11th International Congress
on Development of
Agricultural and Environment
with emphasis on the UN
Development Program

یازدهمین کنگره بین المللی
توسعه کشاورزی و
محیط زیست با تاکید
بر برنامه توسعه ملل

# *Unintended Veterinary Drug Residues in Feed from Upcycled Agricultural By-Products: A Hidden Threat to One Health and the Circular Economy*

Sakineh Khanamani Falahatipour[1], Sana Naseri[2]*
[1] Department of Comparative Biosciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran
[2] Department of Pharmacology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran

**ABSTRACT**

*The global food system faces an unprecedented challenge: feeding a growing population while reducing environmental degradation. Upcycling agricultural by-products and food waste into animal feed has emerged as a promising circular economy strategy, with potential to increase global food supply by up to 13% in calories and 15% in protein content while freeing 31–54 million hectares of cropland. However, this transition introduces hidden food safety threats, particularly unintended veterinary drug residues. This narrative review synthesizes current evidence on the sources, hazards, regulatory frameworks, and risk management strategies associated with veterinary drug residues in upcycled feeds. Residues enter circular feed systems through multiple pathways: carryover during feed manufacturing, contamination of processed animal proteins and distillers grains, environmental pollution from manure-amended soils, and animal-to-animal transfer. Public health consequences include direct toxicity (allergic reactions, hepatotoxicity, carcinogenicity), disruption of intestinal microbiota, and—most significantly—acceleration of antimicrobial resistance (AMR), projected to cause 10 million annual deaths by 2050. Regulatory approaches vary substantially: Japan, South Korea, and Taiwan recycle over 65% of food waste into safe animal feed through mandatory heat treatment (70–90°C for 30–60 minutes) and certification systems, while the European Union and United States recycle only 5–10% due to restrictive regulations. Key knowledge gaps include limited occurrence data for non-European by-product streams, insufficient understanding of residue fate through processing, and lack of empirical validation for long-term accumulation in closed-loop systems. The review concludes that realizing circular economy benefits without compromising food safety requires internationally harmonized action levels, risk-based monitoring of imported feeds, investment in rapid screening technologies, and adoption of successful certification models from Asian leaders.*

**Keywords: veterinary drug residues; upcycled feed; circular economy; antimicrobial resistance; One Health; food safety; carryover**

## 1. INTRODUCTION

The global food system faces an unprecedented challenge as approximately 33–40% of all food produced for human consumption is lost or wasted annually, contributing nearly half of total greenhouse gas emissions from the global agri-food system and wasting 25% of global freshwater resources, 30% of agricultural land area, and 38% of total energy consumption ([23] and [27]. This inefficiency occurs alongside a global crisis of food insecurity, highlighting the urgent need to redesign food production and consumption patterns ([23] ). In response to these challenges, the concept of a circular economy has gained substantial traction within agri-food systems, emphasizing the recovery, recycling, and upcycling of waste streams into valuable products ([7] and [11] ). Upcycling agricultural and food processing by-products into animal feed has been identified as one of the most promising strategies to enhance

resource efficiency, reduce environmental burdens, and improve food security ([20] and [24] ). Approximately 15% (940 million tons in dry matter) of total feedstuffs currently used in livestock and aquaculture production consist of food-competing feedstuffs—primarily cereals, whole fish, vegetable oils, and pulses—that could be directly consumed by humans ([20] ). Replacing even a portion of these with food system by-products and residues has the potential to increase global food supply by up to 13% in calories and 15% in protein content ([20] ). Governments in Japan, South Korea, and Taiwan have successfully implemented policies enabling the conversion of over 65% of food waste into safe animal feed through mandatory heat treatment, certification systems, and dedicated infrastructure ([24] and [23] ).

However, the transition toward circular feed systems introduces new and often overlooked food safety challenges, particularly concerning unintended veterinary drug residues ([6] and [7] ). Veterinary drugs—including antibiotics, coccidiostats, growth promoters, and antiparasitics—are extensively used in food animal production for therapeutic, prophylactic, and metaphylactic purposes ([14] and [5] ). Global antibiotic consumption in livestock is estimated at 63.1 ± 1.5 tons annually, nearly double that used in human medicine, with over 80% of food-producing animals receiving these compounds ([3] ). When agricultural by-products derived from treated animals (e.g., poultry meal, feather meal, processed animal proteins) or crops grown on manure-fertilized soils are recycled into feed, residues of these drugs can enter the feed chain unintentionally ([7] and [9] ).

The problem is further compounded by the phenomenon of carryover—the transfer of veterinary drugs from medicated feed to subsequent batches of non-medicated feed during manufacturing, handling, transportation, or on-farm feeding ([12] and [6] ). Even when following Good Manufacturing Practices and Hazard Analysis Critical Control Point principles, some degree of carryover remains unavoidable, particularly for drugs with electrostatic properties such as sulfonamides and coccidiostats ([6] ). Studies have documented that carryover can lead to violative residues in non-target animal species, with residues of sulfonamides and coccidiostats frequently detected in eggs and milk from animals never directly treated with these drugs ([12] and [8] ).

The public health consequences of unintended veterinary drug residues in the food chain are substantial and multifaceted ([4] and [3] ). Direct toxicity includes allergic reactions (particularly to penicillin residues), hepatotoxicity, nephropathy (gentamicin), bone marrow toxicity (chloramphenicol), carcinogenicity (sulfamethazine, oxytetracycline, furazolidone), and disruption of normal intestinal flora ([14] and [5] ). However, the most significant and far-reaching consequence is the development and spread of antimicrobial resistance (AMR). The World Health Organization has declared AMR one of the top ten global public health threats, estimating that drug-resistant diseases could cause 10 million deaths annually by 2050 if no action is taken ([3] ). Exposure of bacteria to subtherapeutic concentrations of antibiotics—precisely the levels found in carryover-contaminated feed—creates selective pressure that favors the emergence and horizontal transfer of resistance genes, which can then spread from animals to humans through the food chain, direct contact, or environmental contamination ([19] and [7] ).

The One Health framework, which recognizes the inextricable links between human, animal, and environmental health, provides an essential lens for addressing this challenge ([19] and [14] ). Antimicrobial residues in animal manure used as fertilizer contaminate soil and water, where they can be taken up by crops or promote resistance in environmental bacteria, creating transmission cycles that are difficult to break ([7] ). Similarly, insects reared on contaminated substrates for use as feed—a rapidly expanding sector within circular bioeconomy strategies—can accumulate both chemical and biological hazards, including veterinary drugs, heavy metals, and pathogenic bacteria, potentially introducing these hazards into new food chains ([9] and [17] ). The European Food Safety Authority has identified significant knowledge gaps regarding the fate of contaminants in such circular systems, emphasizing the need for rigorous risk assessment ([11] ).

Despite growing recognition of these risks, current regulatory frameworks vary widely across jurisdictions and often fail to adequately address the unique challenges posed by circular feed systems ([24] ). The European Union maintains the most restrictive approach, with animal by-products classified into three risk categories and only Category 3 materials permitted for feed use after specified heat treatments, resulting in only an estimated 5–10% of available food waste being recycled into animal feed ([24] and [1] ). In contrast, Japan, South Korea, and Taiwan have demonstrated that high rates of safe upcycling are achievable through mandatory heat processing (70–90°C for 30–60 minutes), government-subsidized certification systems, and integrated infrastructure, with no disease outbreaks linked to properly treated food waste in over 20 years ([24] ). The United States occupies an intermediate position, with federal regulations including the Swine Health Protection Act (requiring 100°C for 30 minutes for waste containing meat) and the Food Safety Modernization Act, but only three FDA-approved definitions for food waste use in feed, resulting in similarly low recycling rates ([24] and [21] ).

