Integrating Ecotoxicity into Early-Stage Drug Development for Parasitic Diseases: A One Health Position Paper

Action / network: COST Action CA21111 (OneHealthDrugs — OHD)

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Executive Summary

Vector-borne parasitic diseases (VBDs) — including leishmaniasis, trypanosomiases, schistosomiasis and babesiosis — pose an escalating threat to human and animal health across Europe and globally. Approximately 75% of emerging human infections originate from animals, and VBDs account for roughly 17% of the global infectious disease burden, causing an estimated 700,000 deaths annually. Climate change, urbanization, expanding travel and trade are accelerating the geographical spread of vectors and disease reservoirs, with Europe — particularly its Mediterranean and southern regions — facing growing exposure.

Despite this burden, the therapeutic arsenal against human and animal parasitic infections remains critically limited. Available drugs are few, frequently toxic, and increasingly compromised by resistance. Human and veterinary drug discovery pipelines continue to operate largely in isolation from one another and from environmental science. Pharmaceutical residues and manufacturing emissions contaminate water, soil and biota, contributing to ecosystem degradation and the broader crisis of antimicrobial resistance. Yet current R&D frameworks rarely incorporate environmental risk assessment from the outset, and no comprehensive cross-sectoral guidance exists to ensure that antiparasitic drugs are discovered, developed and used in line with One Health principles.

The OneHealthDrugs COST Action (CA21111) was established to address these interconnected challenges. By building a coordinated, pan-European One Health platform, the Action brings together human and veterinary drug discovery, environmental science and key stakeholders to develop the next generation of antiparasitic drugs — combining therapeutic efficacy with a substantially reduced environmental footprint.

This position paper presents **ASPECT** - **A**ntiparasitics through **S**ustainable **P**redictive **E**cotoxicology, **C**hemistry and **T**ranslation - as a concrete, actionable response: a structured approach to embedding sustainability, environmental responsibility and regulatory coherence into antiparasitic drug discovery from the earliest stages of R&D. It is directed at EU policymakers, regulatory authorities, research funding bodies and industry stakeholders with a mandate to advance One Health policies and sustainable pharmaceutical innovation.

The paper supports three sequenced deliverables: a. in July 2026, the public announcement of the position paper at the Brussels stakeholder meeting; b. from July onward, co-development of the policy brief with external stakeholders and policymakers, leading to a September 2026 meeting; a policy visibility package comprising the two-page brief, a slide deck, and a one-page evidence snapshot; c. beyond Year 4, sustaining the work through follow-on activities and embedding the recommendations into ongoing policy engagement.

The September release is timed to coincide with the period in which the new EU pharmaceutical legislation is expected to enter into force, ensuring the Action's recommendations reach decision-makers while implementation is being shaped.

AT A GLANCE — WHAT THIS PAPER RECOMMENDS	
1	Introduce an early-stage environmental screening gate, using a minimal indicator set (the Minimum Information Package), at the hit-to-lead stage.
2	Adopt a staged approach: low-cost predictive screening first, followed by targeted assays for prioritised candidates.
3	Create a simple, shared reporting template so results are comparable across projects.
4	Align funding calls and R&D governance to require environmental data for safe-by-design assessment.
5	Define feasibility criteria for acceptable early tools.
6	Build environmental stewardship into veterinary and research training and capacity.

1. Context and Methodology

1.1 The Problem: Pharmaceutical Pollution as an Environmental Crisis

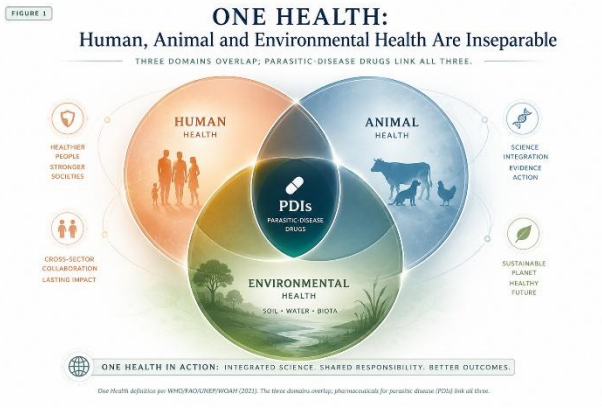


Figure 1 — One Health: human, animal and environmental health are inseparable, with parasitic-disease (PDis) drugs linking all three domains.

The OneHealthDrugs COST Action (OHD) is a multidisciplinary network of pharmacists, medicinal chemists, parasitologists, entomologists, veterinarians and ecotoxicologists. Its position paper addresses one of the most underappreciated environmental emergencies of our time: the contamination of terrestrial and aquatic ecosystems by active pharmaceutical ingredients (APIs). Approximately 4,000 APIs are currently available worldwide for human and veterinary use, and their residues are now detected globally in soils, surface waters, groundwater and even drinking water. The European Environment Agency formally recognised pharmaceutical pollution as an emerging environmental problem as early as 2010, and the evidence accumulated since leaves little doubt that APIs in the wild are causing measurable, potentially irreversible harm to biodiversity and ecosystem function.

The same biological potency that makes these molecules therapeutically valuable also makes them dangerous when they escape into the environment at biologically active concentrations. APIs and their metabolites persist, accumulate and interact with non-target organisms in ways that produce endocrine disruption, neurotoxicity, altered behaviour, epigenetic changes, disrupted reproductive cycles and shifts in energetic metabolism. These effects may be chronic and transgenerational. The simultaneous presence of hundreds of bioactive compounds in any given environmental compartment creates mixture effects that current risk-assessment frameworks were not designed to capture. The paper argues, with urgency, that this crisis demands a fundamentally different approach — one that integrates environmental protection from the earliest stages of drug discovery, rather than managing the consequences after a drug has reached the market.

1.2 Why Now: A Decisive Moment in European Policy

This paper arrives as European policy moves decisively toward the principles it advocates. Three major instruments are converging in 2025 and 2026, each making early environmental consideration more relevant, more expected, and more financially material:

1.2.1 The EU Pharmaceutical Package — the largest reform in two decades

The reform of EU pharmaceutical legislation is the most significant overhaul of the regulatory framework in over twenty years. First proposed by the European Commission in April 2023, it was adopted as a position by the European Parliament in April 2024 and by the Council in June 2025; the compromise texts were endorsed by Member States in March 2026 and approved by the Parliament's Public Health Committee shortly after, with formal adoption expected in summer 2026 and entry into force following publication in the Official Journal, expected in autumn 2026 (EMA; Sidley / GoodLifeSci, 2026). Crucially, the reform strengthens environmental risk assessment (ERA) and, for the first time in EU pharmaceutical law, allows authorities to refuse, suspend or vary a marketing authorisation on the basis of environmental risk that cannot be mitigated, assess environmental impact across the entire product lifecycle including manufacturing, and require retrospective ERA for products authorised before 30

October 2005 under an EMA-led, risk-based prioritisation programme (Osborne Clarke; PMC, 2026).

Why this matters for the paper
Under the current framework, the outcome of an ERA cannot be used to refuse a marketing authorisation. Under the new framework, it can. Environmental performance is moving from a documentation exercise to a potential gate on market access. A company that discovers an environmental liability at Phase III now faces a materially higher risk than before, the strongest possible argument for finding such liabilities early.

1.2.2 The revised EMA ERA Guideline — already in force

The EMA guideline on the environmental risk assessment of medicinal products for human use, originally published in 2006 and left essentially unchanged for almost two decades, was finalised in February 2024 and came into force on 1 September 2024. From that date, an ERA report is required for all new marketing-authorisation applications for human medicinal products (QbD Group, 2024; PMC, 2025). The regulatory baseline has therefore already shifted.

1.2.3 The revised Safe and Sustainable by Design framework — adopted March 2026

On 6 March 2026 the European Commission adopted Commission Recommendation (EU) 2026/510, revising the European assessment framework for Safe and Sustainable by Design (SSbD) chemicals and materials, published in the Official Journal on 10 March 2026 (ChemLinked; EC Research & Innovation, 2026). The revised framework explicitly aims to make safety and sustainability 'the default choice, not a compliance hurdle', integrates these considerations from the earliest stages of innovation, was tested across more than 80 real-world case studies including pharmaceuticals, and introduces tiered (simplified, intermediate, full) implementations so SMEs and early-stage innovators can apply it progressively. The Commission notes that applying an SSbD approach early enhances cost efficiency and improves compliance with current and anticipated regulatory requirements.

