainly applied as pour-ons or spot-ons and comprise macrocyclic lactones, including avermectins (such as ivermectin) and milbemycins, pyrethroids such as deltamethrin, and organophosphate such as phoxim.[17]

As with antibiotics, significant resistance has developed against certain antiparasitics such as benzimidazole, levamisole, and ivermectin.[18]

Up to 75% of antibiotics may be lost into the surrounding environment in aquafarming.

AQUAFARMING

Over 90% of EU aquafarming production is generated by only six commercial species: salmon, trout, oysters, seabass, gilt-head seabream, and mussels.[19]

In the EU, over 30% of veterinary medicines authorised for fish are used for salmon alone. The next highest groups are 20% for rainbow trout and 18% for species such as ornamental fish, carp, turbot, and gilthead.[20] When applying veterinary medicines in aquafarming, responsible management is particularly important because individual treatment is not possible.

Parasite infections are the main cause of concern in all farmed fish species. They are at higher risk due to increased dispersal caused by unnaturally high population densities.[21] Secondary bacterial infection can also follow parasitic infestation. Yet treatment with veterinary medicines against parasites often lacks efficacy due to the development of resistances and limited access.[22] For this reason, parasite infestations are insufficiently cured and antibiotics are used to treat or even prevent secondary bacterial infections.

Of the 304 veterinary medicines authorised for fish in the EU in 2018, only 2% were classified as antiparasitics. The majority consists of vaccines (51%) followed by antibiotics (29%).[23]

To address drug shortages in aquafarming, antibiotics approved for use in terrestrial livestock are being repurposed for fish, for example, oxytetracycline is commonly used whilst it has been attributed to genotoxic and eco-toxic effects in aquatic ecosystems.[24]

To control equipment and water quality, common aquafarming practices use chemical substances such as disinfectants and antifouling agents. More than 170 active substances, mixtures, and natural extracts are used in aquafarming worldwide. Although these substances are assigned to different purposes, they are all aimed at killing certain organisms and can therefore be understood as pesticides in the broadest sense.[25]

IMPACTS OF VETERINARY MEDICINE IN FOOD PRODUCTION

Veterinary medicines can have negative impacts on non-target plants and animals and on human health when in the environment. They can also be misused to sustain intensive farming practices that negatively affect the health of food-producing animals by design.

ENVIRONMENTAL IMPACTS

Veterinary medicines can enter terrestrial and aquatic environments during production, through direct excretion by animals in pastures and by fish in water, and through the application of contaminated slurry and manure on agricultural land. Medicines in the environment can reach water bodies via surface runoff and drainage or leach into groundwater.[26]

The effect of medicines is not limited exclusively to the target organism. Metabolites and up to 90% of the non-degraded active substances are excreted by animals.[27] In aquafarming, up to 75% of antibiotics may also be lost into the surrounding environment.[28]

Determining the origin of medicines in the environment is difficult, as some active ingredients are used in both human and veterinary medicine. According to a pilot project in Northwest Germany, environmental contamination with veterinary medicines can, however, be expected in regions with high livestock densities.[29] Veterinary antibiotic residues have been detected in agricultural fields as well as in plants, including wheat grain.[30]

While it is widely recognised that medicines contribute significantly to the contamination of freshwaters, new evidence was provided on the transfer of active substances from medicines from aquatic to terrestrial ecosystems.[31]

Once released in the environment, medicines and their metabolites can negatively affect non-target species and whole ecosystems due to their specific properties.[32] Persistent, bioaccumulative, and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances pose a serious risk to the environment due to their ability to accumulate in living organisms and their toxicity to non-target animals.[33]

