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Understanding the Importance of Ecological Niches for Pharmaceutical Transfer Among Agroecosystems and Adjacent Natural Habitats: The Need for Precision Exposure Science

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ABSTRACT

Pharmaceutical pollution is now pervasive in ecosystems around the globe and represents a growing component of the broader environmental challenge posed by novel entities. Recent assessments indicate that the Earth System Boundary for Novel Entities has already been surpassed, underscoring the urgency of understanding where and how active pharmaceutical ingredients (APIs) move through the environment and affect exposed wildlife. To date, however, most research on APIs has focused on their presence and impacts in freshwater, coastal marine, and urban aquatic systems. While this focus has been warranted, it has also resulted in significant research gaps regarding exposure pathways and effects of APIs in other environments, including agroecosystems. This is a cause for concern given that agroecosystems are complex landscapes of great ecological and economic importance, where APIs can accumulate via multiple pathways. Here, we highlight how agroecosystems constitute a critical yet underappreciated exposure context for APIs, with widespread potential implications for soil health, crop productivity, terrestrial–aquatic food webs, and human exposure. We further summarise current knowledge on API occurrence and mobility in these systems, identify major exposure routes, and outline emerging ecological effects. We argue that existing risk-assessment approaches for APIs in agroecosystems are insufficient. We instead call for scenario-specific frameworks that draw on advances in precision exposure science within ecotoxicology. To support this timely opportunity, we present a flexible conceptual model that is built on catchment-based assessment, incorporates API flows among biota and across gradients of environmental compartments, and is reflective of ecosystem complexity. Advancing understanding of API dynamics in agroecosystems is essential for improving exposure models, informing effective regulation, and guiding mitigation of novel entities in systems on which both humans and wildlife depend.

Keywords: aquaculture, bioaccumulation, ecological and human health risks, exposure, medicine, pollution, trophic transfer.

Introduction

The ongoing contamination of global ecosystems has resulted in the transgression of the safe operating space for the Earth System Boundary for Novel Entities (1). The Earth System Boundaries framework defines limits within which humanity can operate while maintaining a stable and resilient Earth system; the Novel Entities boundary specifically relates to human-produced substances and organisms, including synthetic chemicals, plastics, and other engineered materials that can accumulate in the environment at scales exceeding society's capacity to assess and manage their risks (2). This transgression underscores the diverse threats posed by novel entities—defined as 'new substances, new forms of existing substances and modified life forms' (3) —to human health, biodiversity, and ecosystem services (4-6). The rapid proliferation and environmental release of synthetic chemicals have prompted their characterisation as agents of global change (7). Within the broader context of novel entities exceeding Earth System Boundaries, active pharmaceutical ingredients (APIs; 8-9) present particular challenges for environmental protection (10). This has occurred because APIs are specifically designed to elicit biological responses at low concentrations, can be temporally persistent in the environment, and can act on drug targets that are highly evolutionarily conserved across diverse taxa (11). As a result, there is an urgent need to fill existing knowledge gaps concerning exposure pathways and ecological impacts of APIs, particularly given the complex and dynamic nature of real-world exposures to novel entities.

APIs are released into the environment during production, use, and disposal (9), with the majority of research efforts to date having focused on ecosystem types that are the most directly impacted by these inputs. For example, environmental introductions of APIs from sewage and effluent discharges have been well established in urban aquatic ecosystems. Studies in these systems have characterised exposure routes and bioaccumulation pathways, and have demonstrated that API exposure can affect development, physiology, reproduction, behaviour, and survival in a wide range of species (12-15), with likely consequences for population dynamics and ecosystem processes (e.g., 16-19). While this research focus has been highly productive (20), it has also led to API pollution in less-obvious contexts receiving comparatively limited attention.

Agroecosystems are managed landscapes used for plant (e.g., cultivated fields, orchards, plantations) and animal (e.g., pasture-based systems, feedlots, aquaculture) production that represent a critically important yet comparatively understudied setting for API contamination

(Figure 1). APIs can enter agroecosystems via several pathways, such as the application of raw sewage, treated wastewater effluent and sewage sludge originating from both human and agricultural sources (21,22) as fertiliser, runoff from livestock operations where animals are treated with veterinary medicines (23), direct discharge of effluent from land-based aquaculture facilities and/or migration of APIs from net-pen aquaculture sites where pharmaceuticals are used to manage aquatic organism health and/or promote growth (24). As a result, a variety of APIs are consistently detected in agricultural soils, surface waters, and drainage systems worldwide, including antibiotics, steroids, antiparasiticides, anti-inflammatory drugs, and anticonvulsants (25, 26). Importantly, agroecosystems comprise a diversity of interconnected environmental compartments and ecological niches that can create distinct opportunities for API exposure, accumulation, and transfer. Throughout this Perspective, we use the term 'ecological niche' to refer to the combination of environmental conditions, resources, interactions, and functional roles that shape how organisms interact with their surroundings within agroecosystems. These niches include, for example, those occupied by decomposers, scavengers, filter feeders, pollinators, herbivores, emergent insects, and higher-order predators. Considering ecological niches alongside environmental compartments provides a more ecologically realistic framework for understanding how APIs can move among soils, sediments, porewater, surface waters, plants, invertebrates, and wildlife, and how exposure may propagate across interconnected food webs.