1.2.4 The Urban Wastewater Treatment Directive — the polluter already pays

The revised Urban Wastewater Treatment Directive (UWWTD), in force from 1 January 2025, requires producers of medicines and cosmetics to finance at least 80% of the cost of removing micro-pollutants from urban wastewater, under the polluter-pays principle. The Commission estimates the additional treatment cost at €1.2 billion per year, and the President of Water Europe states that more than 90% of the micro-pollutants leaving wastewater treatment plants come from pharmaceutical and cosmetic products. The industry response has been to litigate: EFPIA, Medicines for Europe and others have brought sixteen cases before the Court of Justice of the EU, and Poland has made a separate referral (Euronews, March 2025).

The single strongest argument in this paper
The cost of pharmaceutical environmental pollution is no longer hypothetical, and is no longer borne only by ecosystems. It is now a direct, legally-mandated financial liability for producers. Designing lower-impact molecules early is the cheapest available way to reduce that liability at source. Three EU instruments, the Pharma Package, the SSbD framework and the UWWTD, now point in the same direction: environmental performance, decided early, is becoming a determinant of market access, competitiveness and cost. With the EU texts adopting this autumn, 2026 is the moment to act.

1.3 Method and Process — How This Paper Was Developed

1.3.1 A Co-Creation Approach

This paper is not a conventional literature review or a single-author synthesis. It is the product of a structured co-creation process designed to integrate heterogeneous expertise — environmental science, medicinal chemistry, parasitology, veterinary practice, regulatory affairs and industry R&D — into a single, policy-actionable position. This design reflects the nature of the problem: integrating ecotoxicity into early-stage discovery for parasitic diseases (PDis) sits at the intersection of disciplines that rarely engage in sustained dialogue, and whose differing incentives, vocabularies and evidentiary standards have historically impeded joint standard-setting.

The process is anchored in two structured stakeholder meetings complemented by inter-meeting Task Force activity. Meeting I established the framing and the four-pillar evidence architecture. Meeting II translated that architecture into assigned drafting responsibilities, tested emerging positions against expert feedback, and set the consensus rules and consolidation workflow that govern the paper through to its September 2026 policy launch. The approach is consistent with established practice in European scientific consensus documents, including COST Action frameworks, EMA scientific guidelines and WHO technical reports, which rely on structured, stakeholder-inclusive processes to produce positions that represent a community of practice rather than a single institutional view.

1.3.2 Governance: Editorial Group and Task Forces

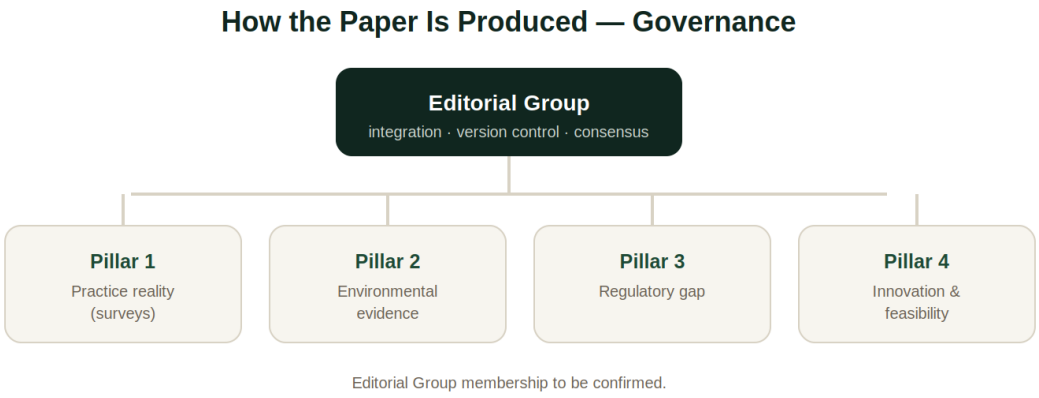


Figure 2 — Governance: an Editorial Group integrating four Pillar Task Forces.

The paper is developed under a two-tier governance model.

- **Editorial Group (EG).** Responsible for narrative coherence, quality, integration, version control and the application of consensus rules. The EG coordinates across Task Forces, resolves structural conflicts, and is the interface with the wider stakeholder community, including journal editors and policy actors. It comprises the lead coordinator, the Chair, and a small number of designated editors from complementary disciplines.
- **Task Forces (TFs).** Each of the four evidence pillars is led by a named section lead supported by a cross-sectoral author team. Task Forces deliver section drafts to an agreed template and flag unresolved disagreements to the EG for resolution under the consensus protocol.

1.3.3 Input Consolidation Workflow

Each Task Force produces a section draft (1.5–2 pages) against the template in Annex D, including one table, one figure and one to two draft recommendations. The EG compiles a single integrated draft, removes duplication, flags cross-pillar inconsistencies, and circulates

it for comment-based review (no open rewriting). Revised drafts are integrated into a coherent full document. All version iterations are tracked and editorial decisions logged, maintaining a transparent record of how the paper's positions evolved — standard practice for a co-created, stakeholder-endorsed document.

1.3.4 Consensus Rules: Managing Differing Views

A process involving industry, environmental science and regulatory experts will surface genuine disagreements — about the strength of evidence, the feasibility of early-stage screens, the interpretation of ERA requirements, and the balance between environmental protection and innovation incentives. Rather than obscuring these, the paper adopts explicit consensus rules. Consensus is defined as 'no sustained objection' across the key stakeholder types after moderated discussion and one revision round.

Situation	Approach
Strong agreement across Task Forces	Included as a direct recommendation, with actor and change-in-practice specified.
Majority view with a dissenting minority	Majority view stated as the paper's position; the dissenting view is recorded in a boxed note attributed to the stakeholder group (not individuals). Both are retained so the Policy Brief reflects the real state of opinion.
Genuine uncertainty in the evidence	Recorded as a declared gap in the relevant Pillar, with a note of what evidence would resolve it. Not stated as a recommendation unless the precautionary case is robust.
Irreconcilable industry / environmental disagreement	Referred to the EG, which may (i) present it as an open policy question, (ii) narrow the recommendation, or (iii) recommend further structured dialogue.
Claims that cannot be evidenced to the EG's satisfaction	Excluded from the recommendation set; noted in Limitations where relevant.

These rules are central to credibility. A document presenting false consensus on contested questions — particularly on the feasibility and cost of early integration — risks rejection by the very regulatory and industry actors it seeks to influence. Acknowledging disagreement where it exists signals scientific maturity and strengthens the paper's standing.

1.3.5 Drafting Timeline: March → July → September

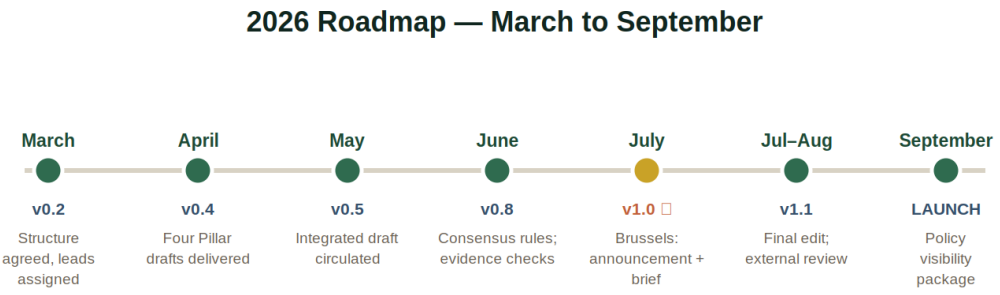


Figure 3 — The 2026 roadmap from March drafting to the September policy launch.

