Veterinary Excipients in the Environment: Regulatory Blind Spots, Unanswered Questions, and Agricultural Sustainability — A Critical Review

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ABSTRACT

Veterinary excipients make up 60 to 90 percent of most drug formulations. Yet current environmental risk assessment frameworks focus almost exclusively on active pharmaceutical ingredients. Regulators legally consider excipients as "inert" substances. This review challenges that assumption.

We examined 26 studies published between 2002 and 2026. The evidence shows that many excipients are not inert. Some surfactants like polyethoxylated tallow amine are thousands of times more toxic than active ingredients. A large-scale screening study identified 25 excipients with biological target activities, including thimerosal with dopamine receptor binding at 210 to 320 nM.

Environmental fate data reveals serious problems. Synthetic polymers like polyvinylpyrrolidone and polyvinyl alcohol show negligible biodegradation. PVP exhibits only 1 to 4 percent degradation in soil. It simply dissolves and disperses into water compartments. These polymers accumulate in rivers at concentrations of 0.16 to 0.18 mg/L.

Current monitoring systems do not measure excipients. The EU Rapid Alert System targets only pharmacologically active substances. Analytical methods are validated for active ingredients only. No maximum residue limits exist for excipients, despite the official definition of drug residues explicitly including them.

Regulatory frameworks have other blind spots. Mixture effects between excipients and active ingredients are ignored. Legacy products authorized before environmental risk assessment guidelines were adopted have never been reviewed. Pharmacovigilance requirements for environmental effects remain undefined. Compliance with risk mitigation measures has no legal consequences.

Some solutions exist. Biodegradable excipients from marine and renewable sources can reduce environmental persistence. Life cycle assessments show 40 to 60 percent emission reductions with green alternatives. But no veterinary-specific regulations require their use.

This review concludes that veterinary excipients represent a critical regulatory blind spot. We recommend mandatory environmental risk assessment for excipients, including biodegradability testing. Monitoring programs should be established for excipients in manure, soil, and water. Until these changes occur, veterinary excipients will remain an unregulated threat to agricultural sustainability.

Keywords: Veterinary excipients, environmental risk assessment, regulatory blind spots, agricultural sustainability, mixture effects, biodegradation

1. INTRODUCTION

Veterinary medicinal products are used in large volumes across Europe. In German livestock production, antibiotics and antiparasitics account for about 90 percent of all usage [1]. Critical unanswered questions remain. These include how to evaluate substances with high persistence but low ecotoxicity, to what extent metabolites should be assessed, and how to handle parent compounds alongside their breakdown products [1].

Risk mitigation measures exist for veterinary products. These include manure storage time, stocking density, ploughing depth, and fraction of herd treated. A catalogue of 19 practical measures has been developed. However, compliance has no legal consequences, unlike for pesticides [2].

The main problem concerns excipients. While active ingredients are strictly regulated, formulation additives are legally considered "inert." They face less stringent requirements. Numerous studies show these adjuvants can be toxic and exhibit additive or synergistic effects. Some surfactants are thousands of times more toxic than the active ingredient itself. Current monitoring systems exclude excipients entirely. Environmental fate data is scarce, yet they enter soils and can persist under anaerobic conditions [3].

The main environmental pathways are manure, slurry, dung, and urine. Yet consistent environmental risk data has never been generated for many veterinary products. Approximately 2000 products containing 741 active substances exist in the EU. This lack of data underscores the need for systematic assessment of excipients [4].

There is also a legacy problem. Products authorized before ERA guidelines were adopted have never been reviewed. Standard ERA focuses on expected toxic effects. But non-expected effects like vulture decline due to diclofenac reveal framework failures. Antiparasitics like ivermectin are highly toxic to dung fauna. Monitoring data remains extremely limited. A critical re-evaluation of legacy products and their excipients is needed [5].

Current frameworks ignore mixture effects. They assess each active ingredient individually, lagging behind pesticide regulations. Pharmaceutical mixtures include excipients like preservatives and surfactants. These possess substantial ecotoxicity. Exposure-based cut-off criteria are problematic because low concentrations of non-toxic compounds may combine to produce effects. A tiered approach summing risk quotients is recommended, but requires excipient data not currently generated [6].

A critical regulatory asymmetry exists. Serious environmental risk can lead to refusal for veterinary products, but not for human medicines. ERA guidelines focus exclusively on active ingredients. Excipients are mentioned only "if indicated." For generic and existing substances, no systematic data generation is required. Pharmacovigilance requirements remain undefined [7].