Emerging evidence suggests that upcycled agricultural by-products—including grain distillers, potato peels, citrus pulp, cane molasses, and cereal processing residues—can be contaminated with a range of veterinary drugs at levels that pose potential risks to animal health, human health, and food safety ([8] and [2] and [15] ). For example, fipronil—a pesticide banned for agricultural use in the EU but still permitted in the Americas, Eastern Europe, and Asia—has been detected in grain distillers at mean levels of 0.49 mg/kg, leading to exceedances of EU maximum residue limits in milk and fat when such contaminated feeds were administered to dairy cows ([8] ). Similarly, residues of tetracyclines, sulfonamides, and fluoroquinolones have been detected in various by-product-based feeds, with potential for accumulation and transfer through the food chain ([14] and [25] ).

The detection of these unintended residues presents substantial analytical challenges. While advanced techniques such as liquid chromatography-tandem mass spectrometry (LC-MS/MS) and high-resolution mass spectrometry (HRMS) enable the identification and quantification of veterinary drugs at trace levels (parts per billion), the complexity and heterogeneity of upcycled feed matrices—which vary by source, processing method, and animal species—can cause signal suppression or enhancement, necessitating matrix-matched calibration and rigorous quality control ([13] and [28] ). Emerging approaches such as background exclusion data-dependent acquisition (BE-DDA) and suspect screening using high-resolution mass spectrometry show promise for retrospective detection of unknown or unexpected contaminants, but these methods are not yet widely implemented in routine monitoring programs ([28] ).

Given the rapid expansion of circular economy initiatives in the agri-food sector, the increasing utilization of upcycled agricultural by-products as animal feed, and the potential for unintended veterinary drug residues to compromise both food safety and the goals of the circular economy itself, a comprehensive synthesis of current knowledge is urgently needed. This narrative review aims to address this gap by: (1) identifying the major sources and routes of unintended veterinary drug residues in upcycled agricultural by-products used as animal feed; (2) characterizing the chemical and biological hazards associated with these residues, including their potential for accumulation, transfer, and contribution to antimicrobial resistance; (3) comparing regulatory frameworks across major global jurisdictions (EU, US, Japan, South Korea, Taiwan, China) and their implications for feed safety; (4) evaluating current analytical methods for detecting and quantifying these residues in complex feed matrices; and (5) proposing risk management strategies and future research priorities to enable the safe expansion of circular feed systems within a One Health framework.

By synthesizing evidence from food safety science, veterinary pharmacology, analytical chemistry, environmental health, and regulatory policy, this review seeks to inform researchers, policymakers, industry stakeholders, and public health professionals about the hidden threats posed by unintended veterinary drug residues in upcycled feeds—and to chart a path forward that realizes the substantial environmental and food security benefits of circular agriculture without compromising the safety of the food supply.

## 2. METHODOLOGY

This narrative review was conducted by synthesizing peer-reviewed literature and official reports from international organizations. A comprehensive literature search was performed in electronic databases including PubMed, Scopus and Google Scholar, as well as the FAO and WHO official websites. The search was conducted using combinations of keywords including "veterinary drug residues," "upcycled feed," "carryover," "circular economy," "antimicrobial resistance," "One Health," "agricultural by-products," and "feed safety." Articles published between 1989 and 2025 were considered. Additional relevant publications were identified through snowball searching of reference lists. Due to the heterogeneous nature of the evidence (different veterinary drugs, animal species, waste streams, and regulatory frameworks), a narrative synthesis approach was adopted rather than a meta-analysis.

## 3. SOURCES AND CAUSES OF UNINTENDED VETERINARY DRUG RESIDUES IN UPCYCLED FEEDS

Understanding the origins of veterinary drug residues in upcycled agricultural by-products is essential for developing effective prevention and mitigation strategies. This section synthesizes current knowledge on the primary sources and causal mechanisms through which veterinary drugs enter circular feed systems, drawing on evidence from field investigations, experimental studies, and regulatory surveillance programs.

### 3.1. Feed Cross-Contamination During Manufacturing (Carryover)

One of the most well-documented and frequently overlooked causes of unintended veterinary drug residues in animal feed is carryover—the transfer of drugs from medicated feed to subsequent batches of ostensibly non-medicated feed during manufacturing, handling, transportation, or delivery ([12] ; [6] ). This phenomenon occurs when residual quantities of medicated feed remain in production equipment (mixers, surge bins, conveyors, elevators, pellet mills, and bulk trucks) and contaminate subsequent batches as they are processed ([6] ).

The extent of carryover depends on multiple factors, including the physical and chemical properties of the drug, the type of feed being manufactured, the design and maintenance of equipment, and the cleaning and sequencing protocols employed ([12] ). Drugs with electrostatic properties—particularly those in powder form such as sulfonamides and coccidiostats—adhere strongly to equipment surfaces, making complete removal between batches extremely difficult ([6] ). Even when manufacturers implement Good Manufacturing Practices (GMP) and Hazard Analysis Critical Control Point (HACCP) principles, the FAO/WHO Expert Meeting concluded that some degree of carryover remains unavoidable ([6] ).

Sequencing—the pre-planned order of feed production designed to control drug carryover—is the preferred industry approach because it minimizes downtime and waste ([24] ). However, sequencing is only effective when medicated feeds containing the same drug are produced in order of decreasing inclusion levels, followed by non-medicated feed for the same species before producing feed for non-target species ([6] ). When sequencing is not feasible or when drugs with special toxicity characteristics (e.g., monensin toxicity to horses) are involved, flushing (using ground grain to "flush" out residual medicated feed) or physical cleanout is required, though these methods are economically burdensome ([24] ).

The regulatory implications of carryover are substantial. A study analyzing 292 field investigative reports from the US Food and Drug Administration (FDA) between 1983 and 1988 found that the primary cause of drug residues was failure to observe withdrawal times, with nearly half of responsible individuals unaware of the correct withholding period ([26] ). While this study predates many modern circular economy initiatives, its findings remain relevant:

producers were held responsible in over 80% of cases, underscoring the need for educational interventions alongside regulatory enforcement ([26] and [21] ).

### 3.2. Contamination of Raw Feed Ingredients from Agricultural By-Products

The increasing use of agricultural and food processing by-products as feed ingredients introduces new contamination pathways that are distinct from traditional carryover. These by-products—including dried distillers grains with solubles (DDGS), processed animal proteins (PAPs), fruit and vegetable peels, and other upcycled materials—may contain veterinary drug residues from their original production or processing ([7] and [20] ).

#### 3.2.1. Processed Animal By-Products

Processed animal by-products, including meat and bone meal, poultry by-product meal, blood meal, and feather meal, can introduce veterinary drug residues into non-target food-producing animal species ([7] and [17] ). Wide-scope qualitative screening of commercially available EU-produced PAPs has revealed the presence of pharmaceutical agents, including monensin, flumequine, enrofloxacin, trimethoprim, and tylosin A ([17] ). Similarly, screening studies on feather meal from the United States and China have detected six classes of antimicrobials, including fluoroquinolones, tetracyclines, folic acid antagonists, and streptogramins ([17] ). These residues originate from veterinary drugs administered to the source animals, which persist through rendering processes and concentrate in the resulting by-products ([7] ).

The European Union has implemented strict regulations to manage these risks. Following the bovine spongiform encephalopathy (BSE) crisis, the use of all PAPs in animal feed was banned in the EU in 2001 ([24] ). Subsequent risk assessments have led to partial re-authorization, with non-ruminant PAPs permitted in aquafeed since 2013 and processed insect proteins in pig and poultry feed since 2021 ([24] ). However, the use of fish sludge—particulate organic waste from aquaculture—as feed for invertebrates remains prohibited due to insufficient data on biological and chemical hazards, including the potential presence and transfer of veterinary pharmaceuticals ([17] ).