Of particular ecological concern is the potential for trophic transfer in these environments, where APIs move through food webs via multidirectional pathways among plants, detritus, herbivores, and predators. While trophic transfer is increasingly recognised as an important exposure pathway for APIs in aquatic ecosystems (27, 28), its role across the diverse habitats and ecological niches that characterise agroecosystems remains poorly understood. The diversity of trophic interactions among soils, sediments, porewater, surface waters, plants, invertebrates, and wildlife creates substantial opportunities for API movement across environmental compartments and food webs, with potential for cumulative and biologically meaningful exposure across multiple trophic levels. For example, veterinary antibiotics administered to livestock may enter adjacent drainage ditches and streams through manure runoff, exposing aquatic invertebrates and subsequently insectivorous wildlife via emergent insect subsidies (Figure 1A). Likewise, the application of wastewater or biosolids to cropland can result in plant uptake of APIs, creating exposure routes for herbivorous insects, pollinators, wildlife, and ultimately humans through food consumption (Figure 1B). Together, these

examples illustrate how source-pathway-receptor linkages can span multiple ecosystem compartments and trophic levels, highlighting the importance of spatially explicit frameworks that account for both landscape connectivity and species ecology.

Here, we consider agroecosystems as a major reservoir of APIs, including in water and soil, and at the water–soil interface (Figure 1). Identification of major API source contributions and the primary mechanisms of environmental fate and transport within agroecosystems (e.g., runoff of veterinary pharmaceuticals from livestock agriculture, application of treated wastewater and biosolids to farmlands) have been investigated and reviewed elsewhere (e.g., 29, 30). Rather than revisiting these established pathways, this Perspective article focuses on ecologically important routes of API transfer that have received comparatively little attention despite their potential to drive exposure across interconnected agroecosystems. In particular, we examine how API movement among environmental compartments intersects with the ecological niches occupied by organisms, creating exposure and transfer pathways that may not be apparent when sources, environmental compartments, or species are considered in isolation.

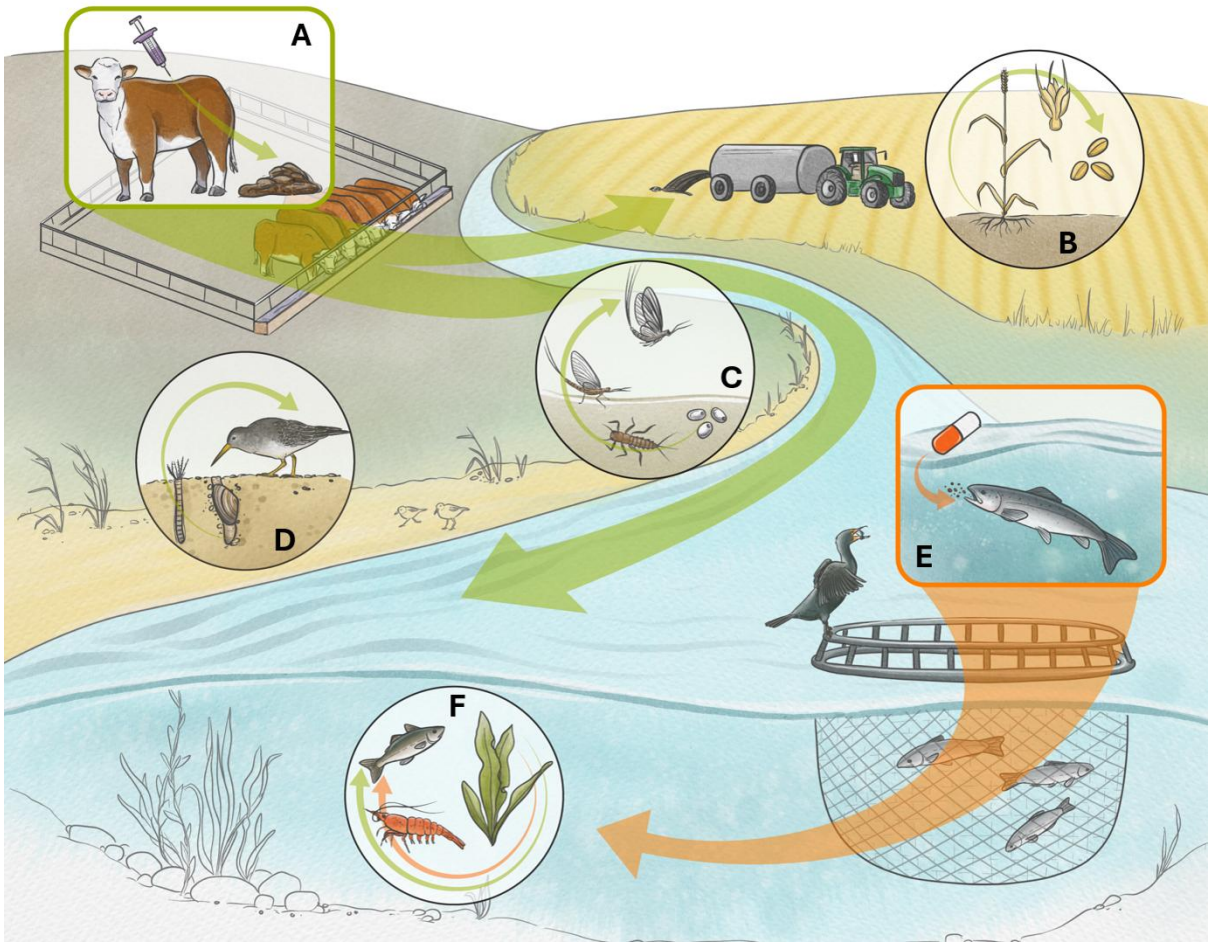


Figure 1. Illustration of the environmental fate, transport and trophic transfer pathways of active pharmaceutical ingredients (APIs) within agroecosystems. The diagram highlights key sources of API entry from livestock production (green arrows) and aquaculture systems (orange arrows). It depicts the movement of APIs through soil and surface water, emphasising processes such as leaching, runoff, plant uptake, and bioaccumulation. Insets show representative exposure pathways, including (A) veterinary pharmaceutical use and release via livestock waste, (B) uptake and translocation of APIs into crops, (C) transfer from aquatic to terrestrial food webs via emergent insects, (D) exposure of waterbirds through sediment-associated prey at the aquatic–terrestrial interface, (E) pharmaceutical inputs and uptake within aquaculture systems, and (F) trophic transfer through aquatic food webs. Arrows indicate the dynamic transfer of APIs between terrestrial, aquatic and interface habitats, showcasing potential exposure routes to non-target organisms.