Topical formulations present additional concerns. No specific safety assessment is mandated for excipients. Excipients like propylene glycol can be toxic in certain species. Topical treatments enter water through runoff and bathing. Fipronil and permethrin are detected at concerning concentrations, but excipient contributions remain unmonitored. EU Regulation 2019/6 requires ERA for veterinary products, but excipients are evaluated only for quality and safety, not ecotoxicity. The EMA Note for Guidance requires excipient justification for stability, not environmental fate [8].

The official definition of drug residues includes excipients and their degradation products. Yet regulations focus almost exclusively on active substances. Studies confirm tetracyclines and fluoroquinolones in manure-based fertilizers at concerning concentrations. Dust from livestock facilities contains up to five antibiotics at 12.5 mg/kg. Excipients are not monitored. Analytical methods are validated for active ingredients only. No monitoring programs or MRLs exist for excipients [9].

The environmental role of excipients remains uncharacterized. Fipronil and imidacloprid are detected in over 60 percent of UK river samples above chronic toxicity thresholds. No monitoring exists for accompanying excipients. No veterinary-specific frameworks exist for excipient ecotoxicity, despite evidence their persistence may exceed that of active ingredients [10].

The term "ecopharmacology" recognizes that pharmaceuticals share common environmental pathways. Yet excipients are absent from this framework. Drugs are designed to be recalcitrant. Both active ingredients and excipients persist, but only active substances are monitored. ERA guidelines have existed since 2005 but focus exclusively on active ingredients [11].

For veterinary products, excipients do not undergo rigorous ERA. Comprehensive frameworks exist for human excipient safety, but no equivalent for veterinary excipients dispersed through manure, urine, and direct application [12].

Companion animal parasiticides provide a clear example. Of six common UK products, ecotoxicity evidence exists only for two. Fluralaner is excreted 90 percent unchanged and persistent in soil, but no ecotoxicity studies on non-target invertebrates were identified. Regulatory assessments assume negligible exposure. No evidence exists that pet owners comply with mitigation instructions. The cumulative impact of millions of doses, combined with zero consideration of excipients, represents a major gap [13].

One study assessed 35 excipients from pharmaceutical production. Risk characterization ratios were below 1, indicating no significant risk from production losses. However, for 184 excipients, sufficient data was available for only half. Sugars, amino acids, and celluloses were poorly documented. Synthetic polymers like crospovidone and PVP were not inherently biodegradable. Yet no regulatory requirement exists for excipient ERA [14].

Another study evaluated 38 excipients and introduced an "Excipient Selection Guide." But this focuses on human pharmaceuticals and manufacturing impacts, not use-phase dispersion. No equivalent exists for veterinary excipients dispersed into agricultural ecosystems [15].

Water-soluble synthetic polymers pose particular concern. PVP and PVA are essentially non-biodegradable. PVP is detected in rivers at 0.16-0.18 mg/L. PVA is found in contaminated soil. They pass through treatment plants unchanged. They are not subject to any ERA or biodegradability requirements before market authorization [16].

A biodegradation study confirmed these findings. PVP/PLA films exhibited only 1-4 percent degradation in soil. PVP was removed by dissolution, not biological degradation. PVP showed no evidence of microbial degradation [17].

Finally, a groundbreaking study challenged the assumption that excipients are inert. Large-scale screening across 44 molecular targets identified 25 excipient activities, plus 109 activities against clinical safety targets. Five excipients showed cellular activity fingerprints predictive of toxicity. This fundamentally challenges regulatory assumptions. Yet veterinary pharmaceuticals continue using these excipients without ERA requirements [18].

Given these regulatory gaps, this review seeks to answer one central question: To what extent do current regulatory frameworks for veterinary excipients fail to protect agricultural ecosystems? To answer this, we first identify regulatory blind spots in ERA guidelines. We then summarize available evidence on excipient toxicity, environmental persistence, and mixture effects. Finally, we propose practical recommendations for closing these gaps.

2. REVIEW METHODOLOGY

This narrative review was conducted following standard guidelines for critical reviews. A literature search was performed using PubMed, google scholar and Scopus databases. The search period covered January 2000 to May 2026. Keywords included combinations of "veterinary excipients," "environmental risk assessment," "regulatory blind spots," "adjuvants," "surfactants," "biodegradation," "mixture effects," and "agricultural sustainability." Additional studies were identified through citation searching of relevant articles. Only peer-reviewed articles, regulatory guidelines, and official EU documents were included. Studies focusing exclusively on human pharmaceuticals or industrial chemicals were excluded unless they directly informed veterinary excipient assessment. The final reference list includes 26 sources.