#### 3.2.2. Distillers Grains and Bioethanol Co-Products

The increasing demand for ethanol as fuel has led to a corresponding increase in distillers grains (DG) as a by-product of the fuel ethanol industry, making DG an attractive alternative feed ingredient due to its high content of energy, protein, and minerals ([6] ). However, during fermentation, antimicrobials are added to combat bacterial contamination that reduces ethanol yield and DG quality. This practice can lead to antimicrobial residues in DG or DDGS that are subsequently fed to food-producing animals ([6] ).

A nationwide survey conducted by the US FDA Center for Veterinary Medicine in 2008 detected quantifiable antimicrobial residues in 17 of 200 DG samples, with virginiamycin estimated at 0.1–0.5 ppm and erythromycin at 0.1–1.5 ppm ([6] ). While subsequent studies have shown low rates of detection and biologically inactive residues, the perceived risk impacts trade in countries with "zero tolerance" policies and has discouraged DDGS use in production systems claiming "free from antibiotics" labeling ([6] ).

#### 3.2.3. Plant-Based By-Products

Plant-based by-products—including brewers' spent grains, sugar beet pulp, citrus pulp, cereal brans, and oilseed meals—can also contain veterinary drug residues, primarily through uptake from manure-fertilized soils or cross-

contamination during processing ([7] and [15] ). When animal manure containing unmetabolized veterinary drugs is applied to agricultural land as fertilizer, these compounds can be taken up by crops and subsequently concentrate in processing by-products ([7] and [11] ).

The extent of plant uptake depends on drug properties (particularly polarity and ionic form), soil characteristics (organic matter content, pH), and plant species ([7] ). Tetracyclines tend to accumulate in surface soil layers and show limited plant uptake, whereas sulfonamides are more mobile and can leach into groundwater or be taken up by crops ([7] ). Although the uptake of antimicrobials by plants is generally low at concentrations typically found in agricultural soils, the widespread and repeated application of manure over time can lead to gradual accumulation and increased risk ([7] and [11] ).

### 3.3. Environmental Contamination and Animal-to-Animal Transfer

Beyond feed manufacturing and ingredient contamination, veterinary drug residues can enter the feed chain through environmental pathways and direct animal-to-animal transfer ([12] and [7] ).

#### 3.3.1. Environmental Contamination

Antibiotic pollution—the release of antibiotic residues, antibiotic-resistant bacteria, and resistance genes into the environment—is a growing concern ([3] and [19] ). Approximately 75% of administered antibiotics are not fully absorbed by animals and are excreted unchanged in urine and feces, entering the environment through manure application, aquaculture discharge, and improper disposal of unused medicines ([3] ). These residues can contaminate soil and water, where they exert selective pressure on environmental bacteria, promote resistance development, and can be taken up by crops grown on manure-amended fields ([7] and [16] ).

The environmental persistence of veterinary drugs varies considerably by compound. Tetracycline and doxycycline have half-lives in soil of up to 500 days, while other compounds degrade more rapidly under aerobic conditions ([17] ). This persistence, combined with repeated manure applications over multiple growing seasons, creates the potential for long-term accumulation and increased risk of crop uptake ([7] ). The FAO/WHO Expert Meeting emphasized that while human health risks from chemical hazards at carryover concentrations are generally negligible, the contribution of environmental contamination to antimicrobial resistance selection is a significant concern requiring further research ([6] ).

#### 3.3.2. Animal-to-Animal Transfer

Another, less recognized route by which violative residues can occur is the transfer of drugs from animal to animal via ingestion of feces and/or urine ([12] ). Brief exposure of unmedicated animals to the excretions of medicated animals in improperly cleaned housing, during transportation, or in lairage at slaughterhouses can result in violative residues ([12] ). This mechanism is particularly relevant for drugs that are poorly absorbed and excreted largely unchanged, and for compounds that are stable in the environment.

The implications for circular feed systems are significant. If animals are exposed to medicated feed or contaminated by-products and subsequently excrete unmetabolized drugs in their manure, that manure—if recycled as fertilizer or as a substrate for insect rearing—can reintroduce those drugs into the feed chain ([17] and [9] ). This creates a potential recirculation pathway that could lead to the accumulation of residues over multiple cycles, a concern that has been modeled for antimicrobials in circular food systems using the CirFSafe framework ([10] ).

### 3.4. Inappropriate Drug Use and Withdrawal Period Violations

While the focus of this review is on unintended and unavoidable residues, it is important to acknowledge that inappropriate drug use remains a major contributor to veterinary drug residues in animal products ([5] and [14] ). The most commonly identified causes include failure to observe withdrawal periods, extra-label drug use (use of an approved drug in a manner not in accordance with label directions), improper dosage, and administration of long-acting or sustained-release products ([26] and [5] ).

The withdrawal period—the time required for drug residues to decline to safe concentrations as defined by the tolerance level—varies from a few hours to several weeks depending on the drug, dosage form, route of administration, and animal species ([1] ). Nearly half of the violative residue cases investigated by the FDA between 1983 and 1988 involved individuals who did not know the correct withdrawal period for the drug they administered ([26] ). More recent data from the US National Residue Surveillance Program (2014–2019) showed that implementation of the Veterinary Feed Directive (VFD) regulations—which restrict the use of medically important antimicrobials administered in feed and water to therapeutic purposes only under veterinary supervision—was associated with significant reductions in violative sulfonamide (36% decrease) and penicillin (24% decrease) residues ([21] ). However, no significant changes were observed for tetracyclines, desfuroylceftiofur, tilmicosin, or florfenicol, highlighting the need for targeted interventions for specific drug classes ([21] ).

### 3.5. The Role of Circular Economy Practices in Residue Amplification

A critical and understudied dimension of this problem is the potential for circular economy practices to amplify, rather than reduce, the risk of unintended drug residues. When by-products are recycled multiple times—for example, when manure from animals fed contaminated feed is used to fertilize crops, those crops are processed into feed, and the resulting by-products are again fed to animals—there is potential for the concentration and recirculation of persistent contaminants ([7] and [10] ).

Modeling studies using the CirFSafe framework, which predicts the fate of five different antimicrobials in a primary circular food production system (mixed farms with maize and bovine components), suggest that over a 5-year timeframe, fertilizing soil with animal manure and feeding animals with maize grown in the same soil are unlikely to cause antimicrobial residues in milk or meat exceeding European regulatory limits ([10] ). However, the distinct residual patterns of different antimicrobials—particularly flumequine and doxycycline, which showed greater tendency to transfer into food products—underscore the need for precautionary monitoring ([10] ). The model also revealed that under a one-off exposure scenario (a single contamination event in the first year), residues in food products became negligible after three years, suggesting that the risk of long-term accumulation from discrete contamination events is low ([10] ).

Nevertheless, these modeling results should be interpreted cautiously. The CirFSafe framework did not consider the effects of repeated cycles of recycling (i.e., closed-loop systems where manure from animals fed contaminated by-products is repeatedly applied to the same fields), nor did it account for the potential for synergistic effects of multiple contaminants or the formation of transformation products with unknown toxicity ([10] ). Further empirical research and refined modeling are needed to predict and prevent unintended consequences of incorporating diverse waste streams into feed systems ([10] and [7] ).

### 3.6. Synthesis and Research Gaps

The evidence reviewed in this section reveals that unintended veterinary drug residues in upcycled agricultural by-products arise from multiple, often interacting sources: carryover during feed manufacturing, contamination of raw by-product ingredients, environmental pollution, animal-to-animal transfer, and inappropriate drug use. Circular economy practices introduce new pathways for residue entry and potential recirculation, which are not yet fully characterized.