Exposure pathways across connected agroecosystems

Although many pharmaceutical exposure pathways in agroecosystems originate within terrestrial production systems, we begin with aquatic environments because they provide the strongest existing evidence base for understanding API occurrence, bioaccumulation, and ecological effects. We then expand to the aquatic–terrestrial interface and terrestrial systems, where exposure pathways are less well characterised but increasingly recognised as important contributors to API transfer across agroecosystems.

Aquatic systems

Aquatic habitats associated with agroecosystems include aquaculture facilities, farm ponds, agricultural drainage networks, irrigation return flows, and receiving waters that collect runoff from manure- or biosolid-amended land. These systems form important exposure environments because they receive API inputs from both agricultural production activities and broader watershed sources. Here, we focus on exposure processes operating in estuarine, coastal, and aquaculture systems, while cross-boundary transfer between aquatic and terrestrial ecosystems is considered separately in the following section.

Urbanisation of coastal watersheds is accelerating globally, placing billions of people, along with their chemical waste streams (31, 32), near coastlines (33). Estuarine systems are highly dynamic, exhibiting spatiotemporal gradients in pH, salinity, suspended sediments, temperature, and dissolved oxygen that strongly influence partitioning of most APIs. Increasing

salinity can “salt out” organic molecules, shifting their distribution from water to sediments and altering the bioavailability of both ionisable and non-ionisable compounds (34-36). Although this behaviour has been characterised most thoroughly for neutral, hydrophobic contaminants such as perfluoroalkyl substances, polycyclic aromatic hydrocarbons, and non-polar pesticides, the salting out effects represents the influence of ionic strength on solute activity and is therefore not restricted to any one contaminant class. However, the magnitude of this effect scales with hydrophobicity; thus, it is most relevant to APIs present in their neutral state at ambient pHs (37). Consequently, the effects of salinity and pH on the partitioning behaviour of APIs along estuarine gradients are inextricably linked, such that the distribution of a given compound reflects both. This coupling makes salting out a more complex, and potentially more consequential, process for APIs than for the neutral organics in which it has been most studied. Nevertheless, these effects are particularly important considerations in tidally influenced systems, where stratification can create distinct exposure zones. Fresh, less-dense inflows can carry elevated API loads in surface waters, while deeper saline layers may show different concentrations and low-oxygen conditions that promote bioaccumulation. Despite these clear implications, depth-dependent API distribution in urbanising estuaries remains understudied, leading to unrecognised contaminant hotspots where upstream inputs converge (38).

Compounding these effects, spatiotemporal pH gradients along the freshwater–marine continuum can also play a critical role in modulating API bioavailability. Since many APIs are ionisable bases with pKa values sensitive to environmental pH, shifts in pH can substantially influence contaminant bioavailability and subsequent bioaccumulation (37). To date, most API bioaccumulation studies have been conducted in freshwater systems, either as field investigations or laboratory experiments with freshwater organisms. This includes those studies that use predictive models to examine how pH influences bioaccumulation (37). However, bioaccumulation and internal disposition of APIs in estuarine fish can differ from freshwater taxa. For example, apparent volume of distribution, which represents a useful proportionality factor to understand API bioaccumulation (37), dramatically differs for APIs between the fathead minnow (*Pimephales promelas*), a common freshwater model (39), and the Gulf killifish (*Fundulus grandis*), a common estuarine species distributed throughout estuaries of the Gulf of Mexico (40). However, it is worth noting that such interspecific differences are not attributable to changes in ambient pH alone. Bioaccumulation also varies with body size, lipid content, biotransformation capacity, ventilation and osmoregulatory physiology, life history,

and habitat use, so comparisons of this kind are most informative among ecologically similar species and are best interpreted as an upper bound on the variability that any single environmental gradient could explain. They nonetheless emphasise that exposure and accumulation dynamics established in freshwater models cannot be assumed to transfer directly to estuarine settings. Moreover, tidally influenced waters often exhibit vertical pH stratification, which can further shape benthic and pelagic API exposure and accumulation patterns (41, 42). But here again, surface water (e.g., depth of 0.3 m) is most commonly sampled during field studies of APIs, which misrepresents water column, and particularly benthic, exposure realities (42).

Both freshwater and marine aquaculture (i.e., mariculture) practices are of particular relevance with regard to API contamination and transfer in aquatic systems (33, 36, 43). While farmed fish and shellfish may bioaccumulate and/or be impacted by exposure to APIs discharged from municipal sources (e.g., raw sewage, treated wastewater effluent), it is also important to note that both land-based and net-pen aquaculture represent additional primary sources of APIs in aquatic environments (33,43). Aquaculture facilities commonly use a variety of antibiotic (e.g., quinolones, sulfonamides), antifungal (e.g., triazoles, methoxy acrylate), and antiparasitic compounds (e.g., emamectin benzoate) to prevent and/or treat diseases and pests (Figure 1E) (33). Many of these constituents and their metabolites can persist in a biologically active form in surrounding waters, particularly in semi-enclosed or poorly flushed systems (38, 39, 44).

Filter feeders (e.g., mussels, oysters) constitute more than 60% of global aquaculture output by biomass and also occupy key ecological niches that may facilitate the transfer of APIs and other novel entities present in aquatic environments (41, 45). Owing to the exceptionally high water-filtration rates characteristic of bivalves, this can lead to dramatically increased exposure rates and rapid accumulation of environmental contaminants, including APIs in aquatic agroecosystems (36, 41). This reality appears especially relevant for integrated multi-trophic aquaculture (IMTA) systems that involve co-culture of aquatic species (45). Bivalve-finfish IMTA systems are implemented to reduce eutrophication risks from excess waste generated by farmed finfish; however, these systems have the unintended consequence of increasing API exposure for filter feeders that are spatially proximal to unconsumed medicated feed or waste (45, 46).