3. REGULATORY LANDSCAPE: WHAT IS REQUIRED VS. WHAT IS MISSING

Environmental risk assessment is required for both human and veterinary medicinal products in the EU. However, a critical asymmetry exists. Serious environmental risk can lead to refusal of marketing authorization for veterinary products if no mitigation is possible. For human medicines, this is explicitly not the case. Only risk mitigation measures are considered [7].

For veterinary products, some risk mitigation measures do exist. Parameters such as manure storage time, stocking density, ploughing depth, and fraction of herd treated can be modified to reduce predicted environmental concentrations. A catalogue of 19 practical risk mitigation measures has been developed. These include specific constraints on manure spreading, pasture management, and treatment of only affected animals. However, compliance with these measures currently has no legal consequences. This is very different from pesticides, where enforcement is strict. Their effectiveness is often unverified in practice [2].

The environmental risk assessment guidelines focus exclusively on active ingredients. Excipients are only mentioned for consideration "if indicated." Metabolites are handled via a "total residue approach." This assumes equal toxicity to the parent compound without experimental verification [7].

For generic applications and existing marketed substances, no systematic environmental data generation is required. This leads to persistent data gaps for successfully marketed compounds that enter the environment at high loads [7].

The Phase I action limit of 0.01 µg/L for human pharmaceuticals waives detailed assessment below this threshold. But this fails to account for mixture effects. Multiple compounds below individual thresholds may combine to cause harm. Despite the legal requirement to consider environmental risks in pharmacovigilance for veterinary products, what information should be gathered and how remains undefined [7].

Table 1 summarizes the key differences between regulatory requirements for active pharmaceutical ingredients and excipients in veterinary products.

Table 1. Regulatory Requirements for Active Ingredients vs. Excipients in Veterinary Products

Aspect	Active Ingredients	Excipients
Environmental risk assessment required	Yes	No (only "if indicated")
Maximum residue limits	Yes	No
Monitoring in manure/soil/water	Limited	None
Biodegradability testing	Sometimes	Not required
Mixture effect assessment	No	No
Pharmacovigilance for environmental effects	Undefined	Undefined

As shown in Table 1, excipients face no mandatory ERA, no MRLs, and no monitoring requirements, despite being intentionally released into agricultural ecosystems.

Current European Regulation EU 2019/6 requires environmental risk assessment for veterinary medicinal products. But excipients are only evaluated for quality and safety within the pharmaceutical development dossier. They are not evaluated for ecotoxicological impact or environmental persistence. The EMA Note for Guidance requires scientific justification for excipient selection, including compatibility and stability. However, there is no requirement to assess the environmental fate, biodegradation kinetics, or ecotoxicity of excipients that are released into agricultural ecosystems through manure, wash-off, and direct application to pasture animals [8].

Another major gap concerns legacy products. Although environmental risk assessment is required for new veterinary medicinal products, existing products authorized before the ERA guidelines were adopted have never been systematically reviewed. This leaves a substantial regulatory gap [5].

The official definition of drug residues includes not only active pharmaceutical ingredients but also excipients and their degradation products and metabolites. Yet current regulatory frameworks focus almost exclusively on active substances when setting maximum residue limits. No monitoring programs, maximum residue limits, or routine analytical methods exist for excipients [9].

For companion animal parasiticides, the problem is similar. Regulatory risk assessments assume environmental exposure is negligible. They rely on mitigation measures such as preventing treated animals from swimming. But there is no evidence that pet owners comply with these instructions [13].

Finally, no regulatory framework requires assessment of the environmental fate, persistence, or ecotoxicity of polymeric excipients and surfactants used in veterinary drug delivery systems when they are excreted or washed off into agricultural and aquatic ecosystems [19].

In summary, the regulatory landscape for veterinary excipients has several critical gaps. Excipients are excluded from routine environmental risk assessment. Legacy products have never been reviewed. Compliance with mitigation measures has no legal consequences. And pharmacovigilance requirements remain undefined.

4. EXCIPIENT TOXICITY: CHALLENGING THE "INERT" ASSUMPTION

The term "excipient" suggests an inactive substance. But this assumption is wrong.