Several critical knowledge gaps remain. First, the occurrence and concentration of veterinary drugs in diverse upcycled by-product streams—particularly those from non-European or non-North American sources—are poorly documented ([11] and [17] ). Second, the fate of these residues through processing steps (e.g., ensiling, fermentation, heat treatment, extrusion) and their subsequent bioavailability to animals consuming treated feeds are insufficiently understood ([6] and [2] ). Third, the potential for long-term accumulation and amplification through multiple cycles of recycling has been modeled but not empirically validated ([10] ). Fourth, the contribution of environmental contamination—particularly from manure-amended soils—to residues in plant-based by-products requires further quantification ([7] ).

Addressing these gaps will require coordinated efforts across analytical chemistry, veterinary pharmacology, feed processing engineering, and risk assessment. The development of standardized monitoring protocols, the establishment of shared databases on residue occurrence, and the application of advanced analytical techniques (e.g., suspect screening and non-targeted analysis) will be essential to characterize the full scope of the problem and inform evidence-based risk management ([28] and [13] ).

## 4. UPCYCLED AGRICULTURAL BY-PRODUCTS AS FEED: OPPORTUNITIES AND HAZARDS

The valorization of agricultural and food processing by-products as animal feed represents a cornerstone of circular economy strategies in the agri-food sector. This section examines the major categories of upcycled feed materials, their nutritional potential, and the specific hazards associated with each stream.

### 4.1. Major Categories of Upcycled Feed Materials

Three major categories of upcycled agricultural by-products are increasingly utilized as animal feed: (1) crop processing by-products (distillers grains, cereal brans, oilseed meals, sugar beet pulp, citrus pulp); (2) processed animal by-products (meat and bone meal, poultry meal, feather meal, blood meal); and (3) food industry waste (brewer's spent grain, fruit and vegetable peels, dairy waste) ([20] and [23] ).

Globally, approximately 940 million tons (dry matter) of food-competing feedstuffs are currently used in animal production, representing 15% of total feed use ([20] ). Replacing these with by-products could increase global food supply by up to 13% in calories and 15% in protein content, freeing 31–54 million hectares of cropland ([20] ). Cereals (maize, wheat, barley) constitute the largest group of replaceable feedstuffs, followed by whole fish used for fishmeal production ([20] ).

### 4.2. Nutritional Value and Feed Safety Considerations

The nutritional composition of upcycled by-products varies considerably by source. Brewer's spent grain, the most abundant by-product of the brewing industry, contains 15–31% protein and 25–52% arabinoxylans, making it valuable for ruminant nutrition ([18] ). Orange peels, after enzymatic saccharification and fermentation, can achieve crude protein content of 21.8% (compared to 7.2% in raw peels) with 23% higher organic matter digestibility ([2] ). Shrimp

waste, which is 40% protein, also contains 20–30% chitin that can be converted to chitosan for value-added applications ([18] ).

However, several factors constrain the use of upcycled by-products. Many have high moisture content (requiring energy-intensive drying), variable nutrient composition, and may contain anti-nutritional factors or physical impurities (paper, plastic, glass) ([22] and [15] ). The presence of mycotoxins in plant-based by-products—particularly deoxynivalenol in cereal brans and aflatoxins in oilseed meals—poses additional risks ([7] and [14] ).

### 4.3. Veterinary Drug Residues in Specific By-Product Streams

The contamination of upcycled by-products with veterinary drug residues varies by source. Processed animal by-products frequently contain residues of drugs administered to source animals. Feather meal has been shown to contain six classes of antimicrobials, including fluoroquinolones and tetracyclines ([17] ). Grain distillers may contain antimicrobials added during ethanol fermentation to control bacterial contamination, with residues of virginiamycin and erythromycin detected at 0.1–1.5 ppm ([6] ).

A case study from Italy detected fipronil at mean levels of 0.49 mg/kg in grain distillers used for dairy cattle feed, leading to exceedances of EU maximum residue limits (MRLs) in milk (0.005 mg/kg) and fat (0.030 mg/kg) ([8] ). Silage-based diets containing contaminated distillers produced hazard indices up to 180 times the EU limit, while hay-based diets with soybean hulls and cane molasses showed negligible risks ([8] ). The study concluded that differing global regulations on fipronil—banned in the EU but permitted in the Americas and Asia—necessitate risk-oriented monitoring of imported circular feeds ([8] ).

### 4.4. Heavy Metals and Other Contaminants

In addition to veterinary drugs, upcycled by-products may contain heavy metals, persistent organic pollutants (POPs), and mycotoxins. Black soldier fly larvae (BSFL) reared on waste streams accumulate cadmium (bioaccumulation factors of 2.9–3.4), though concentrations remained below EU maximum limits for animal feed (2 mg/kg at 12% moisture) ([9] ). Other metals including manganese, iron, zinc, copper, and selenium also accumulated in certain treatments ([9] ).

Fish sludge from aquaculture operations contains variable levels of arsenic (0.44–5.3 mg/kg DM), cadmium (0.19–5.2 mg/kg DM), and lead (<0.01–13.3 mg/kg DM), with some samples exceeding EU MRLs for complete feed ([17] ). Dioxins and dioxin-like PCBs in fish sludge approached EU limits, and organic arsenic forms were the predominant species in BSFL fed on sludge ([17] ). The authors concluded that while fish sludge shows promise as a circular feed resource, targeted monitoring of priority contaminants is required before regulatory approval ([17] ).

### 4.5. The Role of Insects and Polychaetes as Bio-Converters

Insects and polychaetes offer a promising pathway for converting low-value waste into high-quality protein, but they also introduce food safety concerns. BSFL reared on contaminated substrates can accumulate veterinary drugs, heavy metals, and pathogenic bacteria ([9] and [17] ). Only traces of doxycycline, oxytetracycline, and coccidiostats were found in BSFL reared on mixed waste streams, with concentrations too low for quantification ([9] ). However, DNA of ruminant and pig was detected in BSFL samples (including gut contents), raising concerns about compliance with

EU regulations prohibiting intra-species recycling ([9] ). The authors recommended fasting periods or processing steps to clear gut contents before harvest ([9] ).

For polychaetes (Hediste diversicolor) fed on fish sludge, levels of arsenic exceeded EU MRLs for feed materials (2 mg/kg), while cadmium and lead remained below limits ([17] ). The authors emphasized that considerable knowledge gaps exist regarding the fate of both biological and chemical hazards through invertebrate ingestion, and that current EU regulations prohibit the use of fish sludge as feed for invertebrates due to insufficient data ([17] ).

### 4.6. Regulatory Status and Regional Variations

The regulatory landscape for upcycled feeds varies substantially across jurisdictions. Japan, South Korea, and Taiwan have achieved conversion of over 65% of available food waste into safe animal feed through mandatory heat treatment (70–90°C for 30–60 minutes), government-subsidized certification systems, and dedicated infrastructure ([24] and [23] ). In contrast, the US recycles only 5–10% of available food waste into animal feed due to complex federal and state regulations and limited FDA-approved definitions ([24] ). The EU has the most restrictive regulations, recycling only an estimated 5% of food waste into feed, primarily due to historical BSE concerns and complex animal by-product classifications ([24] ).

A summary of major upcycled feed streams, their associated hazards, and current regulatory status is presented in Table 1.