Phase	Period	Key deliverable	'Done' definition
Launch	March 2026	Structure agreed, leads assigned, templates distributed	ToC + owners + deadlines confirmed
Drafting	April 2026	Four Pillar drafts delivered by Task Forces	1–2 pp + 1 table + 1 figure + 1–2 recs each
Integration I	May 2026	Integrated draft circulated for review	Single document; no structural conflicts
Integration II	June 2026	Consensus rules applied; evidence checks	All open issues resolved or flagged
Consolidation	July 2026	Brussels meeting: near-final paper + Policy Brief	Near-final paper + Brief draft
Validation	July–Aug 2026	Final edit; informal review by 2–3 external regulators	Ready for submission
Policy Launch	September 2026	Policy visibility package released	Brief + slide deck + evidence snapshot

1.3.6 What This Paper Is — and Is Not

- **It IS:** a structured, evidence-informed, multi-stakeholder position on integrating ecotoxicity into early-stage PDis discovery, with actionable, proportionate recommendations bounded by the available evidence.
- **It IS NOT a systematic review:** the evidence is assessed for relevance, quality and policy applicability, but the paper does not apply PRISMA-type methodology or quantitative synthesis.
- **It IS NOT regulatory guidance:** it does not carry the legal authority of EMA guidelines or EU instruments. It is a community position advocating regulatory evolution — and that distinction is intentional.
- **It IS NOT a claim of universal agreement:** disagreements are handled transparently; the positions represent the majority view of the co-creation group, not the elimination of dissent.

1.4 Sources and Pathways of API Contamination

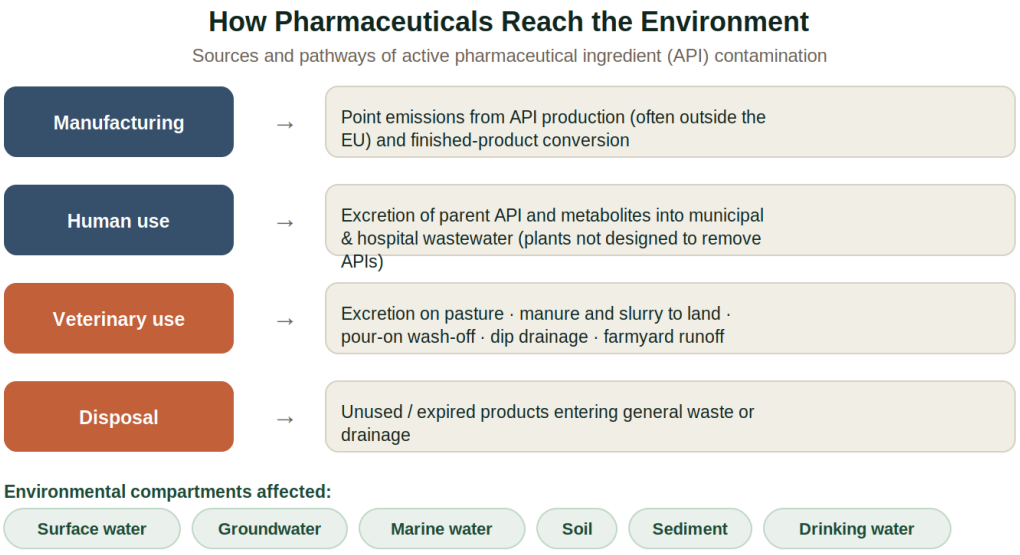


Figure 4 — How pharmaceuticals reach the environment: sources and pathways of API contamination.

Environmental contamination by APIs occurs across the entire lifecycle of a medicinal product , from R&D laboratories and manufacturing facilities through distribution, clinical and veterinary use, excretion by treated organisms, and improper disposal. API manufacturing is geographically concentrated, with much raw-ingredient production in China and finished-product conversion in India; European companies relying on these chains effectively displace the environmental burden of production to regions where regulatory and enforcement capacity may be weaker. Even in countries with modern infrastructure, conventional wastewater treatment plants are not engineered to remove pharmaceuticals, particularly those that are chemically stable, highly polar, or biologically active at trace concentrations.

For veterinary medicinal products (VMPs) the pathways are even more direct: VMPs are excreted as unchanged API or active metabolites after the treatment of animals, entering soils through faecal and urinary deposition on pasture, manure and slurry applied to land, wash-off from pour-on formulations, drainage from dipping facilities, and farmyard runoff. Some classes, such as tetracyclines and macrocyclic lactones including ivermectin, persist for extended periods in manure and soil, prolonging exposure for non-target organisms. The known risks are almost certainly underestimated, since eco-pharmacovigilance data remain limited for most veterinary compounds.

1.5 Stakeholder Landscape and the Limits of Current Stewardship

Within the EU, all medicinal products must undergo an Environmental Risk Assessment (ERA) before marketing authorisation: human medicines under EMEA/CHMP/SWP/4447/00 Rev. 1-Corr.*, veterinary medicines under EMA/CVMP/ERA/418282/2005-Rev.1, reinforced by Regulation (EU) 2019/6. The veterinary ERA follows a two-phase approach: Phase I assesses potential exposure from intended use; Phase II, triggered when exposure is non-negligible, involves detailed ecotoxicological evaluation using predicted environmental concentrations (PECs), predicted no-effect concentrations (PNECs) and risk quotients. Chronic low-level exposure is part of the VICH Phase II assessment.

This framework represents meaningful progress but has substantial limits. It focuses on predicted exposure and acute toxicity in a small number of standard species; sub-individual effects, transgenerational impacts, mixture toxicity, or resistance development in environmental are non standard assessment. Manufacturing, transport and storage contamination fall outside its scope. Post-market initiatives such as eco-pharmacovigilance remain fundamentally reactive, and they act upon problems already materialised.

European stakeholders diverge on how to respond. Industry associations such as EFPIA argue that environmental concerns must not overshadow medicine access and advocate voluntary, science-based stewardship. Companies such as Roche and AstraZeneca accept that residues are undesirable but stress benefit at trace exposure. The European Environmental Bureau treats the current situation as a regulatory failure, calling for binding REACH-style rules. Health-system and pharmacy actors prioritise operational solutions such as medication reviews and collection schemes. These positions are not irreconcilable — but reconciling them requires acknowledging that voluntary stewardship alone is insufficient, and that the most cost-effective point of intervention is the earliest stage of drug development.

Industry and multi-stakeholder initiatives on pharmaceuticals in the environment do exist, but they remain fragmented and largely voluntary. Table 1 summarises the principal European initiatives identified during the preparation of this paper. Several address environmental stewardship in general terms, and one, PREMIER, works directly on environmental risk assessment of medicines. None, however, establishes a binding requirement for early-stage ecotoxicity assessment, and none is specific to antiparasitic drugs.

Entity or initiative	Programme	Scope and relevance
EFPIA	Eco-Pharmaco-Stewardship (EPS)	A holistic environmental risk management programme covering the environmental footprint of medicines and ecotoxicity. Voluntary and industry-led.
Innovative Health Initiative (IHI)	IPIE	Addresses the limited knowledge of what happens to medicines after release into the environment.
Innovative Medicines Initiative (IMI)	PREMIER	Designing an information and assessment system to identify and address environmental risks of medicines, particularly those with limited data availability. The closest existing initiative to the approach proposed here.
AESGP	Sustainable self-care in Europe	Positions responsible self-care within health promotion and disease prevention, with an associated sustainability agenda.

Table 1 — European industry and multi-stakeholder initiatives on pharmaceuticals in the environment. Numerous associations are active, but none imposes a binding early-stage ecotoxicity requirement, and none is specific to antiparasitics.

1.6 Foundational Purpose and Strategic Objectives

The primary objective is to establish an expert-led framework for systematically integrating environmental considerations into the earliest stages of pharmaceutical discovery (PDis). Operationally, the paper provides a practical methodology for R&D teams to identify environmental 'red flags' before significant capital is committed — operationalising a 'fail early, fail cheap' philosophy through 'benign by design' principles and early ecotoxicity screening. From a policy perspective, it aligns industry research priorities with the European Green Deal and the EU Chemicals Strategy for Sustainability, advocating a transition from a reactive, compliance-heavy ERA to a proactive, integrated model.