Numerous studies have demonstrated that adjuvants and formulation additives can be individually toxic. They can also exhibit additive, synergistic, or antagonistic effects with active ingredients. Some surfactants like polyethoxylated tallow amine are thousands of times more toxic than the active ingredient itself [3].

A groundbreaking study systematically examined whether pharmaceutical excipients bind to biological targets. The authors combined large-scale computational screening with targeted experimental testing across 44 molecular targets. They identified 25 excipient activities ranging from low-nanomolar to high-micromolar concentrations. They also found another 109 activities against clinical safety targets. Five excipients showed cellular activity fingerprints predictive of system-level toxicity. For two excipients, including thimerosal, estimated in vivo exposures in certain populations reached levels overlapping with their in vitro target potency. Thimerosal and its major metabolite had dopamine D3 receptor dissociation constant values of 320 and 210 nM respectively. This research fundamentally challenges the regulatory assumption that excipients are inert [18].

Veterinarians and pharmacists are familiar with the safety of active pharmaceutical ingredients. But they are rarely concerned with excipients. These substances are not chemically inert and can produce adverse events in specific animal populations such as cats, dogs, and food-producing animals. A review identified 18 excipients of concern. These include propylene glycol, benzyl alcohol, polysorbate, sodium lauryl sulfate, polyethylene glycol, and ethanol. They can cause adverse reactions ranging from oxidative hemolysis in cats to gastrointestinal and neurological effects. Critically, among 135 manuscripts reviewed, only 24 correctly evaluated these substances as excipients. This reveals a significant gap in safety data when these compounds are considered as formulation components rather than active ingredients. Safety concerns vary dramatically by species due to metabolic differences. Cats are particularly sensitive to propylene glycol and benzyl alcohol. Food-producing animals raise additional concerns about residue transfer to human consumers. The fundamental blind spot is that excipients are considered "generally recognized as safe" without species-specific safety evaluations [21].

Table 2 presents a summary of high-risk veterinary excipients identified in the literature, including their primary use, environmental persistence, known toxicity, and source references.

Table 2. High-Risk Veterinary Excipients and Their Properties

Excipient	Use	Environmental Persistence	Known Toxicity	Source
Polyethoxylated tallow amine	Surfactant	High (persists anaerobically)	Thousands of times more toxic than API	[3]
Polyvinylpyrrolidone (PVP)	Binder, coating	1-4% biodegradation in soil	Accumulates in rivers (0.16-0.18 mg/L)	[16] and [17]
Polyvinyl alcohol (PVA)	Coating agent	Non-biodegradable	Found in contaminated soil	[16]
Propylene glycol	Solvent, preservative	Unknown	Oxidative hemolysis in cats	[21] and [8]

These examples illustrate that excipients vary widely in their environmental behavior. However, none of these compounds are subject to routine ERA or monitoring.

Topical formulations provide another example. Excipients such as propylene glycol can be toxic in certain species due to metabolic differences. Yet formulation components are often assumed inert and are not systematically evaluated for ecotoxicological impact [8].

Animal-derived excipients pose additional risks. Animal-derived ingredients account for up to 75 percent of prescription drugs. They function as both active ingredients and excipients including gelatin, lactose, magnesium stearate, glycerin, and lanolin. The immunological risk is exemplified by alpha-gal syndrome. IgE antibodies to the galactose-α-1,3-galactose epitope found in mammalian-derived gelatin, heparin, and lactose can cause delayed anaphylaxis. An estimated 450,000 cases exist in the US alone. A proposed dual-risk stratification framework categorizes excipients as high-risk, intermediate-risk, and low-risk. Yet no regulatory framework requires environmental risk assessment of animal-derived excipients or their persistence, biodegradability, and ecotoxicological impact on non-target organisms [22].

The critical point is this. Regulatory frameworks for veterinary medicinal products do not require environmental risk assessment for excipients. This is despite evidence that their persistence and bioaccumulation potential may exceed those of active ingredients [10]. Despite the legal requirement to consider environmental risks in pharmacovigilance, what information should be gathered and how remains undefined [7].

In short, the assumption that excipients are inert is scientifically false. But regulations still treat them as if it were true.

5. ENVIRONMENTAL FATE: PERSISTENCE, BIODEGRADATION, AND ACCUMULATION

Veterinary excipients do not stay in the laboratory or factory. They enter the real environment.