**Table 1. Summary of major upcycled feed streams, associated hazards, and regulatory status**

| Feed Stream | Main Hazards | Key Findings | Regulatory Status (EU) |
|---|---|---|---|
| **Processed Animal Proteins (PAPs)** | Veterinary drug residues (fluoroquinolones, tetracyclines), prions | Detected in feather meal, meat and bone meal ([17] ) | Restricted; only Category 3 permitted after heat treatment |
| **Distillers Grains (DDGS)** | Antimicrobial residues (virginiamycin, erythromycin) | 0.1–1.5 ppm residues detected in US survey ([6] ) | Permitted but monitored |
| **Fish Sludge** | Heavy metals (As, Cd, Pb), dioxins, PCBs | Exceeds EU MRLs for As; dioxins approach limits ([17] ) | Currently prohibited as invertebrate feed |
| **Orange Peels (after processing)** | Initially low protein; processing increases value | Protein content increased from 7.2% to 21.8% ([2] ) | Permitted after heat treatment |
| **Black Soldier Fly Larvae** | Cadmium accumulation, animal DNA carryover | BAF for Cd: 2.9–3.4; ruminant/pig DNA detected ([9] ) | Permitted for aquaculture, pig, poultry feed |

Recent EU regulatory changes (Regulation EU 2021/1372) have re-authorized the use of processed animal proteins from pigs and poultry in non-ruminant feeds, and insects are now permitted as feed for aquaculture, pigs, and poultry ([24] and [1] ). However, substrates for insect rearing remain restricted, and fish sludge is currently prohibited ([17] ). China, despite ongoing challenges with African swine fever control, has initiated pilot projects to develop feed manufacturing technologies for converting food waste into safe animal feed as part of its Soybean Meal Reduction and Replacement 3-Year Action Plan ([24] ).

### 4.7. Synthesis

Upcycled agricultural by-products offer substantial nutritional and environmental benefits but also introduce food safety hazards that vary by source and processing method. Processed animal by-products, grain distillers, and fish sludge carry the highest risk of veterinary drug contamination, while plant-based by-products present risks from mycotoxins and heavy metals. Insect and polychaete bio-converters can accumulate hazards from their substrates, requiring careful substrate selection and post-harvest processing. Successful implementation of circular feed systems requires harmonized regulatory frameworks, risk-based monitoring, and processing technologies that effectively mitigate hazards while preserving nutritional value.

## 5. PUBLIC HEALTH AND ONE HEALTH IMPLICATIONS

The presence of unintended veterinary drug residues in upcycled agricultural by-products poses significant threats to human health, animal health, and environmental integrity. This section examines these risks through the lens of the One Health framework, which recognizes the inextricable linkages between human, animal, and ecosystem health ([19] and [14] ).

### 5.1. Direct Toxic Effects on Human Health

Antibiotic residues in food of animal origin can cause a range of direct toxic effects, from mild allergic reactions to life-threatening conditions ([3] and [5] ). The most frequently reported allergic reactions are associated with beta-lactam antibiotics (penicillins and cephalosporins), manifesting as skin rashes, serum sickness, anaphylaxis, hemolytic anemia, vasculitis, and acute interstitial nephritis ([3] ). Cases of anaphylaxis have been documented following consumption of beef and pork containing penicillin residues ([3] ).

Beyond allergic reactions, specific antibiotics have been linked to severe pathologies. Chloramphenicol—banned in food-producing animals in most jurisdictions due to its toxicity—causes dose-independent bone marrow toxicity (aplastic anemia) that can be fatal ([3] and [5] ). Gentamicin residues are associated with nephrotoxicity and ototoxicity, while tetracyclines can cause hepatotoxicity and teeth discoloration in young children ([14] ). Sulfamethazine, oxytetracycline, and furazolidone have demonstrated carcinogenic potential in animal studies ([5] and [4] ). The acceptable daily intake (ADI) for fipronil—which affects thyroid function—is set at 0.0002 mg/kg body weight, yet studies have shown this level is exceeded in most dairy cow feeding scenarios using contaminated circular feeds ([8] ).

### 5.2. Antimicrobial Resistance: The Hidden Pandemic

The most significant and far-reaching consequence of antibiotic residues in the food chain is the development and spread of antimicrobial resistance (AMR) ([6] and [4] ). Exposure of bacteria to subtherapeutic concentrations of antibiotics—precisely the levels found in carryover-contaminated feed and upcycled by-products—creates selective pressure that favors the emergence of resistant strains ([3] ).

The mechanisms of resistance acquisition include spontaneous mutations, horizontal gene transfer via plasmids and other mobile genetic elements, alteration of target sites, enzymatic degradation of antibiotics, and efflux pump activation ([3] ). Once resistance genes emerge in animal-associated bacteria, they can transfer to human pathogens through the food chain, direct contact with animals, or environmental contamination ([19] and [14] ).

The World Health Organization estimates that if no action is taken, drug-resistant diseases could cause 10 million deaths annually by 2050, with economic damage equivalent to the 2008–2009 global financial crisis ([3] ). Critically important antimicrobials (CIAs) for human medicine—including fluoroquinolones, third-generation cephalosporins, macrolides, and polymyxins (colistin)—are regularly used in food animal production, creating particular concern ([14] ).

### 5.3. Disruption of Intestinal Microbiota

The human gastrointestinal tract harbors approximately 1,000 bacterial species that play essential roles in digestion, immune function, and protection against pathogens ([3] ). Exposure to antibiotic residues through food can disrupt this delicate ecosystem, leading to gastrointestinal disturbances, reduced colonization resistance against pathogens, and long-term metabolic consequences ([5] and [4] ). While direct evidence of such disruption from residue-level exposure is limited, the potential for adverse effects is recognized by regulatory authorities ([6] ).

### 5.4. Animal Health and Welfare Implications

Unintended drug residues also affect the animals consuming contaminated feed. Exposure of bacteria in the animal gut to subtherapeutic antibiotic levels promotes resistance among commensal and pathogenic bacteria, potentially compromising the efficacy of veterinary treatments ([19] ). Additionally, certain drugs are toxic to non-target species; for example, ionophores (e.g., monensin) commonly used in poultry and cattle feed are highly toxic to horses, causing myocardial degeneration and death even at low carryover levels ([6] ).

### 5.5. Environmental Contamination and Recirculation

Approximately 75% of administered antibiotics are excreted unchanged by animals, entering the environment through manure ([3] ). These residues contaminate soil and water, where they exert selective pressure on environmental bacteria, promote resistance development, and can be taken up by crops grown on manure-amended fields ([7] ). Manure application has been shown to significantly increase soil concentrations of heavy metals (cadmium, lead, zinc) and antibiotic resistance genes (tetracycline, sulfonamide, macrolide resistance determinants) ([7] and [16] ).

The persistence of veterinary drugs in the environment varies considerably. Tetracyclines and doxycycline have half-lives in soil of up to 500 days, while flumequine is also highly persistent ([17] ). This persistence, combined with repeated manure applications over multiple growing seasons, creates potential for long-term accumulation and increased risk of crop uptake ([7] ). Modeling studies suggest that circular systems—where manure from animals fed contaminated by-products is repeatedly applied to the same fields—could lead to gradual accumulation of persistent contaminants ([10] ).

### 5.6. The One Health Approach to Risk Mitigation

The One Health framework, which recognizes the interconnectedness of human, animal, and environmental health, provides an essential approach for addressing the complex challenge of unintended drug residues in circular feed systems ([19] ). This approach requires coordinated interventions across multiple sectors: prudent use of antibiotics in veterinary medicine, improved manure management to reduce environmental contamination, enhanced feed safety monitoring, and public health surveillance for AMR ([14] ).

Successful examples of One Health interventions include Denmark's ban on antibiotic growth promoters (implemented in the 1990s), which was accompanied by veterinary oversight, farm health plans, and monitoring systems, resulting in reduced antibiotic use without compromising animal health or productivity ([19] ). Similarly, the implementation of the US Veterinary Feed Directive (VFD) was associated with significant reductions in violative sulfonamide (36%) and penicillin (24%) residues in food animal tissues ([21] ).

However, significant gaps remain. Only 7 of 20 studies evaluating interventions to reduce antibiotic resistance reported positive outcomes, and risk of bias was high in 28 of 57 positive interventions ([19] ). The authors concluded that more research is needed in low-resource settings and on structural interventions addressing social, economic, and policy contexts ([19] ).