More generally, waste produced by finfish aquaculture can contribute to the transfer of APIs to wild organisms occupying a range of ecological niches. Benthic detritivores such as sea

cucumbers, crabs, and amphipods that inhabit aquaculture-impacted habitats may ingest APIs bound to organic matter and sediment particles, particularly those that persist at the sediment–water interface (e.g., quinolones) (35, 47). Through bioturbation, these organisms can resuspend sediment-associated APIs, thereby increasing exposure risks for other aquatic species, including scavengers and benthic feeders that incidentally consume sediment (48, 49). These secondary consumers may also be exposed through trophic transfer when feeding on contaminated detritivores (Figure 1F) (48, 50, 51).

In addition, trophic transfer of veterinary pharmaceuticals may occur in higher-order consumers such as invertivores, scavengers, and predatory fish that feed on farmed shellfish or fish that have escaped from net-pens (34, 36). Many of these species, including aquatic-dependent birds such as ospreys, are commonly attracted to aquaculture sites due to the high density of available prey, uneaten feed, and the structural complexity provided by net-pens (52-54). Although not yet directly linked to API exposure, osprey foraging at aquaculture sites has recently been associated with increased mortality, highlighting the need to better understand API exposure in higher trophic levels (55-57). Importantly, examples such as these illustrate that API transfer is not necessarily confined to aquatic food webs. Organisms that move between aquatic and terrestrial habitats can transport contaminants across ecosystem boundaries, creating exposure pathways that cannot be understood when these systems are considered in isolation. This is particularly relevant at the aquatic–terrestrial interface, where ecological connectivity, wildlife movement, and resource exchange can facilitate the transfer of APIs between environmental compartments.

Aquatic–terrestrial interface

The aquatic–terrestrial interface functions as a critical zone of exchange between land and water ecosystems, where APIs can move across habitat boundaries via hydrological processes, food-web linkages, and organism movement. In agroecosystems, these interfaces include riparian margins adjacent to livestock operations, drainage ditches, constructed wetlands, floodplains receiving agricultural runoff, and channels receiving aquaculture effluent. Characterised by dynamic exchanges of water, nutrients, and energy, these compartments can accumulate APIs through runoff, leaching, freshwater inflows, and sedimentation, creating hotspots of ecological exposure. This section therefore focuses on cross-boundary transfer pathways, including those mediated by waterbirds, emergent insects, and soil-water interactions.

Although data on API levels in waterbirds (e.g., shorebirds, wading birds) and piscivorous predatory bird species (e.g., ospreys, eagles) are sparse, existing studies suggest that these species may represent an important pathway for API transfer from aquatic to terrestrial ecosystems (50, 58, 59). These birds commonly forage in intertidal and nearshore areas that often overlap with aquaculture operations and other contaminated coastal zones (Figure 1D). Their diet, therefore, includes invertebrates and fish that may have bioaccumulated APIs from polluted feed or water (52, 54, 59). Moreover, many species exhibit high food-ingestion rates relative to body weight, strong site fidelity, and foraging behaviours that result in frequent contact with, and incidental ingestion of, contaminated sediments (60-62). This is especially relevant for sediment-foraging birds in shallow estuarine and intertidal zones, where salinity-driven contaminant partitioning tends to favour sediment accumulation.

Such foraging behaviours not only increase the likelihood of direct API exposure but further can facilitate the transfer of contaminants among positions within food webs, potentially affecting terrestrial predators and scavengers (55, 57). Waterbirds, therefore, may serve as both sentinel species and vectors for the spread of APIs. Their ecological characteristics combined with known sensitivities to other contaminant classes make waterbirds especially valuable as indicator species for understanding the broader environmental footprint of API contamination (63-65). However, despite their relevance, research on API exposure in waterbirds remains limited. Nevertheless, research is moving in this direction as a recent study detected measurable API concentrations in the feathers of fledglings from two waterbird species, which evidenced the need for integrated, cross-ecosystem studies of API exposures (66).

Among the various vectors of contaminant movement across ecosystem boundaries, emergent aquatic insects also play a particularly critical role in facilitating the trophic transfer of APIs from aquatic to terrestrial food webs (Figure 1C) (28, 67). During their larval stages, these insects, such as mayflies, caddisflies, and midges, reside in sediments or water columns where they are directly exposed to APIs dissolved in water or bound to particles (68). As they mature and emerge into their adult aerial forms, they retain bioaccumulated contaminants within their tissues. These emergent insects are a major food source for a wide range of terrestrial predators, including insectivorous birds, bats, spiders, and amphibians, thereby acting as a primary conduit through which APIs leave aquatic systems and enter terrestrial ecosystems. Although these ecologically relevant exposure pathways remain comparatively understudied, recent work has begun to address this gap; for example, Rosi et al. (69) model how freshwater

contamination by antivirals can lead to exposure in insectivorous bats via the consumption of emergent insects with aquatic larval stages.

Furthermore, animals may use contaminated soil or vegetation for nesting or burrowing, increasing the risk of chronic exposure for both adults and their offspring (70). Disruption of microbial communities at the soil–water interface can also have profound and far-reaching ecological consequences, particularly in terms of nutrient cycling and food web dynamics. Microorganisms such as bacteria, fungi, and protozoa play a foundational role in breaking down organic matter, recycling nutrients like nitrogen and phosphorus, and supporting the base of the aquatic and semi-aquatic food web. When APIs (e.g., antibiotics, antifungals) enter this interface, they can alter the composition, diversity, and activity of these microbial communities. This disruption can hinder essential biogeochemical processes, such as nitrification, denitrification, and decomposition, leading to nutrient imbalances or the accumulation of harmful byproducts (71, 72).