The main pathways for veterinary pharmaceuticals entering the environment are through manure and slurry from intensively reared animals applied to soil, as well as dung and urine from grazing pasture animals [4].Topical

veterinary treatments can enter aquatic environments through runoff, bathing, and disposal [8]. Pharmaceutical residues also enter the environment through excretion, waste disposal, and runoff [10].

Once in the environment, what happens to excipients? For many, we simply do not know.

Environmental fate data for adjuvants and additives is scarce. Yet they enter soils and waters through manure application and can persist under anaerobic conditions [3]. Biodegradable engineered nanoparticles used as veterinary drug delivery systems include polymeric excipients and surfactants whose environmental fate remains poorly understood. When administered orally, nanoparticles that are not fully degraded during gastrointestinal transit are excreted in feces. For parenterally administered nanoparticles, studies have shown renal clearance of intact polymeric nanoparticles in mice. This means nanoparticle excipients can enter the environment via urine from treated livestock. No established guidelines exist for environmental risk assessment of these delivery systems [19].

Current environmental risk assessment guidelines for groundwater use simplified default scenarios. These do not account for real-world variability in livestock numbers, manure storage times, and field application practices. A study comparing generic default scenarios with a case study of 12 veterinary pharmaceuticals in Northern Italy found that the generic approach consistently underestimated groundwater vulnerability. Differences of up to three vulnerability classes were observed for compounds such as sulfadiazine and tylosin. Default assumptions about manure storage time (91 days) and nitrogen application rates (170 kg/ha) do not reflect real farming practices. Higher nitrogen loads and different seasonal spreading patterns significantly increase leaching potential. This regulatory blind spot affects both active ingredients and their associated formulation excipients [20].

Some of the clearest evidence comes from studies on synthetic polymers. Polyvinyl alcohol and polyvinylpyrrolidone are water-soluble synthetic polymer excipients that are essentially non-biodegradable. They possess the capacity to accumulate in virtually all environmental media. PVP has been detected in river water at concentrations of 0.16 to 0.18 mg/L downstream of wastewater treatment plants. PVA has been found in contaminated soil samples. Both polymers pass through wastewater treatment plants unchanged. They can increase the mobility of toxic metals or organic pollutants through complexation and surfactant effects. PVA-degrading microorganisms are not found in every environmental compartment. They are typically absent from uncontaminated environments, meaning PVA persists unless pre-adapted microbial populations are present. PVP shows no biodegradation even after extended periods in river water, marine environments, and activated sludge systems [16].

A biodegradation study confirmed these findings. PVP/PLA films exhibited only 1 to 4 percent biodegradation in soil. Pure PLA showed up to 19 percent biodegradation in aerobic water conditions. But PVP was quickly removed from the polymer matrix not by biological degradation. It was removed by simple dissolution in water due to its high water solubility. Electron microscopy and FTIR spectroscopy confirmed that PVP eluted from the PLA matrix leaving pores. This could make PLA more accessible to microorganisms. But PVP itself showed no evidence of microbial degradation. PVP exhibits negligible biodegradation regardless of environmental conditions. It simply dissolves and disperses into water compartments [17].

What about other excipients? A study that assessed 35 excipients used at two pharmaceutical sites found that natural excipients like starch and sugars are readily biodegradable. But synthetic polymers such as crospovidone and polyvinylpyrrolidone were not inherently biodegradable in their tests. For a broader set of 184 excipients, sufficient environmental data for risk assessment was available for only about half of the compounds. Sugars, sugar alcohols, amino acids, peptides, celluloses, and oils/fats were particularly poorly documented [14].

Classical remediation methods in sewage treatment plants show very low removal efficiency for pharmaceuticals. For many drug classes, removal is less than 10 to 25 percent. No data exist on excipient removal rates because excipients are not included in any monitoring program [11].

Veterinary excipients are not the only concern. Animal-derived excipients such as gelatin, lactose, magnesium stearate, glycerin, and lanolin are also released into the environment. No regulatory framework requires environmental risk assessment of these substances or their persistence, biodegradability, and ecotoxicological impact on non-target organisms [22].

The problem is made worse by current practices. Veterinary facilities generate 0.5 to 1.2 kg of waste per patient per day. Of this, 60 to 70 percent is non-infectious and potentially recyclable. But excipients in pharmaceutical products are not segregated or tracked in any waste management stream [10].

The critical regulatory blind spot is clear. Water-soluble synthetic polymer excipients used extensively in veterinary pharmaceuticals are not subject to any environmental risk assessment or biodegradability requirements before market authorization. Furthermore, default scenarios for groundwater risk assessment do not reflect real farming practices. Site-specific manure management practices, storage times, and field application patterns all dramatically affect the environmental fate of both active ingredients and their associated formulation excipients. Yet current guidelines do not require consideration of these factors [16], [17] and [20].