Objective type	Description	Key strategic benefit
Operational	Early-stage screening tools (ADME–ecotoxicology prediction, short-term predictive ecotox assays, GREENER approach and green chemistry in lead optimisation); timely regulatory recommendations.	Selection of scaffolds, hits and leads with the lowest ecotoxicological impact; reduced R&D waste; optimised synthetic pathways; lower manufacturing costs; increased environmental protection.
Policy	Alignment with voluntary SSbD frameworks and international sustainability goals (e.g. UN SDGs).	Enhanced regulatory readiness; alignment with ESG investor criteria; improved reputation.
Scientific	Integration of One Health concepts and comparative genomics in drug design.	Prediction of off-target effects in environmentally relevant species; reduced ecological risk.

1.7 Defining the Parameters of Scope

The scope is intentionally focused on early-stage integration of environmental intelligence within human and veterinary pharmaceutical discovery — the phases of target identification, hit-to-lead and lead optimisation, where molecular modification is still technically feasible and economically viable. The dual human/veterinary focus reflects the shared pathways through which bioactive substances reach the environment. Two key exclusions maintain focus:

- The proposed discovery-stage screening is not a replacement for the mandatory regulatory ERA required for marketing authorisation; it is a precursor that ensures only environmentally viable candidates advance.
- The paper does not address retroactive withdrawal of marketed products; re-evaluation of legacy products involves distinct legal, economic and clinical considerations beyond this R&D-focused framework.

1.8 Antiparasitic Drugs: A Critical and Under-Regulated Environmental Risk

Among VMPs, antiparasitic drugs warrant particular attention. These drugs are effective against a broad and diverse range of parasite species, including protozoa, helminths (gastrointestinal and lung nematodes, cestodes and trematodes), and ectoparasites such as ticks and mites, among others. They are applied globally across livestock, companion animals, birds, fish and molluscs, both therapeutically and prophylactically. They are specifically designed to be potent at low concentrations and chemically stable — properties that make them effective medicines and environmentally persistent hazards simultaneously. Their potential for widespread contamination is intrinsic to their pharmacological design.

Despite this, in veterinary medicine antiparasitics have received far less regulatory and academic attention than antimicrobials. This asymmetry partly reflects the fact that, within the One Health framework, antimicrobial resistance is recognised as a major threat to human health, driving substantial regulatory and research efforts. In contrast, parasitic infections in livestock, particularly those caused by helminths, as well as some protozoa (for example coccidia) or ectoparasites (for example ticks and mites), are often associated with chronic or subclinical infections that primarily reduce animal productivity, through lower weight gain or milk yield, rather than causing severe disease. Consequently, antiparasitics have historically received comparatively less attention. Ivermectin, a macrocyclic lactone endectocide, has become the model compound for these effects, with extensive and unambiguous evidence of impact on dung beetle communities, aquatic invertebrates and soil fauna. Companion-animal parasiticides such as fipronil and imidacloprid reach the environment through bathing, rainfall and household wastewater; EMA acknowledged in 2023 that parasiticides used in cats and dogs may no longer have negligible environmental exposure and initiated a dedicated reflection process.

A further critical gap is the absence of any EU-wide surveillance system for parasiticide sales or use. While Regulation (EU) 2019/6 requires harmonised antimicrobial sales reporting (published through ESUAvet), no equivalent exists for parasiticides — meaning emission volumes and environmental burden cannot be robustly estimated at population scale. This is not a minor technical deficiency; it is a structural obstacle to evidence-based environmental risk management.

The case of certain VMPs, such as anthelmintics, illustrates this risk particularly well. These compounds are typically administered to entire herds or flocks, using the default treatment fraction of 100% established in VICH GL6. In Phase I a deliberately conservative total residue approach is applied, assuming that the administered dose is fully available for environmental exposure unless scientifically justified refinements, supported by appropriate data, indicate otherwise. Consequently, veterinary anthelmintics frequently exceed the Phase I trigger values and therefore require a Phase II environmental risk assessment. This is foreseeable from the very start of drug development, which strengthens the case for screening ecotoxicity early rather than discovering these risks late.

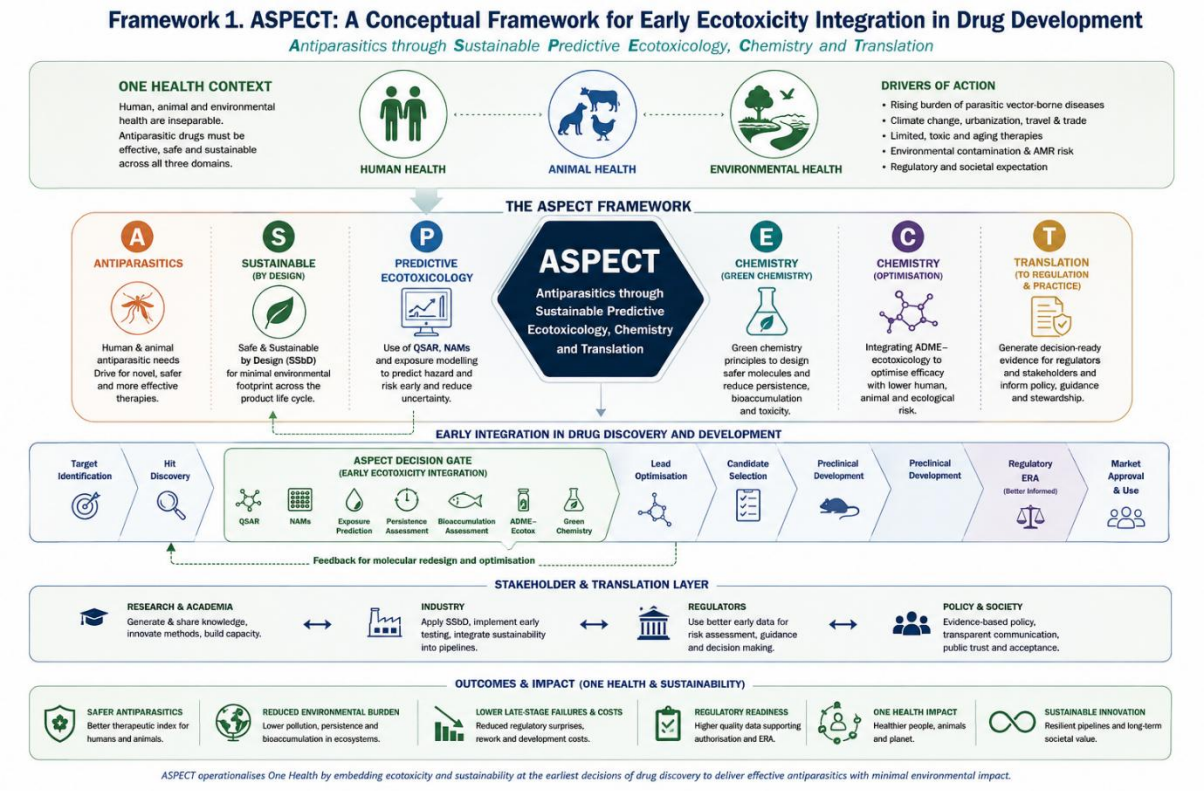
1.9 Identification of Target Audiences

This paper is prepared by a stakeholder team of academic researchers, experts familiar with ERA procedures in national and European regulatory bodies, and pharmaceutical and

representative organisations. Its primary target audiences are regulatory entities such as the European Medicines Agency (EMA) and the European Commission. It is further tailored to:

- **Research teams and medicinal chemists** — technical guidance on 'benign by design', green chemistry metrics and in silico prediction of persistence and bioaccumulation.
- **Regulatory affairs and compliance professionals** — how early-stage data facilitates regulatory readiness under the 2024 EMA update.
- **Industry R&D leadership and executives** — how environmental sustainability drives long-term value, reduces operational risk and achieves cost savings.
- **Funders and ESG investors** — criteria to evaluate a pipeline's sustainability credentials under frameworks such as the Sustainable Finance Disclosure Regulation (SFDR).
- **Policymakers and healthcare educators** — a basis for curricula and policy incentives supporting Green Pharmacy.