### 5.7. Synthesis

Unintended veterinary drug residues in upcycled agricultural by-products pose significant threats across the One Health spectrum: direct toxicity to consumers, acceleration of the AMR pandemic, disruption of intestinal microbiota, animal health risks, and environmental contamination. The complex, interconnected nature of these threats requires coordinated, multi-sectoral interventions that address root causes (inappropriate antibiotic use, inadequate manure management, regulatory gaps) rather than merely treating symptoms. The One Health framework offers a valuable lens for designing and evaluating such interventions, but evidence of effectiveness remains limited, particularly in low-resource settings.

## 6. REGULATORY FRAMEWORKS AND RISK MANAGEMENT STRATEGIES

Effective management of unintended veterinary drug residues in upcycled feeds requires robust regulatory frameworks and evidence-based risk management strategies. This section compares regulatory approaches across major jurisdictions and synthesizes recommended interventions.

### 6.1. European Union: Precautionary but Restrictive

The EU maintains the most precautionary regulatory framework for animal feed safety. Regulation (EC) No 1069/2009 classifies animal by-products into three categories, with only Category 3 materials (low-risk, from animals deemed fit for human consumption) permitted for feed use after specified heat treatments ([1] ). Method 1 requires 133°C for 20 minutes at 3 bar pressure, while Method 7 (approved for fishmeal) requires ≥80°C for ≥20 minutes ([6] and [1] ).

Maximum residue limits (MRLs) for veterinary drugs in food are established under Regulation (EU) No 37/2010, with fipronil MRLs set at 0.005 mg/kg in milk and 0.030 mg/kg in fat ([8] ). For carryover in non-target feed, the EU has established action levels for coccidiostats following the ALARA (As Low As Reasonably Achievable) principle ([6] ). However, only an estimated 5% of available food waste is recycled into animal feed due to these stringent restrictions ([24] ).

### 6.2. United States: Federal-State Complexity

The US regulatory system combines federal and state jurisdiction. The Swine Health Protection Act (1980) requires heat processing of food waste containing meat at 100°C for 30 minutes before feeding to pigs ([24] ). The FDA's Veterinary Feed Directive (VFD), fully implemented in 2017, restricted medically important antimicrobials in feed to

therapeutic use under veterinary oversight, resulting in 24–36% reductions in violative sulfonamide and penicillin residues ([21] ).

However, only three FDA-approved definitions exist for food waste in feed (Recovered Retail Food, Food Processing Waste, Restaurant Food Waste), and state regulations vary considerably ([24] ). Consequently, only 5–10% of available food waste is upcycled to animal feed ([24] ).

### 6.3. Asian Leaders: Japan, South Korea, and Taiwan

Japan, South Korea, and Taiwan have achieved the highest rates of food waste upcycling (>65%) through mandatory heat treatment (70–90°C for 30–60 minutes), government-subsidized certification systems, and integrated infrastructure ([24] and [23] ). Japan's Eco-feed certification system requires heating at 70°C for 30 minutes or 80°C for 3 minutes for poultry and fish feed, with strict record-keeping and traceability ([24] ). No disease outbreaks have been linked to properly heat-treated food waste in over 20 years ([23] ).

The key features of regulatory frameworks across major jurisdictions are compared in Table 2.

**Table 2. Comparison of regulatory frameworks for food waste upcycling across major jurisdictions**

| Jurisdiction | Recycling Rate | Heat Treatment Required | Certification System | Key Legislation |
|---|---|---|---|---|
| **Japan** | >65% | 70–90°C for 30–60 min | Eco-feed certification | Food Waste Recycling Law (2007) |
| **South Korea** | >65% | ≥80°C for 30 min | MOE certification | Waste Management Act |
| **Taiwan** | 60–75% | >90°C for >1 hour | EPA certification | Waste Management Act |
| **European Union** | ~5% | Method 1: 133°C, 20 min, 3 bar; Method 7: ≥80°C, ≥20 min | None unified | Reg (EC) No 1069/2009 |
| **United States** | 5–10% | 100°C for 30 min (Swine Health Protection Act) | None; limited FDA definitions | Swine Health Protection Act (1980), FSMA |
| **China** | Emerging | Under development (pilot projects) | Under development | Save Food Action Plan (2021); Soybean Meal Reduction Plan (2023) |

### 6.4. Risk Management Strategies

The FAO/WHO Expert Meeting (2019) recommended several key strategies for managing carryover risks ([6] ):

**At feed mills:** Dedicated production lines for medicated feed where possible; validated sequencing and flushing protocols; regular cleaning and maintenance; HACCP-based monitoring.

**At farms:** Awareness training for farmers and workers; proper feed storage and handling; avoidance of cross-contamination between medicated and non-medicated feed.

**At regulatory level:** Establishment of science-based action levels for unavoidable carryover in non-target species; strengthening national capacities for implementing Codex Code of Practice on Good Animal Feeding; pre-import testing of high-risk feed materials ([8] ).

### 6.5. Gaps and Recommendations

Critical regulatory gaps remain. First, MRLs for veterinary drugs in non-target species are lacking for many compounds, leading to trade disputes ([6] ). Second, the classification of fish sludge as Category 2 or 3 material remains unresolved in the EU, prohibiting its use as invertebrate feed despite promising nutritional potential ([17] ). Third, global harmonization of MRLs is incomplete, with US-EPA and Codex Alimentarius standards differing substantially from EU limits ([8] ).

The authors recommend: (1) establishment of internationally harmonized action levels for unavoidable carryover; (2) increased investment in monitoring infrastructure, particularly for imported feeds; (3) development of cost-effective rapid screening methods; and (4) adoption of Japan's multi-stage certification model in other regions ([24] and [8] ).

## 7. LIMITATIONS

This review has several limitations that should be acknowledged. First, the available literature on veterinary drug residues specifically in upcycled agricultural by-products is limited, with most studies focusing on conventional feed contamination pathways such as carryover. Second, the majority of studies originated from high-income countries (EU, US, Japan, South Korea), limiting the generalizability of findings to low- and middle-income settings where waste upcycling practices and regulatory frameworks differ substantially. Third, the heterogeneity of methodologies, drug classes, and waste streams across studies precluded quantitative meta-analysis. Fourth, publication bias may exist, as studies reporting positive findings (e.g., successful interventions) are more likely to be published than those with negative or neutral results. Fifth, data on emerging hazards such as transformation products of veterinary drugs, combined effects of multiple contaminants, and long-term accumulation in closed-loop systems remain scarce. Future research should prioritize these understudied areas to enable more comprehensive risk assessments.

## 8. CONCLUSIONS AND FUTURE PERSPECTIVES

### 8.1. Summary of Key Findings

This narrative review has synthesized current evidence on unintended veterinary drug residues in upcycled agricultural by-products used as animal feed, revealing a complex problem with significant implications for food safety, public health, and the sustainable development of circular food systems.

The evidence demonstrates that veterinary drug residues enter upcycled feed through multiple, often interacting pathways: carryover during feed manufacturing ([12] and [6] ), contamination of raw by-product ingredients including processed animal proteins and distillers grains ([17] and [9] ), environmental pollution from manure-amended soils ([7] ), and animal-to-animal transfer ([12] ). Circular economy practices, while offering substantial environmental and food security benefits ([20] and [23] ), can also create new pathways for residue entry and potential recirculation ([10] ).

The public health consequences are substantial and multifaceted. Direct toxicity includes allergic reactions (particularly to penicillins), hepatotoxicity, nephropathy, bone marrow toxicity (chloramphenicol), carcinogenicity

(sulfamethazine, oxytetracycline), and disruption of intestinal flora ([3] and [5] and [4] ). However, the most significant threat is the acceleration of antimicrobial resistance (AMR), which the World Health Organization has identified as one of the top ten global public health threats, with projections of 10 million annual deaths by 2050 if unaddressed ([3] and [14] ).