6. MIXTURE EFFECTS: THE OVERLOOKED SYNERGY PROBLEM

Excipients do not enter the environment alone. They enter with active ingredients, other excipients, and degradation products. Together, they create mixtures.

Current regulatory frameworks for environmental risk assessment of pharmaceuticals largely ignore mixture effects. They assess each active ingredient individually. This lags considerably behind pesticide and biocide regulations. Those explicitly mandate consideration of cumulative and synergistic effects [6].

Pharmaceutical mixtures in the environment typically consist not only of multiple active ingredients but also excipients such as preservatives and surfactants. These excipients possess substantial ecotoxicity yet are often considered biologically inert [6].

The common practice of using exposure-based cut-off criteria (action limits) to waive risk assessment is problematic from a mixture perspective. Even low concentrations of individually non-toxic compounds may combine to produce significant mixture effects. A tiered approach summing risk quotients (PEC/PNEC ratios) across all co-occurring compounds is recommended as a pragmatic first step. But this requires data on excipients that are currently not generated or disclosed [6].

The critical regulatory blind spot is twofold. First, the exclusion of excipients from routine monitoring and risk assessment. Second, the failure to account for additive mixture effects between active ingredients and their formulation components [6].

The problem is not only theoretical. Numerous studies have demonstrated that adjuvants can exhibit additive, synergistic, or antagonistic effects with active ingredients. Some surfactants like polyethoxylated tallow amine are thousands of times more toxic than the active ingredient itself [3].

The Phase I action limit of 0.01 µg/L for human pharmaceuticals waives detailed assessment below this threshold. But this fails to account for mixture effects where multiple compounds below individual thresholds may combine to cause harm [7].

For veterinary products, the situation is similar. Despite the legal requirement to consider environmental risks in pharmacovigilance, what information should be gathered and how remains undefined. This leaves a regulatory blind spot for both legacy products and formulation excipients [7].

The problem extends to companion animal parasiticides. Regulatory risk assessments assume environmental exposure is negligible and rely on mitigation measures such as preventing treated animals from swimming. But there is no evidence that pet owners comply with these instructions. The cumulative impact of millions of doses, combined with the complete absence of ecotoxicity data for newer active ingredients and zero consideration of formulation excipients, represents a major gap [13].

What happens when excipients degrade? The official definition of drug residues includes not only active ingredients but also excipients and their degradation products and metabolites. Yet current regulatory frameworks focus almost exclusively on active substances. No monitoring programs or routine analytical methods exist for excipient degradation products [9].

The problem is made worse by the "total residue approach." This assumes metabolites have equal toxicity to the parent compound without experimental verification [7]. For excipient mixtures, no approach exists at all.

Some research has addressed mixture effects for active ingredients. But for excipients combined with active ingredients, the data gap remains. A study of 184 excipients found that sufficient environmental data for risk assessment was available for only about half of the compounds. This means we cannot even calculate basic risk quotients for most excipients, let alone their mixture effects [14].

The regulatory asymmetry is also relevant. Serious environmental risk can lead to refusal of marketing authorization for veterinary products if no mitigation is possible. For human medicines, this is not the case. But for mixture effects involving excipients, neither system has adequate frameworks [7].

In summary, current regulations fail to address three critical facts. First, excipients are toxic on their own. Second, excipients interact with active ingredients. Third, excipients degrade into other compounds that may also be toxic. Until regulations account for all three, mixture effects will remain a major blind spot.

7. MONITORING AND DETECTION: WHAT WE DON'T MEASURE

If we do not measure something, we cannot find it. If we cannot find it, we cannot regulate it. This is the core problem with veterinary excipients.

Current monitoring systems like the EU Rapid Alert System for Food and Feed target only pharmacologically active substances. They completely exclude excipients and adjuvants [3].

Analytical methods for detecting drug residues include microbiological, immunological, and physicochemical techniques. But these are all designed and validated for active ingredients only. They are not designed for formulation excipients [9].

The official definition of drug residues includes not only active pharmaceutical ingredients but also excipients and their degradation products and metabolites that persist in animals, food, or the environment. Yet no monitoring programs, maximum residue limits, or routine analytical methods exist for these compounds. Their contribution to environmental risk and human exposure remains completely uncharacterized [9].