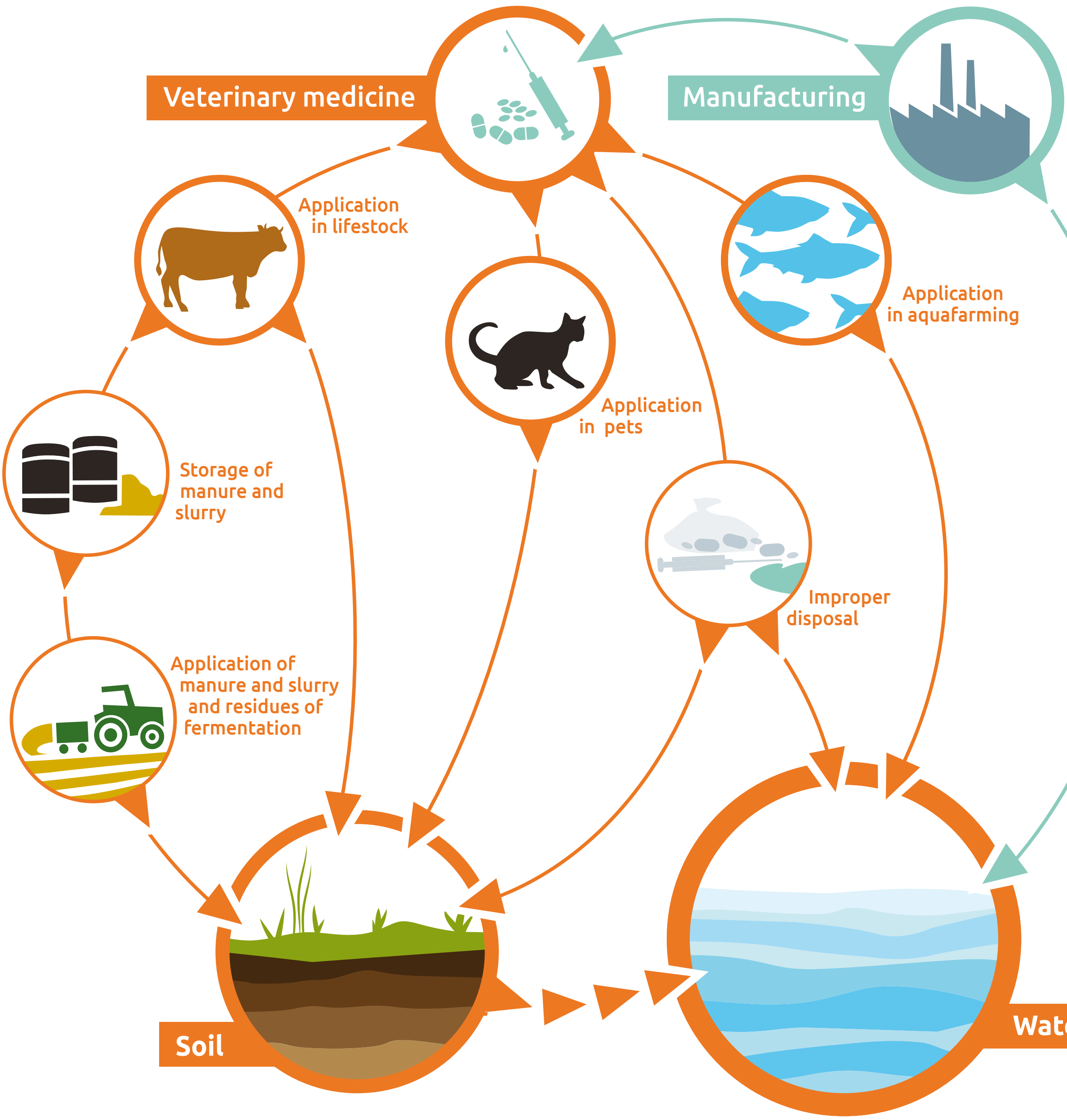
Open aquafarming facilities are linked to a significant decline in species diversity in their immediate environment because medicines and other chemicals, such as pesticides, are directly released into the aquatic environment.[34]

Beneficial insects can be harmed by antiparasitics. Pyrethroids, such as deltamethrin, are highly toxic to bees, for example. Antiparasitics can reduce manure decomposition to an extent that the pasture will no longer be accepted by grazing animals. Insect feeding animals may take up contaminated dung fauna and harmful substances may then enter the food chain.[35]

The steroid hormone altrenogest, used in pig breeding for oestrus synchronisation, can have strong effects on fish reproduction and can shift the sex ratio in favour of male fish when entering aquatic ecosystems.[36]

Antibiotics can inhibit the growth of plants and primary aquatic producers such as algae and cyanobacteria.[37] They can also affect the composition of microorganisms in soils, which can negatively affect soil fertility and nitrate degradation.[38]