As a result of these disruptions, primary productivity may decline, reducing the availability of food resources for higher trophic levels, including invertebrates, fish, and ultimately the birds and mammals that rely on them. In sensitive habitats like wetlands or floodplains, this decline in primary productivity can cascade into broader ecosystem degradation (73). For wildlife, these changes not only reduce food availability but also increase physiological stress and competition for limited resources, potentially affecting survival, reproduction, and population dynamics. Thus, maintaining the integrity of microbial communities at the soil–water interface is critical for sustaining the ecological balance and resilience of interconnected terrestrial and aquatic ecosystems. Collectively, these pathways highlight the ecological importance of the soil–water interface as both a critical habitat and a potential zone of API transfer in agroecosystems. However, not all environmentally relevant exposures originate at ecosystem boundaries. Many APIs enter terrestrial food webs directly through agricultural practices, creating exposure pathways that can subsequently extend across trophic levels and beyond the farmed landscape.

Terrestrial systems

Exposure to APIs is an increasing issue in terrestrial ecosystems, where these compounds can enter the environment through several agricultural practices. The most widespread pathways are associated with the land application of organic wastes including livestock manure, slurry,

sewage sludge and wastewater, all of which may contain residues of APIs (74). Because these materials are applied repeatedly over large areas, they represent a landscape-scale and often chronic source of API contamination in soils, creating opportunities for transport and uptake into non-target organisms.

One important consequence of these inputs is the uptake of APIs by crops grown in contaminated soils (Figure 1B). Active pharmaceutical ingredient residues can be taken up by the roots of crops and translocated into edible tissues such as leaves, fruits, and grains (75). Most existing research has focused on the implications of this pathway for human health; however, the potential for indirect exposure of herbivorous wildlife and insects to APIs through contaminated crops is rarely considered. Nectar- and pollen-feeding insects such as bees may also be at risk when flowering crops or wild plants take up APIs and sequester them in floral resources (76). This exposure pathway has yet to be thoroughly investigated but could represent a significant risk to pollinator health and the pollination services they provide (77).

APIs can also be introduced through direct animal mediated pathways. In grazing systems, veterinary pharmaceuticals may be excreted directly onto pastures in dung and urine (78), resulting in the localised deposition of biologically active compounds into natural and semi-natural habitats. Although this pathway is typically more spatially restricted than manure spreading, it represents an ecologically distinct exposure route as APIs are introduced directly into habitats occupied by dung-associated invertebrates, soil organisms and the wildlife that feed on them.

A further, highly localised but potentially acute exposure pathway arises from livestock carcasses and associated waste-disposal practices. Active pharmaceutical ingredients such as the anti-inflammatory drug diclofenac can persist in livestock tissues and expose scavenging species, including top predators, to acute toxicity when they consume contaminated carcasses left in the environment. Certain highly toxic compounds, such as nonsteroidal anti-inflammatory drugs, which are particularly toxic to some vertebrates, and barbiturates (e.g., pentobarbital), pose significant risks and have been linked to documented cases of secondary poisoning in avian and mammalian scavengers (79-82).

While supplementary feeding stations have been established as a low-cost conservation strategy to remove livestock carcasses and support scavenger populations, these sites often become hotspots of API exposure. They attract both obligate and facultative scavengers, as

well as opportunistic species, including invertebrates and passerines, that exploit these food subsidies. However, such anthropogenic provisioning alters natural foraging behaviours and species' spatial distribution patterns, with largely unknown ecological consequences (83). Moreover, the consistent presence of veterinary drugs at these feeding stations contributes to long-term inputs of APIs, particularly antibiotics, into the local environment. Despite this reality, field-based data on API concentrations, pharmacokinetics, and sublethal or cumulative effects in wildlife are scarce, leaving significant knowledge gaps regarding long-term risks (84).

Opportunistic mammals that access contaminated carcasses may also suffer adverse effects. For example, pentobarbital, commonly used for livestock euthanasia, persists in the tissues of buried or discarded carcasses and has caused lethal secondary poisoning in wildlife (81, 82). Furthermore, several studies have detected APIs in soil surrounding these carcasses for up to a year post-deposition, highlighting leachability into terrestrial substrates and persistence over long periods (85, 86). Such observations raise concerns for soil-dwelling invertebrates and the broader soil food web (87). Indeed, scavenging invertebrates (e.g., beetles, flies), which play essential ecosystem service roles in carcass decomposition and nutrient cycling, can be exposed to APIs present in livestock tissue (88, 89). Such exposures could facilitate trophic transfer of APIs, whereby insectivorous birds, amphibians, reptiles, and mammals consuming contaminated invertebrates are themselves exposed to these compounds, with largely unknown but potentially significant ecological consequences (88).

Lastly, APIs can enter terrestrial systems through intentional human actions, particularly in the context of human–wildlife conflict. In some cases, toxic baits laced with pharmaceuticals are illegally deployed to kill unwanted animals, such as livestock predators. Elsewhere research has suggested that an orally-ingested lethal dose of acetaminophen could be a humane method for lethal control of invasive brown treesnake species following the identification that acetaminophen is a proven lethal toxicant in some reptiles (90). These deliberate exposures underscore the complexity of API pathways in agroecosystems and highlight the need for improved understanding, surveillance and regulatory assessments, particularly for reptiles, which remain severely understudied in relation to API exposure.