1.10 Conceptual Framework for Early Ecotoxicity Integration in Drug Development



This conceptual figure illustrates the proposed integration of an early-stage ecotoxicity decision-support layer within the pharmaceutical drug discovery pipeline. The traditional development sequence—from target identification through hit discovery, lead optimisation, candidate selection, and preclinical development—is complemented by an intermediate ecotoxicity screening gate introduced between the hit and lead optimisation stages.
This early-stage layer incorporates predictive and experimental methodologies, including quantitative structure–activity relationship (QSAR) models, new approach methodologies (NAMs), and environmental exposure and persistence assessments, generating actionable feedback for molecular redesign and optimisation.

The framework establishes a bidirectional feedback loop between environmental risk signals and compound design, enabling iterative refinement of candidate molecules prior to late-stage development.
Existing regulatory structures, including Environmental Risk Assessment (ERA), the European Medicines Agency (EMA) evaluation process, and relevant EU policy frameworks such as the Pharmaceutical Strategy and Safe and Sustainable by Design (SSbD) principles, remain intact but are informed by improved upstream data inputs.
The model further highlights the role of policy and stakeholder interfaces—including regulatory authorities, industry actors, and research networks—in enabling future adoption and harmonisation of early ecotoxicity integration approaches.
Overall, the framework supports a transition from reactive environmental assessment at the end of the development pipeline to proactive, design-stage environmental risk mitigation, aligned with One Health and sustainability objectives.

2. The Four Pillars — The Evidence Base

2.1 Pillar 1 — Empirical Field Evidence (Practice Reality)

2.1.1 Veterinary Professionals as Key Actors in One Health Environmental Stewardship

Figure 5 — Veterinary survey respondents by region (1,065 respondents, 39 countries; coverage varied by country; see Annex A). Detailed country-level figures for all 39 countries are available in the interactive survey map (at https://gss.cost-action.eu/OHD_Survey_Map_by_Country.html.

Veterinarians occupy a unique position at the interface of animal, human and environmental health. As prescribers of veterinary medicinal products (VMPs), they play a critical role in animal welfare, zoonotic disease prevention and public health. The OHD pan-European survey received valid responses from 1,065 veterinarians in 39 countries, distributed almost equally across regions and across rural, urban and mixed practices, early-career and experienced practitioners, and all practice types. The survey found practitioners overwhelmingly aware of One Health principles, with 91.6% reporting familiarity with the concept, yet it reveals important gaps in awareness, education and prescription practices concerning the environmental impact of veterinary pharmaceuticals.

However, awareness of the environmental consequences of prescribed VMPs against parasitic vector-borne diseases remains incomplete: close to 50% overall across Central, Northern and Southern European regions. Approximately half of practitioners therefore prescribe VMPs without awareness of their potential for harm to ecosystems and non-target species, and their contributions to contamination, and resistance. Veterinary parasiticides may be released as non-modified compounds or metabolized and enter the environment through excretion and wash-off; continuous low-concentration exposure may affect biodiversity, disrupt ecosystem functions and animal behaviour, and may also contribute to the development of resistance, particularly in parasites with free-living infective stages.

Environmental education is the critical missing component. Nearly two-thirds of respondents (62%) reported never receiving any information, education or training on the environmental impacts of veterinary medicines; only a minority obtained information through continuing professional development (12%), pharmaceutical companies (15%) or other sources (10%). Of those with no formal training, 36% had never considered the issue but were interested to learn, and only 3.7% indicated a lack of interest. By contrast, veterinarians overwhelmingly reported familiarity with the mechanism of action (93.8%) and excretion (82.4%) of the antiparasitics they prescribe, a high level of pharmacological knowledge alongside a clear environmental education gap. The Summary of Product Characteristics (SPC) by regulatory bodies (EMA or national veterinary authorities) explicitly address the environmental safety and toxicity to ensure proper risk management (section 5.3, 4.5, 6.6) and outlines how a veterinary medicinal product should be safely used. However, this is not enough.

Environmental considerations rarely influence prescribing decisions. Veterinarians base decisions primarily on efficacy and safety, market availability, ease of administration and professional guidelines; environmental impact ranked among the least influential factors, considered by only 15% of respondents. This does not reflect a lack of responsibility but the absence of practical tools, transparent data and regulatory guidance, and the often limited options available. Waste-management practices also require improvement: while 53% reported appropriate disposal through incineration and 12% request distributor collection, a considerable proportion reported disposal in general waste (21%) or donation of unused or expired products (25%).

The growing companion-animal sector increases urgency. Demand for antiparasitic prophylaxis is expected to rise substantially, accompanied by parasiticide market expansion and climate-change-driven spread of vectors. Antiparasitic VMPs applied to companion animals represent an emerging environmental concern in urban as well as rural contexts, warranting greater scientific, regulatory and professional attention. The whole document titled ‘Data Report on Veterinary Professionals as Key Actors in One Health Environmental Stewardship is open access(https://doi.org/10.15490/fairdomhub.1.document.4436.1)’

2.1.2 Raising Sustainability Standards in PDis Drug Research

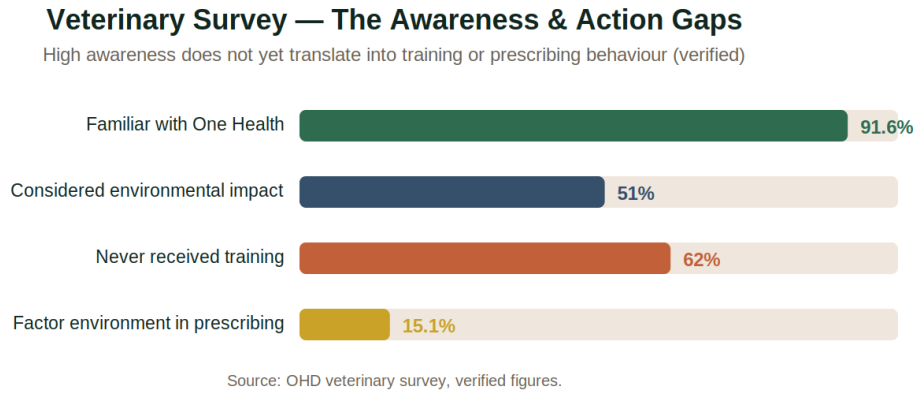


Figure 6 — The awareness and action gaps: high One Health awareness does not yet translate into training or prescribing behaviour.

A complementary OHD survey of PVBD researchers (conducted 2022–2023) revealed strong support for environmentally responsible research alongside shared concern over its footprint, but awareness did not consistently translate into operational change. Few researchers implemented measures to reduce plastic, energy use or broader laboratory impacts; sustainability implementation lagged well behind technological development. Researchers frequently lack the expertise, methodologies, training and funding to incorporate

ecotoxicological evaluation into routine workflows, and few standardised assays exist. The primary barriers are structural, not attitudinal.

The most striking finding concerns the very limited integration of ecotoxicology into discovery pipelines: a limited number of research activities incorporated ecotoxicological assessment in early discovery, and none identified ecotoxicology as a primary research activity. This includes also pharma company in different association (EFPIA, AGESP and those involved in EU projects such as IPIE - IHI (Innovative health initiative) (2016-2019) and PREMIER IMI (innovative medicine initiative (2020-2026). This gap matters because decisions made during early discovery largely lock in the pharmacological and environmental characteristics of future medicines; once a compound has progressed through efficacy and safety studies, redesign becomes increasingly limited and costly.

The survey also highlighted the need for new funding models. Almost all groups were small (63% with 1–4 researchers, 63% of whom were under 35), relying heavily on undergraduate and Master's students. Collaboration with governmental and private institutions was low (17% and 12% respectively), reflecting low prioritisation by mainstream funders. Research funders should incorporate sustainability criteria into grant evaluation, as ethical review and animal welfare have become standard, and dedicated streams should support ecotoxicological testing, environmental risk modelling, biodegradability studies and interdisciplinary collaboration.

OHD is promoting practical initiatives towards environmentally safer discovery: standardised in vitro and in vivo screening protocols that reduce waste and enable lab-to-lab comparison; standardised ecological toxicity tests; computational tools for predicting pharmacokinetics, metabolism, safety and toxicity; agreed go/no-go decision points within pipelines; sharing of green laboratory practice; an overview paper on the environmental impacts of the main veterinary parasiticides; and an edited book, One Health Drugs Against Parasitic Diseases, featuring contributions from discovery to environmental impact.