What is the evidence that excipients are actually out there? For many, we do not know because we do not look. But some data does exist.

Topical veterinary treatments can enter aquatic environments through runoff, bathing, and disposal. Chemicals like fipronil and permethrin from spot-on products have been detected at concentrations posing environmental risk. But excipient contributions to this pollution remain unmonitored [8].

Companion animal ectoparasiticides like fipronil and imidacloprid have been detected in over 60 percent of UK river samples. Levels exceed chronic toxicity thresholds for aquatic invertebrates. Yet no monitoring exists for the surfactant and solvent excipients that accompany these active ingredients [10].

For fluralaner, which is excreted 90 percent unchanged in feces and is very persistent in soil, no ecotoxicity studies on non-target invertebrates were identified. The cumulative impact of millions of doses, combined with the complete absence of ecotoxicity data for newer active ingredients and zero consideration of formulation excipients, represents a major monitoring gap [13].

Water-soluble synthetic polymers like PVP have been detected in river water at concentrations of 0.16 to 0.18 mg/L downstream of wastewater treatment plants. PVA has been found in contaminated soil samples. Yet these excipients are not subject to any environmental monitoring requirements [16].

Human exposure pathways also reveal gaps. Veterinary drug residues enter the environment through manure application to agricultural land. Studies confirm tetracyclines and fluoroquinolones in manure-based organic fertilizers at concentrations posing risks. Human exposure occurs through drinking water, food, air, and dust. Dust from intensive livestock facilities contains up to five different antibiotics at total concentrations reaching 12.5 mg/kg. Yet excipients are not monitored in any of these exposure routes [9].

The pharmacovigilance system is also failing. Environmental effects are formally part of the pharmacovigilance system for veterinary products. But in practice, it is very unlikely that such effects are detected through this system. The pharmacovigilance system has very low reporting rates for environmental adverse events [5] and [8]. Despite the legal requirement to consider environmental risks in pharmacovigilance, what information should be gathered and how remains undefined [7].

Even when researchers try to study excipients, they face problems. A study of 184 excipients found that sufficient environmental data for risk assessment was available for only about half of the compounds. Sugars, sugar alcohols, amino acids, peptides, celluloses, and oils/fats were particularly poorly documented [14].

No data exist on excipient removal rates in sewage treatment plants because they are not included in any monitoring program [11]. Excipients in pharmaceutical products are not segregated or tracked in any waste management stream [10]. And no detection methods exist for tracking nanoscale excipients released from drug delivery systems [19].

The regulatory blind spot is clear. We have the definition. We have the pathways. We have evidence that some excipients persist and accumulate. But we have no monitoring. No routine analysis. No maximum residue limits. No pharmacovigilance. And no requirement to collect any of this information before a veterinary product reaches the market.

8. PRACTICAL RECOMMENDATIONS FOR FARMERS AND VETERINARIANS

While regulatory reform is essential, some practical steps can be taken now.

For veterinary medicines, parameters such as manure storage time, stocking density, ploughing depth, and fraction of herd treated can be modified to reduce predicted environmental concentrations. A catalogue of 19 practical risk mitigation measures exists. These include specific constraints on manure spreading, pasture management, and treatment of only affected animals [2].

However, compliance with these measures currently has no legal consequences. Their effectiveness is often unverified in practice [2]. Therefore, farmers and veterinarians should adopt these measures voluntarily while awaiting regulatory enforcement.

For companion animal parasiticides, regulatory risk assessments rely on mitigation measures such as preventing treated animals from swimming. But there is no evidence that pet owners comply with these instructions [13]. Veterinarians should actively counsel pet owners about environmental risks.

The selection of biodegradable, bio-derived excipients such as chitosan, alginate, and pectin can reduce environmental persistence. Veterinarians and pharmacists can request information about excipient composition from manufacturers and prefer products with greener excipients [8].

Veterinary facilities generate 0.5 to 1.2 kg of waste per patient per day. Of this, 60 to 70 percent is non-infectious and potentially recyclable. Better waste segregation can reduce environmental release of excipients [10].

9. FUTURE PERSPECTIVES AND SUSTAINABLE SOLUTIONS

Long-term solutions require regulatory and industrial change.

Eco-compatible excipients derived from renewable resources such as modified starches, cellulose derivatives, and marine-sourced materials offer enhanced biodegradability with half-lives of weeks to months. Life cycle assessments

demonstrate that renewable excipients achieve 40 to 60 percent reduction in greenhouse gas emissions and 30 to 50 percent lower energy consumption compared to synthetic alternatives [23].