Significance to ecological processes

Contamination of agroecosystems with APIs is an emerging environmental crisis, reshaping ecosystems in ways we are only beginning to understand. APIs, particularly those used in livestock, aquaculture, and crop production systems, are increasingly recognised for their ability to disrupt key ecological functions (91). Yet, many diverse exposure pathways and ecological niches remain critically understudied in this context. Growing evidence shows that APIs can profoundly affect soil organisms, community structure, and ecosystem function (92). Antiparasiticides like ivermectin, moxidectin, and eprinomectin that are routinely administered to livestock and wildlife have been shown to induce lethal and sublethal effects in dung beetles (e.g., *Scarabaeus cicatricosus*) and other invertebrates, altering ecosystem services, and impairing reproduction, behaviour, and survival (93-95). Furthermore, anthelmintics such as albendazole similarly affect earthworms (*Eisenia fetida*) (96), undermining the ecological services they provide, from decomposition and nutrient cycling to pest and disease suppression. Critically, these disruptions can propagate across food webs. Soil invertebrates can act as exposure vectors, transferring API residues to predators and species higher in the food chain. Although many effects remain poorly quantified, early signs suggest that physiological and behavioural disruptions may have long-term consequences for population viability and food web stability (88, 97). Despite this mounting evidence, many exposure pathways in agroecosystems remain understudied, particularly those involving often-overlooked ecological niches such as scavengers and decomposers, as well as invertebrate prey and their predators. Recognising these research gaps is critical, as insights into the diversity of biotic interactions in agroecosystems provide a powerful foundation for directing future research toward the pathways most likely to drive environmentally relevant exposures.

More broadly, these knowledge gaps highlight the need for new approaches to conceptualise API exposures in agroecosystems that support more progressive and realistic risk assessments. Current risk assessment frameworks remain inadequate, relying heavily on prospective, hydrophobicity-based models and simplified laboratory designs with just a few species that fail to reflect how APIs behave as novel entities in complex agroecosystems. The growing weight-of-evidence shows that APIs are widespread and can accumulate across trophic interactions in ways not captured by traditional bioaccumulation methods with commonly studied fish (e.g., salmonids, bluegill sunfish) or compartment-focused models. Retrospective approaches offer particular promise in this regard. Lessons from contaminated site assessments demonstrate that conceptual model development during problem formulation can effectively capture spatial heterogeneity, biological interactions, and chemical flows across environmental compartments.

Applying these principles to agroecosystems will strengthen our capacity to map realistic API transport and exposure pathways, identify critical trophic interactions and potential transfer processes, and understand how individual-level responses may scale to food web and ecosystem effects.

Our conceptual framework outlines an approach, inspired by retrospective ecological risk assessment for contaminated sites, to more precisely understand how APIs accumulate and behave in agroecosystems (Figure 2). It begins by reconstructing historical loading, identifying where and when APIs have entered the landscape (Figure 2A). This establishes the spatial and temporal foundations needed to interpret present-day environmental conditions. Employing a catchment-scale conceptual site model then links API sources to the exposure pathways through which these novel entities move and the receptors that may be exposed (Figure 2B). This foundational step clarifies how APIs travel through soil, water, and biota, grounding the assessment in the real structure of agroecosystems. A multi-compartment fate and transport perspective then describes how APIs are transformed, transferred, and stored across water–sediment systems, soils, and organisms (Figure 2C). Understanding these dynamic exchanges is essential for determining effective exposure and the potential for persistence and/or bioaccumulation (Figure 2D). These exposure patterns are interpreted through ecological and functional responses, highlighting where thresholds may be crossed and how ecosystem processes and/or wildlife populations could be affected. Environmental and climatic conditions further influence not only exposure but also the magnitude of biological responses to APIs. Factors such as temperature, drought, salinity, pH, hypoxia, and resource limitation can modify organism physiology, toxicokinetics, and stress tolerance, potentially increasing or decreasing susceptibility to pharmaceutical exposure (98). Consequently, species sensitivity should be considered as a dynamic property that varies across environmental gradients rather than a fixed endpoint derived from standard laboratory conditions. Incorporating these interacting stressors into precision exposure science frameworks will improve ecological realism and strengthen predictions of risk under future environmental change.

This approach connects environmental concentrations to meaningful biological outcomes. Finally, this precision exposure science framework integrates multiple lines of evidence into a clear risk characterisation, identifying when and where management action is warranted (Figure 2E). By emphasising spatial co-occurrence, species sensitivities, and API hotspots, the

approach supports targeted, informed decisions that align with real-world ecological contexts, a key component of precision ecotoxicology (99, 100).