2.2 Pillar 2 — Environmental Scientific Evidence (Ecological Legitimacy)

BOX — CASE STUDY: Isoxazoline antiparasitic drugs

The environmental trajectory of isoxazoline ectoparasiticides used in pets highlights a critical need for integrating environmental considerations into the very beginning of the drug discovery process (Berny et al., DOI 10.1093/etojnl/vgaf285).

These compounds are largely excreted in their active form through faeces and possess remarkably long half-lives, meaning they persist in the environment well beyond the duration of their clinical efficacy. Scientific assessments indicate that residues of substances such as fluralaner and lotilaner can remain detectable in pet waste for several months, creating a continuous exposure route for non-target species such as dung-feeding insects.

Because current regulatory frameworks often bypass detailed environmental impact studies for companion-animal medicines, there is a risk that chemical scaffolds with high ecological persistence and toxicity are advanced through development without sufficient scrutiny.

This case demonstrates that an appropriate and predictive evaluation of environmental fate must be established during the initial scaffold selection and lead-optimisation phases. Identifying potentially harmful structures early is essential to prevent long-term ecological damage and to ensure that new pharmaceutical developments are sustainable from their inception.

Antiparasitic cases — the specific evidence

Several studies point to the environmental presence of antiparasitics, especially benzimidazoles and macrocyclic lactones, in the aquatic compartment at noteworthy levels: 280.00 ng/L in surface water and 662.19 ng/g in sediments (Lei et al., 2026, Lhasa River).

Even chemicals used for aquaculture, such as emamectin benzoate, often exceed environmental quality standards (Langford et al., 2014) and are likely to affect benthic communities (Arnberg et al., 2026).

Concerns are not limited to parent compounds: metabolites of anthelmintics often show higher toxicity to wild organisms (Horvat et al., 2012).

Some antiparasitics, such as ivermectin, are likely to bioaccumulate in the tissues of wild, environmentally exposed organisms (Wang et al., 2019).

The presence of pharmaceutical drugs of both human and veterinary use across environmental matrices is now an undisputed reality. The most frequently detected include steroid hormones, antibiotics, neuroactive compounds, non-steroidal anti-inflammatory drugs, blood-lipid-lowering agents and beta-blockers, though the list grows continually. These chemicals can reach levels that pose significant risks to exposed species. Their environmental presence results largely from the general inefficacy of sewage treatment plants in removing such molecules, producing widespread and continuous presence in surface water, marine water, groundwater, soil, and even tap and drinking water. Waste management devoted to pharmaceutical residues remains a major gap, especially in the Global South. The regulatory framework for pharmaceutical residues is internationally fragmented and not comprehensively regulated, and strong asymmetries exist between countries driven by income and treatment infrastructure.

Pharmaceuticals typically occur at vestigial levels (ng L^{-1}), though local concentrations of specific drugs can reach µg L^{-1}. The picture is further complicated by metabolites and transformation products, which add ecotoxicological concern and are analytically difficult to monitor. Major sources include municipal and hospital sewage treatment plants, alongside

point emissions from pharmaceutical manufacturing. ERA improvements have been implemented, but the regulatory reach is not entirely protective; ERA processes for medicinal products must be updated regularly to incorporate recent ecotoxicological findings.

Despite the low levels usually found, pharmaceuticals are high enough to adversely alter physiological processes responsible for the homeostasis of wild organisms, and their considerable persistence favours long-term interaction. For some compounds, environmental half-lives surpass months; given systematic input and removal rates that sometimes equal degradation, many can be characterised as pseudo-persistent. Sediment plays a key role in sequestration; moderate lipophilicity favours bioaccumulation and transfer along food chains. Documented effects of pharmaceuticals in wild biota include antibiotic resistance, endocrine disruption, behavioural changes in crustaceans, polychaetes and fish, epigenetic changes in fish, oxidative stress in bivalves, reduced photosynthetic pigments in aquatic plants, and population alterations in cladocerans. These effects are frequently mediated by the compounds' known mechanisms of action, since humans and wild species share evolutionarily conserved molecular targets.

Recognising this, the scientific community has begun to include ecological criteria in the development, production and (eco)prescription of medicinal products. The final disposal of medicinal substances is a key issue, and eco-pharmacovigilance, systematic monitoring of environmental presence and adverse effects over time, has been proposed to prevent release of untreated forms into the wild. Regarding prescription practices, the approach to controlling helminth infections in livestock, where resistance to anthelmintic drugs is already established, is to move towards a targeted selective treatment strategy. Individual treatments are then based on indicators of parasite infection, such as worm burden assessed via faecal egg counts, or on indirect indicators including anaemia (for example the FAMACHA score), reduced weight gain or antibody titres, rather than treating the whole flock or herd.

2.3 Pillar 3 — Regulatory Gap Analysis (Structural Issues)

The current paradigm for drug discovery and development is a multi-decade, high-risk, capital-intensive endeavour. On average it takes 12–15 years for a new drug to reach market, with development costs estimated between $1 billion and $2.23 billion. For every 5,000–10,000 compounds initially screened, only five progress to human trials and only one achieves approval. An animal health products typically require 5 to 10 years. On average, development takes about 6.5 years for companion animals and 8.5 years for livestock. The development costs are drastically lower, generally ranging between $20 million and $62 million per new product, which is a fraction of the $1 billion to $2.23 billion required for human pharmaceuticals. Companion animal pharmaceuticals average approximately $22.5 million. Livestock pharmaceuticals average approximately $30.5 million.
A primary driver of this attrition in both cases is the discovery of safety and toxicity issues late in development, which accounts for roughly 30% of candidate failures.

The traditional model prioritises therapeutic efficacy and safety during early discovery, while Environmental Risk Assessments are relegated to the end of the cycle, often coinciding with Phase III. This 'environmentally blind' approach creates a significant risk: a candidate may succeed clinically yet possess intrinsic ecotoxicological properties that lead to late-stage rejection or post-launch ecological damage. The lock-in of financial resources and expertise at late stages makes it difficult to pivot to safer scaffolds — underscoring the necessity of integrating ecotoxicity screening at the molecular design stage.

Stage of development	Primary activity	Environmental consideration status	Cost / risk implication
Target identification	Biological target mapping	Traditionally absent	Lowest cost; opportunity to select 'green' targets
Hit-to-lead	Screening & scaffolding	Rare / minimal	Identification of structural liabilities early ◄ PROPOSED GATE
Lead optimisation	Refinement of SAR	Growing focus on PBT	High leverage for 'benign by design' changes
Preclinical testing	In vivo & in vitro safety	Acute toxicity assays	High cost; animal-model reliance
Phase I–III clinical	Human trials	ERA preparation (late phase)	Peak investment; failure here is catastrophic
Regulatory review	Marketing authorisation	Mandatory ERA submission	Potential refusal on environmental grounds

2.4 Pillar 4 — Innovation and Feasibility (The 'Doable' Now)

Pillar 4 summary. Pharmaceutical environmental risks are traditionally assessed late in development, limiting opportunities to modify compounds once major investments have been made. Integrating environmental fate and hazard information early, during hit identification, lead optimisation and candidate selection, supports safer, more sustainable pharmaceuticals and aligns with Safe and Sustainable by Design principles. Early ecotoxicological screening provides rapid hazard signals; standard assays (aquatic assays taken as example - Daphnia, algae/cyanobacteria, fish embryo) offer pragmatic first-tier information, and in Animal Health and Crop Science such assays are already routine in hit-to-lead and lead optimisation. A broad range of computational tools (QSAR models, ECOSAR, OECD QSAR Toolbox, VEGA, OPERA, GDS) supports early prediction, with AI/ML systems and integrated platforms such as G.AI.A extending these capabilities. Successful implementation requires a structured feasibility gate addressing validation, standardisation, TRL, cost-benefit and scalability.