ENTRY PATHWAYS AND DISTRIBUTION



Environmentally persistent pharmaceutical pollutants

The 4th International Conference of Chemicals Management (ICCM4) identified Environmentally persistent pharmaceutical pollutants (EPPPs) as a new emerging policy issue within the Strategic Approach to International Chemicals Management (SAICM) in 2015. In its final resolution, ICCM4 recognised "the potential adverse effects associated with exposure to EPPPs on human health and the environment and the need to protect humans and ecosystems".[39]

In 2020, the UN's *Assessment Report on Issues of Concern* recommended to expand "the scope from EPPPs to pharmaceuticals in the environment in order to include those pharmaceutical pollutants that may accumulate in the environment due to continuous use and releases, and those that may cause effects that are difficult to reverse, such as antimicrobial resistance".[40] There are, however, currently no criteria within SAICM for defining pharmaceutical pollutants as EPPPs or even pharmaceuticals in the environment.

HUMAN HEALTH IMPACTS

Veterinary medicines can accumulate in crops, vegetables, and non-target animals and can ultimately end up in drinking water through the water cycle. This means humans can be unintentionally exposed to veterinary medicines when drinking water and consuming food.

There is scientific evidence that low concentrations of pharmaceutical residues in the environment can have adverse effects on animals and other organisms.[41] This raises questions about how humans can be affected by continuous, long-term exposure to low levels of medicines.

There have been particular concerns about exposure to medicines through drinking water due to potentially long exposure times and data gaps on exposure effects to both individual substances and mixtures. While studies showed that adverse human health impacts are unlikely, the precautionary principle should prevail.[42]

Antimicrobial use in animals can also drive the development and spread of antimicrobial resistance (AMR), a process where microorganisms (such as bacteria) develop resistance to medicine. AMR makes infections harder to treat and increases the risk of disease spread, severe illness, and fatality.

Scientific evidence shows correlations between antimicrobial use in food-producing animals and AMR in humans. For example, a significant positive association was found between the consumption of fluoroquinolones and other quinolones in animals and resistance in invasive *E. coli* and in *C. jejuni* bacteria found in humans.[43] Studies show aquafarming environments in most countries also present high levels of resistance.[44]

Manufacturing discharges, runoff waste from slaughterhouses and farms, and animal waste used as fertiliser all contribute to making the environment a reservoir for AMR, particularly areas with inadequate water, sanitation, and hygiene (WASH).[45]

Antimicrobial resistance (AMR)

Antimicrobial resistance is annually responsible for 33,000 deaths and € 1.5 billion in healthcare costs and productivity losses in the EU.[46] Nearly 40% of the health burden of AMR in the EU is already caused by bacteria resistant to last-resort antibiotics.[47] If no effective action is taken, AMR could cause 390,000 deaths in Europe by 2050.[48]

THE ISSUE OF ANIMAL WELFARE

In the EU, food producers must protect the welfare of animals under their care and ensure that those animals are not caused any unnecessary pain, suffering, or injury.[49]

Whilst veterinary medicines are necessary tools to treat sick animals and ensure their welfare, they are not just used to cure diseases and to alleviate pain. Many are used to support desired bodily functions such as dry cow treatment, fattening gain, or rutting synchronisation. In Germany, approximately 80% of dairy cows are treated with antibiotics against possible infections during the usual drying off period before calf birth.[50]

Indoor housing systems are known to be more stressful for animals. Higher volumes of noise, odour pollution, dust levels, as well as lack of light and individual space have all been linked to weakening animals' immune systems and promoting the spread of disease, that not only lead to a higher reliance on the use of veterinary medicines for treatment, but the anticipation of increased disease also leads to the disputed preventative use of medicines.[51]

Using veterinary medicines to compensate for poor animal husbandry comes at the expense of animal welfare.

Using veterinary medicines to compensate for poor animal husbandry comes at the expense of animal welfare. Year-round housing, wet litter, restricted mobility and the limitation of natural behaviour increase the risk of infections such as claw diseases, mastitis, metritis, dystocia, and ketosis in dairy cows.[52,53] Poor air circulation, and the consequent harmful gases and germs, have been shown to significantly increase the occurrence of respiratory diseases in the rearing of calves.[54]

Husbandry measures that increase animal welfare, such as more space from lower stocking density or improved housing climate, demonstrably lead to reduced germ pressure and contribute to reduced disease rates in pigs.[55] Regular access to fresh air and sunlight positively affects animals' immune systems, which improves their resilience.[56] There is scientific evidence that alternative preventive measures such as later weaning, better hygiene, and more intensive animal care, could also significantly reduce the need for antibiotics, such as colistin, during the entire lifetime of pigs.[57,58]

Thanks to higher animal welfare standards, lower levels of antibiotic use in livestock are being achieved in organic farming in comparison.[59,60] These include a range of higher animal husbandry standards related to individual space, floor condition, exercise area, and litter.