Regulatory frameworks vary substantially across jurisdictions. The European Union maintains the most precautionary approach, with only an estimated 5% of food waste recycled into animal feed ([24] ). The United States achieves similarly low rates (5–10%) due to complex federal-state regulations and limited FDA-approved definitions ([24] ). In contrast, Japan, South Korea, and Taiwan have demonstrated that high rates of safe upcycling (>65%) are achievable through mandatory heat treatment, government-subsidized certification systems, and integrated infrastructure, with no disease outbreaks linked to properly treated food waste in over 20 years ([24] and [23] ).

### 8.2. Knowledge Gaps

Despite growing research attention, several critical knowledge gaps remain, as summarized in Table 3.

**Table 3. Key knowledge gaps and research priorities**

| Knowledge Gap | Priority Research Need | Relevant References |
|---|---|---|
| **Occurrence data for non-European by-product streams** | Systematic global surveys of veterinary drug residues in upcycled feeds | [11] and [17] |
| **Fate of residues through processing** | Experimental studies on thermal, enzymatic, and fermentation processing effects | [6] and [2] |
| **Long-term accumulation in closed-loop systems** | Empirical validation of modeling predictions (e.g., CirFSafe) | [10] and [7] |
| **Emerging hazards (insects, polychaetes, algae)** | Risk assessment of novel feed sources and transformation products | [17] and [9] |
| **Low-resource settings** | Intervention studies in smallholder and subsistence farming systems | [19] |

First, the occurrence and concentration of veterinary drugs in diverse upcycled by-product streams—particularly those from non-European or non-North American sources—are poorly documented ([11] and [17] ). Second, the fate of these residues through processing steps (e.g., ensiling, fermentation, heat treatment, extrusion) and their subsequent bioavailability to animals are insufficiently understood ([6] and [2] ). Third, the potential for long-term accumulation and amplification through multiple cycles of recycling has been modeled but not empirically validated ([10] and [7] ). Fourth, emerging hazards from novel feed sources (insects, polychaetes, algae), plastic-associated chemicals in recycled packaging, and transformation products of veterinary drugs remain largely unexplored ([17] and [11] ). Fifth, very few studies have evaluated interventions in smallholder or subsistence farming systems, where the burden of food insecurity and inappropriate antibiotic use is highest ([19] ).

### 8.3. Recommendations for Policy and Practice

Based on the evidence synthesized in this review, the following recommendations are proposed:

**For regulators and policymakers:**

- Establish internationally harmonized action levels for unavoidable carryover of veterinary drugs in non-target feed ([6] and [8] )
- Adopt mandatory heat treatment requirements (minimum 70–90°C for 30–60 minutes) for food waste destined for animal feed, with verification through certification systems ([24] )
- Increase investment in monitoring infrastructure, particularly for imported feeds from countries with differing veterinary drug regulations ([8] )
- Re-evaluate MRLs for lipophilic drugs (e.g., fipronil) on a fat basis to better reflect residue distribution ([8] )

**For feed manufacturers and farmers:**

- Implement validated sequencing and flushing protocols; use dedicated production lines for medicated feed where possible ([6] )
- Maintain detailed production and treatment records to enable traceability ([24] )
- Provide regular training on withdrawal periods, proper drug use, and feed safety to farm workers ([26] and [21] )

**For researchers:**

- Conduct systematic surveys of veterinary drug residues in diverse upcycled feed streams, with particular attention to emerging sources (insects, polychaetes, seaweed) ([17] and [9] )
- Develop and validate rapid, cost-effective screening methods suitable for use at feed mills and border inspection points ([28] and [13] )
- Investigate the fate of drug residues through processing and their bioavailability in target animal species ([2] and [15] )
- Evaluate the effectiveness of structural interventions (e.g., manure treatment requirements, antibiotic use reporting systems) in reducing residues ([19] )

### 8.4. A Path Forward: Balancing Circularity and Safety

The transition toward circular food systems is not only desirable but necessary to address environmental and food security challenges ([20] and [23] ). However, this transition must be guided by the precautionary principle and informed by rigorous, context-specific risk assessment ([6] and [11] ).

The evidence reviewed here does not support abandoning circular feed systems. Rather, it calls for their optimization through: (1) improved monitoring and surveillance; (2) targeted interventions for high-risk pathways (processed animal proteins, distillers grains, manure-amended crops); (3) harmonization of regulatory frameworks to facilitate safe international trade; and (4) investment in research to close critical knowledge gaps.

Crucially, the success of circular feed systems depends not only on technological solutions but also on behavioral and structural changes: prudent use of antibiotics in veterinary medicine, adherence to withdrawal periods, proper manure management, and a culture of shared responsibility across the feed-fork continuum ([19] and [23] ).

### 8.5. Final Remarks

Unintended veterinary drug residues in feed from upcycled agricultural by-products represent a hidden threat to the One Health triad of human, animal, and environmental well-being. This threat is neither insurmountable nor a reason to abandon circular economy aspirations. Rather, it is a challenge to be met with scientific rigor, regulatory wisdom, and collaborative action across sectors and borders.

The substantial environmental and food security benefits of upcycling food loss and waste into animal feed—including reduced greenhouse gas emissions, spared land and water resources, and increased food availability ([20] and [23] and [16] )—are too significant to ignore. With appropriate safeguards, including mandatory heat treatment, risk-based monitoring, and certification systems modeled on successful Asian programs, the vision of a safe, circular, and sustainable food system is achievable.

The hidden threat of unintended drug residues must be brought into the light—not to halt progress, but to guide it responsibly.

## 9. CONCLUSIONS

The transition toward circular food systems, while essential for addressing environmental degradation and global food insecurity, introduces unintended veterinary drug residues into upcycled agricultural by-products as a hidden threat to food safety and public health. This review has demonstrated that residues enter circular feed systems through multiple pathways—carryover during manufacturing, contamination of processed animal proteins and distillers grains, environmental pollution from manure-amended soils, and animal-to-animal transfer—with significant consequences including direct toxicity, disruption of intestinal microbiota, and acceleration of the antimicrobial resistance pandemic. The comparative analysis of regulatory frameworks reveals a stark contrast: Japan, South Korea, and Taiwan have achieved safe upcycling of over 65% of food waste through mandatory heat treatment, government-subsidized certification, and integrated infrastructure, while the European Union and United States recycle only 5–10% due to restrictive regulations and complex jurisdictional frameworks. Critical knowledge gaps remain, including limited occurrence data for non-European by-product streams, insufficient understanding of residue fate through processing, and lack of empirical validation for long-term accumulation in closed-loop systems. Addressing this challenge requires internationally harmonized action levels for unavoidable carryover, risk-based monitoring of imported feeds, investment in rapid screening technologies, adoption of successful Asian certification models, and a coordinated One Health approach integrating prudent antibiotic use, improved manure management, and enhanced feed safety surveillance. The substantial environmental and food security benefits of upcycling—reduced greenhouse gas emissions, spared land and water resources, and increased food availability—are too significant to abandon, but realizing these benefits without compromising safety demands rigorous science, regulatory wisdom, and collaborative action across sectors and borders.

## REFERENCES

[1] Anadón A., Martínez-Larrañaga M.R., Ares I., Martínez M.A. (2025). Regulatory aspects for the drugs and chemicals used in food-producing animals in the European Union. In: Gupta R.C., editor. Veterinary Toxicology: Basic and Clinical Principles, 4th ed. Academic Press, pp. 97-130.

[2] Andrianou C., Passadis K., Malamis D., Moustakas K., Mai S., Barampouti E.M. (2023). Upcycled animal feed: Sustainable solution to orange peels waste. Sustainability, vol. 15, no. 3, p. 2033.