Environmental considerations traditionally enter pharmaceutical development late, mainly through regulatory Environmental Risk Assessment (ERA). While ERA is essential, it offers limited opportunity to modify compounds once substantial investment has been made. A more effective strategy is the early integration of environmental fate and hazard information into hit identification, lead optimisation and candidate selection. This aligns with Safe and Sustainable by Design (SSbD) and 'benign-by-design' principles, where environmental behaviour becomes a design parameter alongside efficacy and safety. Extensive evidence shows that active pharmaceutical ingredients can persist, affect non-target organisms and contribute to ecological disturbances; the challenge is therefore not to establish whether risks exist, but to translate environmental data, persistence, biodegradability, bioaccumulation, transformation pathways and ecotoxicological liabilities — into actionable guidance during discovery.

2.4.1 Early-Stage Ecotoxicological Screening

Early ecotoxicity screening provides rapid hazard signals before major preclinical investment and supports prioritisation of safer analogues. Standard assays, for aquatic compartment Daphnia immobilisation and behaviour, algal or cyanobacterial growth inhibition, and fish embryo toxicity; for terrestrial compartment requested for vet meds: earthworms, soil nitrification, plant toxicity to dung beetles and dung flies for parasiticides, offer pragmatic first-tier information across relevant trophic levels.

In Animal Health and Crop Science, such assays are already routine during hit-to-lead and lead optimisation, well before a lead compound enters pre-development. As outlined in Selzer & Epe (Trends in Parasitology, 2021), Animal Health discovery pipelines apply a strict 'fail early, fail cheap' approach, integrating environmental fate, ecotoxicity and regulatory constraints from the outset. While early integration is still emerging in parts of human pharma, it is long-established in Animal Health and should be framed accordingly. Effective early screening requires coupling hazard data with exposure modelling and environmental fate predictions to identify candidates requiring further optimisation or definitive testing.

2.4.2 Computational Tools for Early Environmental Assessment

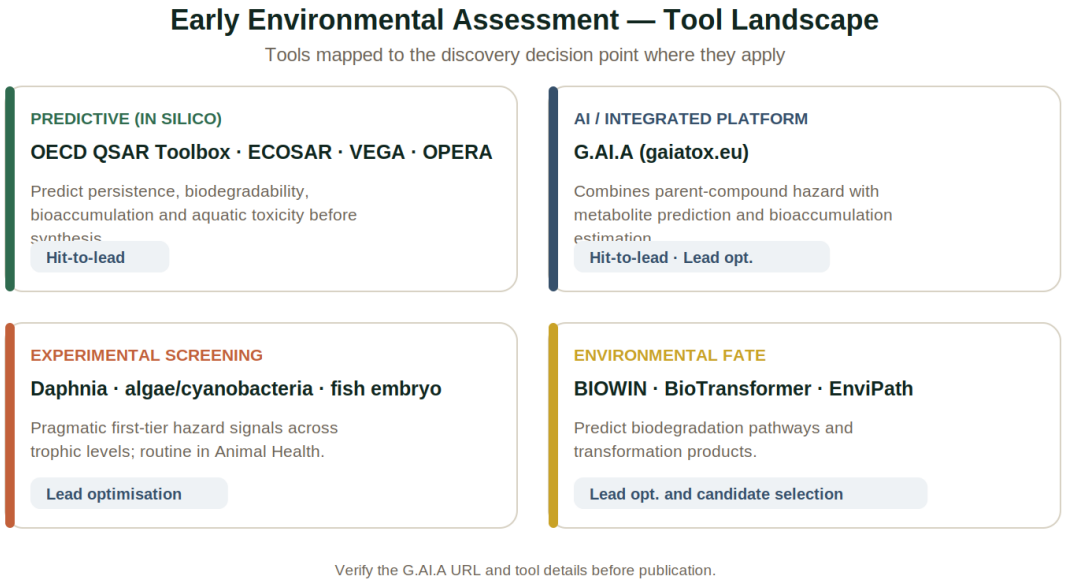


Figure 7 — Early environmental assessment tool landscape, mapped to discovery decision points.

A broad range of computational tools supports early environmental decision-making. Established platforms such as the OECD QSAR Toolbox, ECOSAR, VEGA and OPERA predict persistence, biodegradability, bioaccumulation and aquatic toxicity, enabling rapid first-tier screening before synthesis. AI/ML-based systems extend these capabilities by integrating large toxicological and environmental datasets. G.AI.A (gaiatox.eu) further advances the field by combining parent-compound hazard assessment with metabolite prediction and bioaccumulation estimation, offering improved accuracy for acute toxicity and bioconcentration predictions. GDS (Green Drug Score) prioritize the lowest ecotox compounds from virtual screening studies.

Beyond in silico prediction, a further category of early-stage tools is increasingly important: New Approach Methods (NAMs). NAMs use cell-based in vitro systems and computational models in place of whole-animal testing, and are well suited to early discovery for three reasons. First, they can be applied at hit-to-lead and lead optimisation, when many compounds are screened and when redesign is still feasible, rather than only at the advanced stages where traditional animal ecotoxicity studies are typically run. Second, they are substantially cheaper and faster per compound, which matters most precisely when large libraries are being triaged. Third, they align with the 3Rs principle of replacement, reduction and refinement of animal use, an ethical and increasingly regulatory expectation in Europe. Established cell-based assays and in silico models are already usable as first-tier NAM screens; their main current limitation is the need for continued validation and standardisation against regulatory endpoints, which is itself an argument for the funding and standardisation recommendations made in this paper.

Link to the recommendations

This NAM framing reinforces three of the paper's recommendations: the staged, low-cost-first screening approach; the call to fund standardisation and calibration of accessible ecotoxicity assays; and the alignment of early environmental testing with the 3Rs, echoing the established model in which funders require such evaluation, comparable to the treatment of laboratory-animal use.

2.4.3 Feasibility Gate: Validation, Standardisation, TRL, Cost–Benefit, Scalability

Successful implementation depends on improved communication between computational toxicologists, medicinal chemists and environmental scientists, as a key feasibility condition for integrating environmental endpoints alongside efficacy and safety in lead optimisation.

The availability of innovative tools does not guarantee their suitability for discovery workflows. A structured feasibility gate helps determine when a tool is sufficiently mature for decision-making.

- **Validation.** Tools must demonstrate reproducibility, robustness and relevance. Computational approaches require defined applicability domains and external validation datasets; experimental methods require inter-laboratory reproducibility. Validation depth should match intended use — early prioritisation versus regulatory support.
- **Standardisation.** Harmonisation remains a major barrier. Alignment with OECD guidelines, EMA ERA requirements and emerging SSbD frameworks increases confidence and comparability — particularly for microbiome-based degradation studies, AI-assisted prediction platforms and environmental fate modelling.
- **Technology Readiness Level (TRL).** QSAR models, ECOSAR, the OECD QSAR Toolbox and standard ecotoxicity assays have high TRLs and can be used immediately as first-tier screens. Advanced AI/ML systems, microbiome-informed degradation prediction and novel fate models remain at lower TRLs and require further validation.
- **Cost–benefit and scalability.** Early predictive approaches are attractive because they apply to large libraries with minimal resources. High-throughput computational models, medium-throughput ecotoxicity assays and integrated environmental databases are currently the most operationally feasible solutions.

2.4.4 What Is Ready Now vs What Requires Further Validation

Table — Validation hierarchy of early-assessment tools

Tier	Status	Tools / methods	Use
1	Regulatory-ready	OECD-validated QSAR (QSAR Toolbox), standard OECD ecotoxicity assays (Daphnia, algae, fish embryo)	Can support regulatory-facing evidence; highest confidence.
2	Screening-level	ECOSAR, VEGA, OPERA, BIOWIN, GDS.	Reliable first-tier prioritisation in discovery; not stand-alone regulatory evidence.
3	Experimental / emerging	AI/ML platforms (e.g. G.AI.A), BioTransformer, EnviPath, microbiome-informed and medium-throughput biodegradability assays.	Promising, mechanistically rich, but require further validation and standardisation before routine or regulatory use.