Husbandry measures that increase animal welfare contribute to reduced disease rates in pigs.

THE NEW EU REGULATORY FRAMEWORK ON VETERINARY MEDICINES

The EU regulatory framework on veterinary medicines is evolving to adapt to scientific progress and current market conditions, while seeking to ensure continued protection of the environment, public health, and animal welfare. A number of new rules will require changes in practice for veterinary medicinal use in the EU.

THE FARM TO FORK STRATEGY

The Farm to Fork Strategy, adopted on 20 May 2020, identifies targets and describes upcoming initiatives in relation to veterinary medicines to accelerate the transition to a sustainable food system:

- ► Reduce overall EU sales of antimicrobials for farmed animals and in aquafarming by 50% by 2030, through the new Regulations on Veterinary Medicinal Products and Medicated Feed.
- ► Revise the animal welfare legislation to ensure a higher level of animal welfare to improve animal health and food quality, reduce the need for medical treatment, and help preserve biodiversity through:
  - Strategic Plans and new EU strategic guidelines on aquafarming.
  - Potential options for animal welfare labelling.
- ► Make at least 25% of the EU's agricultural land organic by 2030 and significantly increase organic aquafarming through a new action plan on organic farming.

THE LEGISLATION ON VETERINARY MEDICINAL PRODUCTS AND MEDICATED FEED

The legislation on Veterinary Medicinal Products and Medicated Feed aims to provide for a wide range of measures to fight antimicrobial resistance (AMR), promote the availability of veterinary medicines, establish a fit-for-purpose legal framework for veterinary medicines, and ensure an economically-viable production of safe medicated feed.[61]

The Regulation on Veterinary Medicinal Products (Regulation 2019/6)

This regulation, which enters into force on 28 January 2022, updates the previous regulatory framework on veterinary medicines with the following key rules:

- ► Member States must collect relevant and comparable data on the volume of sales and the use of veterinary antimicrobials used for all food-producing animal species within five years.
- ► Marketing authorisation holders must update relevant environmental safety documentation for veterinary medicines identified as potentially harmful to the environment that were authorised before 1 October 2005 without environmental risk assessment.

- The supply of a veterinary medicinal product can be prohibited or ceased if the benefit-risk balance points to a risk for public health, animal health, or the environment.
- Member States must ensure that appropriate systems are in place for the collection and disposal of waste of veterinary medicines.
- The quantity of the medicinal products prescribed must be limited to the amount required for the treatment or therapy concerned.

This regulation also strengthens the rules governing the use of veterinary antimicrobials in the fight against AMR:

- Antimicrobials can no longer be applied routinely, nor used to compensate for poor hygiene, inadequate animal husbandry, lack of care, or poor farm management.
- Antimicrobials can no longer be used to promote growth or to increase yield (the previous ban was limited to antibiotics).
- Antimicrobials can no longer be used for prophylaxis, other than for an individual animal or a restricted number of animals when the risk of an infection or of an infectious disease is very high with likely severe consequences.
- Antimicrobials can no longer be used for metaphylaxis, except when the risk of spread of an infection or of an infectious disease in the group of animals is high and there are no appropriate alternatives available. In these cases, prescriptions can only be issued after a diagnosis by a veterinarian (derogations possible).
- Antimicrobials can only be prescribed for a limited duration to cover the period of risk in the cases of prophylaxis or metaphylaxis use.
- A list of antimicrobials or groups of antimicrobials will be designated as reserved for human medicine.
- The ban on antimicrobial use for growth promotion and the list of antimicrobials or groups of antimicrobials reserved for human medicine will also apply to third-country operators exporting to the EU.

Zinc oxide

Veterinary medicines containing zinc oxide are often used for the treatment, prevention, and control of post-weaning diarrhoea in piglets.

As part of Directive on the Community code relating to veterinary medicinal products (Directive 2001/82/EC), which the Regulation on Veterinary Medicinal Products is repealing, the European Commission decided in 2017 to withdraw all marketing authorisations for veterinary medicines containing zinc oxide administered orally to food producing animals.