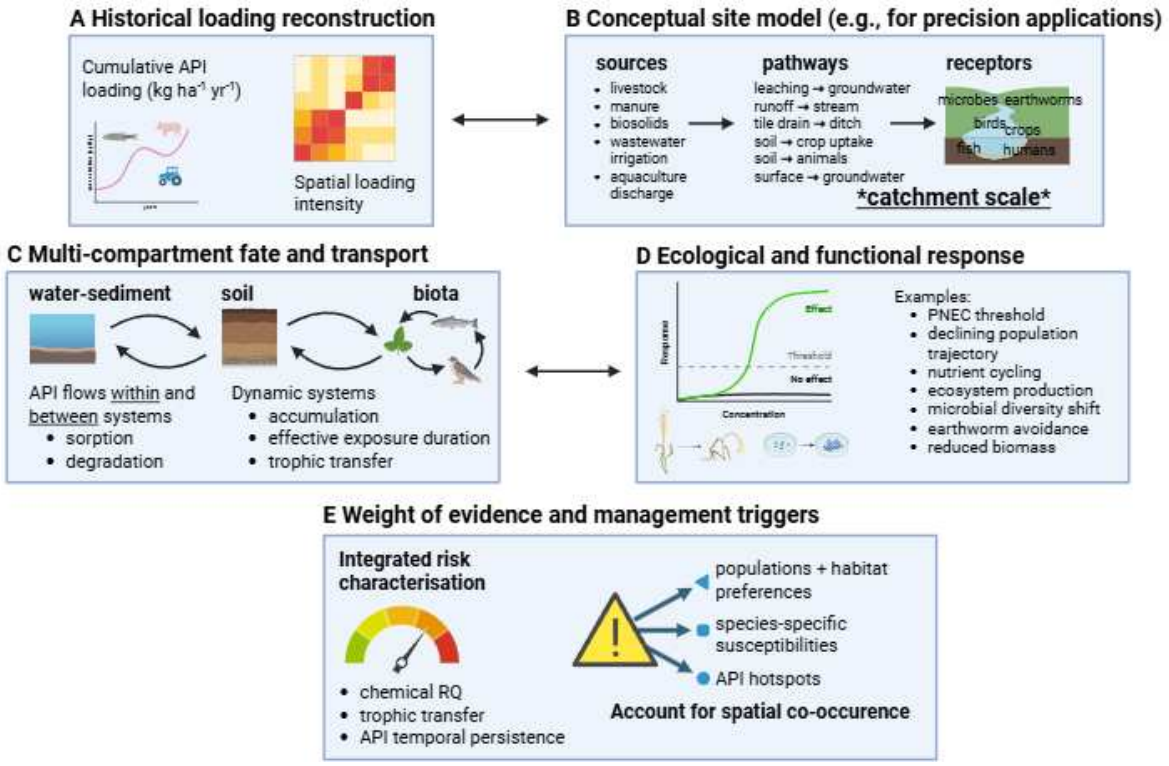


Figure 2. Conceptual framework for precision exposure science of active pharmaceutical ingredients (APIs) in agroecosystems. The framework links (A) historical API loading, (B) catchment-scale sources and pathways, (C) multi-compartment fate and transport, and (D) ecological response. These components integrate into (E) a weight-of-evidence evaluation that highlights spatial hotspots, species sensitivities, and triggers for management actions. RQ = risk quotient.

As highlighted, current ecotoxicological research frameworks do not adequately address four interrelated knowledge gaps: (i) overlooked ecological pathways of API transfer, (ii) limited understanding of how organism movement shapes real-world exposure, (iii) poor ability to scale effects from molecular targets to ecosystem responses, and (iv) artificial separation of terrestrial and aquatic exposure domains. Addressing these gaps is essential for advancing precision ecotoxicology for APIs (100) and for operationalising the conceptual framework proposed here. Accordingly, we outline four priority research areas that build directly on these challenges and aim to strengthen our capacity to anticipate, detect, and mitigate API exposures in agroecosystems and adjacent natural habitats.

1. **Map overlooked exposure pathways**

As highlighted in the terrestrial and aquatic–terrestrial interface sections, many potentially important routes of API transfer in agroecosystems involve ecological niches that remain poorly represented in conventional ecotoxicology, including scavengers, decomposers, pollinators, and emergent insects. Future research should prioritise mechanistically distinct but understudied exposure routes such as detrital, carrion-based, and manure- or sludge-mediated transfer, which connect soils, sediments, pore waters and surface waters, through the functional groups that are often ignored in standardised bioaccumulation and ecotoxicology experimental protocols. To operationalise this priority, future work should move beyond presence-absence mapping towards mechanistic prioritisation, identifying how, where and when different pathways contribute to exposure, and distinguishing pathways that amplify exposure through repeated recycling (e.g., biosolid application, dung accumulation, carcass persistence) from those that generate short-lived, pulsed exposure. Integrating historical land-use data, livestock treatment records, carcass management practices and sludge application histories into retrospective conceptual site models will allow us to identify legacy sources and persistent exposure routes that are invisible to prospective screening (Figure 2A). Explicitly linking each pathway to functional ecological roles and associated ecosystem services (e.g., decomposition, nutrient cycling) will further clarify how, where and when API exposure propagates from individual organisms to ecosystem-level processes.

2. **Integrate movement ecology and spatial exposure data**

Building on examples involving waterbirds, scavengers, migratory species, and aquaculture-associated wildlife, the Perspective highlights that exposure is often determined by movement, habitat use, and behaviour rather than environmental concentration alone. It is therefore important to combine animal movement, behavioural ecology, and spatially explicit API measurement to quantify how time spent in contaminated habitats, repeated site use, and foraging behaviour translate into chronic and cumulative exposure (e.g., 101). Integrating these data will allow for the identification of high-risk species, exposure hotspots, and critical ecological interfaces where API uptake and potential trophic transfers are most likely to occur. This can be achieved by explicitly treating exposure as a function of space × time × behaviour, rather than spatial overlap alone. This includes accounting for residence time,

518 revisitation frequency, life history stage, and behavioural state (e.g., foraging, nesting,
519 dispersal). Movement-informed exposure assessments should extend beyond highly
520 mobile vertebrates to include invertebrate dispersal, crop–herbivore dynamics, and
521 livestock movements, which are key to API redistribution in agroecosystems. Linking
522 these spatial exposure histories to internal dose metrics will improve attribution of
523 cumulative exposure and help to explain why ecologically meaningful effects may
524 occur even at low environmental concentrations.
525
526 **3. Develop predictive tools across scales**
527 Addressing the limitations of current risk assessment approaches discussed above, there
528 is a need for predictive frameworks that connect molecular mechanisms of action to
529 ecological consequences across agroecosystems. Future approaches should link
530 overlooked exposure pathways with molecular, trait-based, and ecological models to
531 predict API sensitivities from conserved molecular targets to population- and
532 ecosystem-level responses (e.g., using SeqAPASS; 102). To provide more precise
533 predictive utility, tools should explicitly articulate scale translation, connecting
534 molecular target conservation to physiological disruption, altered behaviour, and
535 downstream effects on species interactions and ecosystem functions associated with
536 exposure pathways. Predictive frameworks must move beyond single compound
537 assessments to account for API mixtures and co-occurring stressors, for example where
538 APIs interact with nutrient or pesticide pollution. Uncertainty should be treated as a
539 design feature in this approach and not a limitation, with iterative validation against
540 soil, water, and biotic measurements embedded into the study design. Emphasising
541 modular, transferable tools will allow uptake in ecologically vulnerable but data-poor
542 regions, supporting global equity in API risk assessment (103).
543
544 **4. Bridge ecosystem boundaries in research designs**
545 Responding to evidence presented throughout that APIs move among aquatic,
546 terrestrial, and interface habitats via hydrological and trophic pathways, future
547 approaches should treat aquatic and terrestrial systems as integrated exposure networks
548 shaped by agroecological practices, hydrological connectivity, and wildlife movement,
549 rather than isolated compartments. If we conceptualise agroecosystems as networks of
550 connected nodes (e.g., fields, waterways, wetlands, farms, carcass sites) linked by flows
551 of organisms, water, nutrients, and APIs, research can be designed to integrate cross-