[3] Arsène M.M.J., Davares A.K.L., Viktorovna P.I., Andreevna S.L., Sarra S., Khelifi I., Sergueïevna D.M. (2022). The public health issue of antibiotic residues in food and feed: Causes, consequences, and potential solutions. Veterinary World, vol. 15, no. 3, pp. 662-671.

[4] Atta A.H., Atta S.A., Nasr S.M., Mouneir S.M. (2022). Current perspective on veterinary drug and chemical residues in food of animal origin. Environmental Science and Pollution Research, vol. 29, pp. 15282-15302.

[5] Beyene T. (2016). Veterinary drug residues in food-animal products: its risk factors and potential effects on public health. Journal of Veterinary Science & Technology, vol. 7, no. 1, p. 1000285.

[6] FAO & WHO. (2019). Carryover in feed and transfer from feed to food of unavoidable and unintended residues of approved veterinary drugs: Report of the Joint FAO/WHO Expert Meeting. FAO Animal Production and Health Report No. 13. Rome: FAO.

[7] Focker M., van Asselt E.D., Berendsen B.J.A., van de Schans M.G.M., van Leeuwen S.P.J., Visser S.M., van der Fels-Klerx H.J. (2022). Review of food safety hazards in circular food systems in Europe. Food Research International, vol. 158, p. 111505.

[8] Gasparini M., Brambilla G., Menotta S., Albrici G., Avezzù V., Vitali R., Buonaiuto G., Lamanna M., Cavallini D. (2024). Sustainable dairy farming and fipronil risk in circular feeds: insights from an Italian case study. Food Additives & Contaminants: Part A, vol. 41, no. 12, pp. 1582-1593.

[9] Hoffmans Y., Veldkamp T., Meijer N.P., Brust G.M.H., van der Schans M.G.M., Prins T.W., van Rozen K., Elissen H., van Wikselaar P., van der Weide R., van der Fels-Klerx H.J., Hoek-van den Hil E.F. (2024). Can black soldier fly larvae (Hermetia illucens) be reared on waste streams for food and feed? – A safety perspective. Journal of Insects as Food and Feed, vol. 10, no. 7, pp. 1211-1221.

[10] Huang W., Focker M., van der Fels-Klerx H.J. (2025). Modeling antimicrobial fate in the circular food system. Risk Analysis, vol. 45, no. 12, pp. 2790-2807.

[11] James K., Millington A., Randall N. (2022). Food and feed safety vulnerabilities in the circular economy. EFSA Supporting Publication, vol. 19, no. 3, p. EN-7226.

[12] Kennedy D.G., Cannavan A., McCracken R.J. (2000). Regulatory problems caused by contamination, a frequently overlooked cause of veterinary drug residues. Journal of Chromatography A, vol. 882, no. 1-2, pp. 37-52.

[13] Lopes A.L., Leite M., P. P. Oliveira M.B., Freitas A. (2025). Multi-detection of veterinary medicines in animal feed for production: A review. Antibiotics, vol. 14, no. 12, p. 1233.

[14] Mesfin Y.M., Mitiku B.A., Admasu H.T. (2024). Veterinary drug residues in food products of animal origin and their public health consequences: A review. Veterinary Medicine and Science, vol. 10, no. 6, p. e70049.

[15] Nahi O., Siankevich S. (2023). Upcycling of cereal byproducts: A sustainable opportunity to valorize wasted nutrients and derive bioactive compounds for humans and animals nutrition and health. CHIMIA, vol. 77, no. 12, pp. 858-866.

[16] Peng X., Jiang Y., Chen Z., Osman A.I., Farghali M., Rooney D.W., Yap P.S. (2023). Recycling municipal, agricultural and industrial waste into energy, fertilizers, food and construction materials, and economic feasibility: A review. Environmental Chemistry Letters, vol. 21, pp. 765-801.

[17] Pettersen K.S., Sele V., Araujo P., Belghit I., Benestad S.L., Bernhoft A., Booth A.M., Eriksen G.S., Farkas J., Handå A.H., Hansen B.H., Helgesen K.O., Holst-Jensen A., Johannessen G.S., Liland N.S., Lundebye A.K., Malzahn A.M., Nilsen H., Nordtvedt T.S., Norström M., Owczarek-Kościelniak M.M., Øines Ø., Patel S.J., Sindre H., Standal I.B., Hagemann A. (2025). Fish sludge as feed in circular bioproduction: Overview of biological and chemical hazards in fish sludge and their potential fate via ingestion by invertebrates. Reviews in Aquaculture, vol. 17, no. 2, p. e12996.

[18] Piercy E., Verstraete W., Ellis P.R., Banks M., Rockström J., Smith P., Witard O.C., Hallett J., Hogstrand C., Knott G., Karwati A., Rasoarahona H.F., Leslie A., He Y., Guo M. (2023). A sustainable waste-to-protein system to maximise waste resource utilisation for developing food- and feed-grade protein solutions. Green Chemistry, vol. 25, pp. 808-832.

[19] Pinto Jimenez C.E., Keestra S., Tandon P., Cumming O., Pickering A.J., Moodley A., Chandler C.I.R. (2023). Biosecurity and water, sanitation, and hygiene (WASH) interventions in animal agricultural settings for reducing infection burden, antibiotic use, and antibiotic resistance: A One Health systematic review. The Lancet Planetary Health, vol. 7, no. 5, pp. e418-e434.

[20] Sandström V., Chrysafi A., Lamminen M., Troell M., Jalava M., Piipponen J., Siebert S., van Hal O., Virkki V., Kummu M. (2022). Food system by-products upcycled in livestock and aquaculture feeds can increase global food supply. Nature Food, vol. 3, no. 9, pp. 729-740.

[21] Sarkar S., Okafor C.C. (2022). Effect of changes in Veterinary Feed Directive regulations on violative antibiotic residues in the tissue of food animals from the inspector-generated sampling in the United States. Microorganisms, vol. 10, no. 10, p. 2031.

[22] Shurson G. (2025). Upcycling food loss and waste to animal feed is essential for a circular and sustainable food system. In: Intensive Livestock Production in Transition. Springer, pp. 279-297.

[23] Shurson G.C., Chen T., Dou Z. (2024). Food waste upcycling via livestock to address multiple sustainability objectives. Resources, Conservation & Recycling, vol. 209, p. 107809.

[24] Shurson G.C., Dierenfeld E.S., Dou Z. (2023). Rules are meant to be broken – Rethinking the regulations on the use of food waste as animal feed. Resources, Conservation & Recycling, vol. 199, p. 107273.

[25] Sin J.E.V., Shen P., Teo G.S., Neo L.P., Huang L., Chua P., Tan M.W., Wu Y., Li A., Er J.C., Chan S.H. (2023). Surveillance of veterinary drug residues in food commonly consumed in Singapore and assessment of dietary exposure. Heliyon, vol. 9, no. 11, p. e21160.

[26] Van Dresser W.R., Wilcke J.R. (1989). Drug residues in food animals. Journal of the American Veterinary Medical Association, vol. 194, no. 12, pp. 1700-1705.

[27] Wani N.R., Rather R.A., Farooq A., Padder S.A., Baba T.R., Sharma S., Mubarak N.M., Khan A.H., Singh P., Ara S. (2024). New insights in food security and environmental sustainability through waste food management. Environmental Science and Pollution Research, vol. 31, pp. 17835-17857.

[28] Zhu C., Lai G., Jin Y., Xu D., Chen J., Jiang X., Wang S., Liu G., Xu N., Shen R., Wang L., Zhu M., Wu C. (2022). Suspect screening and untargeted analysis of veterinary drugs in food by LC-HRMS: Application of background exclusion-dependent acquisition for retrospective analysis of unknown xenobiotics. Journal of Pharmaceutical and Biomedical Analysis, vol. 210, p. 114583.