This decision was taken due to concerns related to environmental risk and the potential increase of prevalence of antibiotic resistant bacteria from the use of products containing zinc oxide. It will come into force on 26 June 2022.

Monograph system

The new regulation considers an active substance-based review, or monograph system for the environmental risk assessment of veterinary medicines, to replace the current product-based environmental risk assessment of veterinary medicines, including for those authorised on the market before 1 October 2005.

This monograph system would result in a more consistent and up-to-date assessment while saving resources, protecting animal welfare, and improving the availability of environmental data on substance assessment.

A recent feasibility study commissioned by the EU Commission concluded that the monograph system is justified and proportionate and that, whilst it would be more expensive and resource-intensive in the short term, the benefits should overbalance the disadvantages in the long term.[62]

The Regulation on Medicated Feed (Regulation 2019/4)

This regulation, which enters into force on 28 January 2022, updates the regulatory framework on medicated feed with the following key rules:

- Medicated feed requires a veterinary prescription and a clinical examination of the animal(s) by a veterinarian (derogations possible).
- The duration of a treatment in medicated feed must comply with the summary of product characteristics (SmPC) of the veterinary medicines in the feed. The

SmPC contains data on the pharmaceutical form and strength, indications, dosage, efficacy, side effects, drug interactions, and contraindications of the preparation. When not otherwise specified, the duration of the treatment through medical feed cannot exceed one month for all veterinary medicines or two weeks when containing antibiotic veterinary medicine.

- Veterinarians are no longer allowed to prescribe medicated feed with more than one veterinary medicinal product containing antimicrobials.
- Prophylaxis, or use of medicated feed to enhance the performance of animals, is no longer allowed (exceptions exist for medicated feed with antiparasitics and immunological veterinary medicines).
- The use of medicated feed containing antimicrobials for metaphylaxis is only possible when there is a high risk of an infection or of an infectious disease spreading.
- Member States must ensure that appropriate collection or discard systems are in place for expired medicated feed.

The Farm to Fork Strategy aims to accelerate the transition to a sustainable food system in the EU.

SYSTEMIC CHANGE IS NEEDED

Veterinary medicines play an essential role in ensuring animal health, yet they can have negative impacts on ecosystems and human health. They can also be misused to uphold unsustainable, intensive farming practices that prioritise profits over animal welfare.

There is a crucial need to implement health-oriented food systems based on animal health, which ensure responsible use of veterinary medicines. Husbandry and aquafarming systems need to adapt to the demands of animals – not the other way around.

The EU regulatory framework on veterinary medicines, which comes into force in January 2022, aims to adapt to scientific progress and new market conditions, while ensuring a high level of protection for public health, animal welfare, and the environment.

The framework introduces new rules across the EU on veterinary medicines, particularly on antimicrobials, which will no longer be allowed to compensate for poor hygiene, inadequate animal husbandry, or poor farm management. This ambition is supported by a 50% reduction target for the sales of antimicrobials for farmed animals and in aquafarming by 2030.

To comply with this updated regulatory framework and safeguard human, animal, and environmental health, health-oriented actions urgently need to be taken. A business-as-usual scenario is no longer possible. Measures to sustain animal health, which do not solely rely on veterinary medicines, need to be implemented on a large scale.

Recommendations for the food production sector

Health Care Without Harm (HCWH) Europe and Pesticide Action Network (PAN) Germany recommend the following measures to move towards a health-oriented system that provides for a responsible use of veterinary medicines and embraces the 'One Health' approach, which recognises that animal health is interconnected with both human and environmental health.

- **Restrict the use of veterinary medicines for the treatment of livestock and fish to medical necessity.**
- **Improve animal welfare and reduce stress levels through measures such as rearing animals in outdoor spaces, introducing longer weaning periods, and lowering stocking density.**
- **Adopt more stringent surveillance and prevention measures and improve hygienic conditions in farms to increase biosecurity.**
- **Include robustness and resilience as breeding criteria to allow animals to grow up healthier and require less medication.**
- **Adopt alternatives to the use of veterinary medicines, in particular antiparasitics and antibiotics, including vaccination and biological methods.**
- **Engage in labelling initiatives that ensure high standards of animal welfare in livestock and aquafarming to create transparency for consumers.**

A health-oriented food production system will provide for a responsible use of veterinary medicines.

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