boundary taxa (e.g., waterbirds, emergent insects) that integrate exposure across compartments. This will reveal mismatches between regulatory assumptions and ecological realities, thereby providing opportunities to advance risk assessments more holistically with improved precision. Furthermore, co-producing field experimental designs and studies with farmers and regulatory agencies will enable examination of practical interventions and quantification of ecological risk reduction within operational farming and aquaculture realities (e.g., buffer strips, carcass protocols, waste handling).

Together, these recommendations move precision ecotoxicology beyond compartment-based hazard identification toward an integrated understanding of exposure networks, cumulative risk, and ecosystem-level consequences, enabling the proposed conceptual framework to be applied in diverse agroecosystems with realism and regulatory relevance.

Conclusions

Pharmaceuticals are increasingly recognised as contaminants that can reshape the ecological dynamics of agroecosystems in complex, cumulative, and often invisible ways. The diversity, potency, and persistence of APIs now exceed our capacity to monitor and manage them effectively, contributing to the exceedance of the safe operating space for the Earth System Boundary for Novel Entities (10). As such, there is an urgent need to rethink how API exposure and movement, as well as ecological complexity and sensitivity, are conceptualised in the context of agroecosystems. Advancing beyond conventional assessment tools requires an integrative, spatially explicit, and ecologically grounded research paradigm—one that is captured in our proposed conceptual model, which links exposure with molecular targets, trophic interactions, and catchment-scale flows of APIs across environmental compartments. By prioritising overlooked exposure pathways, vulnerable species, and high-exposure zones, we can better anticipate and work towards mitigating the ecological disruptions caused by APIs. To make these concepts actionable, their delivery could be embedded within the newly established UNEP Intergovernmental Science-Policy Panel on Chemicals, Waste and Pollution (ISP-CWP) and related activities. Specifically, the ISP-CWP could convene the agriculture, environment, health, and water sectors to co-produce spatially explicit chemical usage maps, monitoring frameworks, and cross-scale predictive tools. Within this process, essential-use and stewardship principles should guide risk reduction so that API mitigation does not undermine agricultural yields, animal welfare, or equitable access to medicines.

Conflicts of interest

The authors declare that they have no competing interests.

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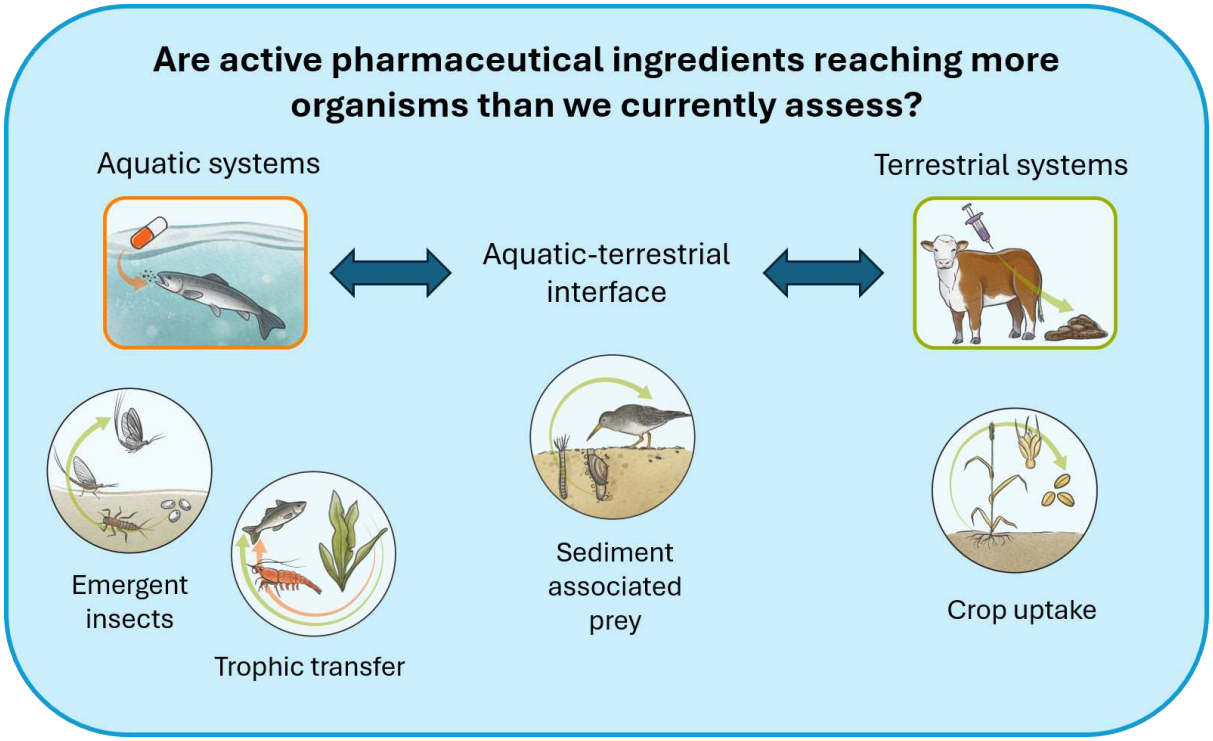
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961

962 Table of Contents Graphic



963