Marine-derived excipients including alginate, chitosan, carrageenan, agar, fucoidan, marine collagen, and krill oil phospholipids offer renewable, biodegradable alternatives. Green extraction technologies including enzyme-assisted extraction, ultrasound-assisted methods, and supercritical CO_2 extraction enable sustainable production. However, critical barriers include inconsistent raw material quality and geographic monopolies [24].

A life cycle assessment study compared two different excipient formulations for ibuprofen tablets. The results showed that excipient selection significantly influences the environmental footprint of pharmaceutical production. The formulation using lactose and pregelatinized starch generated 30 to 35 percent lower environmental damages across human health, ecosystem, and resource categories compared to the formulation using raw starch. This was primarily due to lower energy requirements and reduced use of high-impact excipients like polyvinylpyrrolidone and magnesium stearate. Critically, excipients such as PVP and magnesium stearate contributed significantly to human toxicity and ecotoxicity impacts. This was due to hazardous precursors (formaldehyde for PVP, sulfuric acid for magnesium stearate) and energy-intensive production processes. This study establishes that excipients play as large a role as active ingredients in determining environmental impacts of oral drug products [25].

However, no equivalent life cycle assessment framework exists for veterinary pharmaceuticals. This is particularly concerning for topical products where excipients constitute 70 to 90 percent of formulation mass and are intentionally dispersed into agricultural ecosystems through manure, wash-off, and direct application [25].

An "Excipient Selection Guide" with relative environmental ranking data exists for human pharmaceuticals. No equivalent framework exists for veterinary products [15]. This gap needs urgent attention.

The AOSC model's "substitute" strategy explicitly calls for transition to biodegradable excipients and formulations with shorter environmental half-lives [10].

Agricultural and animal husbandry wastes represent a circular economy opportunity. Approximately 140 billion metric tons of agricultural biomass waste are generated annually worldwide. These can be valorized into excipients like cellulose and keratin (“Development of Pharmaceutical Aids,” 2023).

Pharmacy education also needs reform. Current curricula focus on active ingredients and completely neglect the environmental impact of excipients. No program requires students to assess the ecotoxicological risk of formulation excipients or their degradation products [26].

The critical regulatory blind spot is that while human pharmaceutical development is increasingly requiring environmental impact assessment of excipients through life cycle analysis and biodegradability testing, veterinary excipients remain unregulated for environmental persistence. This is despite being intentionally dispersed into agricultural ecosystems through manure, urine, and direct application to pasture and aquaculture [23] and [25].

10. LIMITATIONS

This review has several limitations. First, we focused primarily on terrestrial agricultural ecosystems. Aquatic environments, including surface water contamination from runoff and aquaculture, were not systematically reviewed.

Second, we did not address the pharmacokinetics of excipients within treated animals, which determines excretion rates and metabolite formation. Third, acidic soils and tropical agricultural systems were outside our scope. Fourth, most included studies originated from Europe and North America, limiting generalizability to other regions. Fifth, we relied on published data only; we did not perform original experimental testing. Finally, this is a narrative review, not a systematic review or meta-analysis, so quantitative synthesis was not performed.

11. CONCLUSION

This review has identified several regulatory blind spots concerning veterinary excipients.

First, excipients are legally considered "inert" but scientific evidence proves otherwise. They are toxic, persistent, and capable of mixture effects [3] and [18].

Second, current regulations require environmental risk assessment for active ingredients only. Excipients are mentioned only "if indicated" [7].

Third, no monitoring programs, analytical methods, or maximum residue limits exist for excipients, despite the official definition of drug residues explicitly including them [9].

Fourth, synthetic polymer excipients like PVP and PVA show negligible biodegradation and accumulate in rivers and soils [16] and [17].

Fifth, legacy products have never been systematically reviewed for environmental risk [5].

Sixth, pharmacovigilance requirements for environmental effects remain undefined [7].

The following recommendations emerge from this review.

Regulators should mandate environmental risk assessment for veterinary excipients, including biodegradability testing. Monitoring programs should be established for excipients in manure, soil, and water. Mixture effects between excipients and active ingredients should be addressed in regulatory frameworks. Legacy products should be systematically reviewed. And green excipients from renewable sources should be incentivized.

Until these changes occur, veterinary excipients will remain a hidden threat to agricultural sustainability.

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