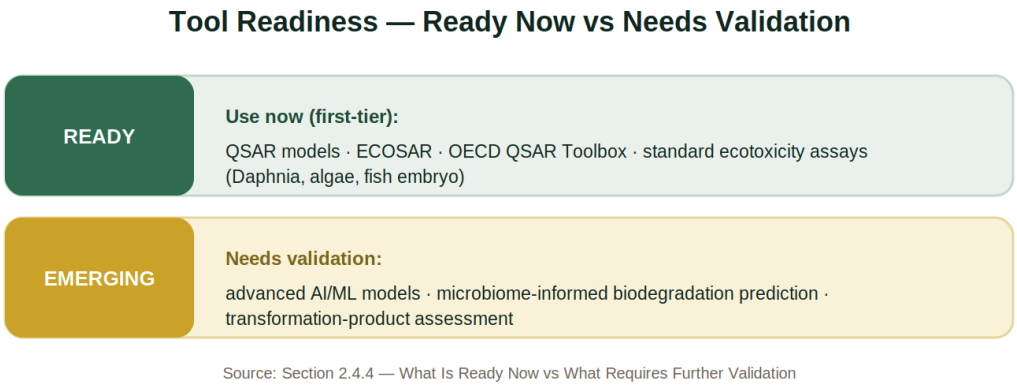


Figure 8 — Tool readiness: established tools usable now versus emerging approaches needing validation.

Established tools, QSAR models, ECOSAR, the OECD QSAR Toolbox, GDS and standard ecotoxicity assays, already support early prioritisation by providing first-tier information on persistence, bioaccumulation and hazard. Emerging approaches, including advanced AI/ML models, microbiome-informed biodegradation prediction and transformation-product assessment, require further validation regarding predictive accuracy, applicability domains and real-world relevance. Prediction of transformation products remains a major challenge.

2.4.5 Emerging Opportunity — Environmental Fate

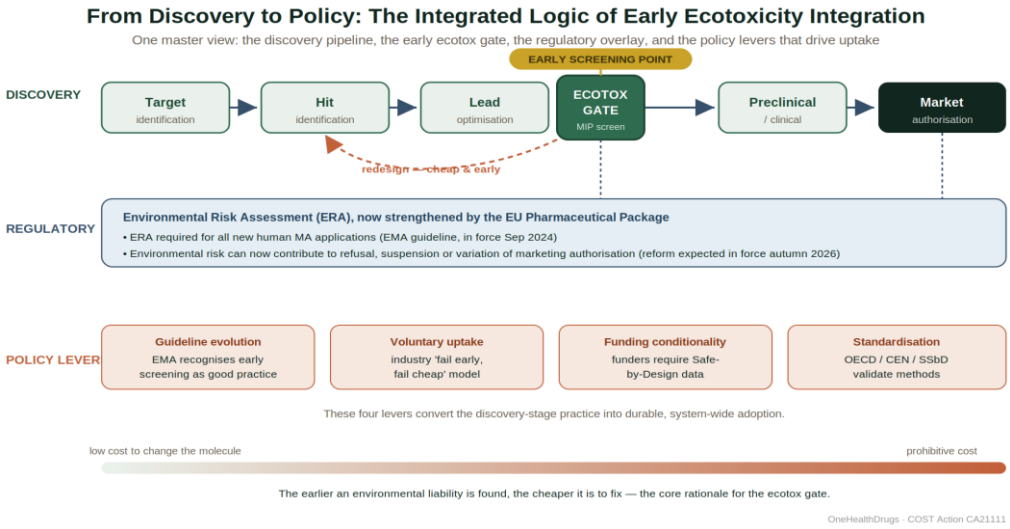
Environmental impact depends strongly on what happens to pharmaceuticals after release. Early prediction of biodegradation, biotransformation and environmental fate would significantly improve compound prioritisation. Tools such as BIOWIN, OPERA, VEGA, BioTransformer and EnviPath already support biodegradation prediction and transformation pathway analysis, and medium-throughput biodegradability assays (e.g. activated sludge microplate formats) are increasingly available. Key challenges include limited high-quality degradation datasets, insufficient representation of environmentally relevant microbial processes, and difficulty predicting complex transformation networks. Integrated platforms such as G.AI.A represent promising steps toward holistic early-stage environmental assessment.

Table 3 — Tool-to-decision mapping

Tool category	Decision point	Output	Readiness
QSAR models, ECOSAR, OECD QSAR Toolbox, VEGA, OPERA and GDS	Hit-to-lead	Predicted persistence, biodegradability, bioaccumulation, aquatic toxicity, compound library low ecotox prioritization	Ready now (high TRL)
G.AI.A (gaiatox.eu)	Hit-to-lead / lead optimisation	Parent-compound hazard plus metabolite and bioaccumulation prediction	Ready now
Daphnia, algae / cyanobacteria, fish embryo assays	Lead optimisation	First-tier experimental hazard signals across trophic levels	Ready now
BIOWIN, BioTransformer, EnviPath	Lead optimisation / candidate selection	Biodegradation pathways and transformation products	Emerging — needs validation
AI / ML, microbiome-informed degradation models	Candidate selection	Advanced environmental fate and degradation prediction	Emerging — needs validation

3. The Position: Recommendations and Implementation

In practice, ASPECT brings together six elements, one for each letter, which the paper develops in turn. Antiparasitics: the therapeutic focus, addressing unmet needs across human and animal health. Sustainable by design: safety and sustainability treated as design criteria from the earliest stage. Predictive: early ADME and in silico prediction to anticipate a candidate's environmental fate before synthesis. Ecotoxicology: short-term predictive assays that provide first-tier hazard signals. Chemistry: greener chemistry and synthetic routes that design out hazard and waste. Translation: timely translation of the resulting evidence into regulatory recommendations and practice for parasitic and vector-borne diseases.



Master figure *— The integrated logic of early ecotoxicity integration: the discovery pipeline, the early ecotox gate, the strengthened regulatory overlay (ERA), and the four policy levers that convert discovery-stage practice into system-wide adoption.*

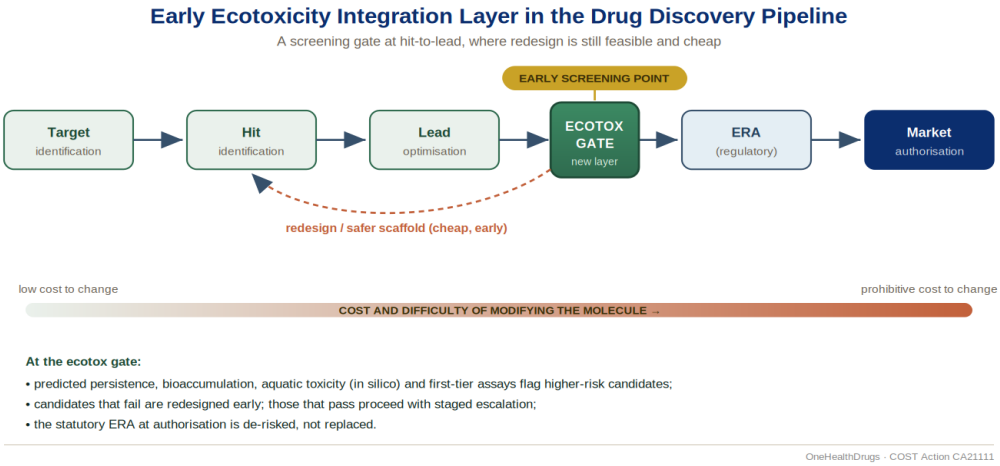


Figure 9 The Early Ecotoxicity Integration Layer in the drug discovery pipeline: a screening gate at hit-to-lead flags higher-risk candidates for redesign while modification is still feasible and cheap; it de-risks, but does not replace, the statutory ERA.

3.1 'Early Integration' in Practice

The paper's core argument — and its most actionable contribution — is that the most effective, cost-efficient and genuinely sustainable response to pharmaceutical pollution is to integrate ecotoxicological assessment into the earliest phases of drug development. This means applying Green Chemistry principles and early ecotoxicological screening during preclinical

discovery, so that environmental red flags can be identified and addressed, or used to disqualify candidates, before years of investment have been committed. The logic is straightforward: if environmental criteria can prevent an API from receiving marketing authorisation, identifying those characteristics early is in the rational commercial interest of developers, as well as an environmental and ethical imperative. This aligns with the Quadripartite One Health Joint Plan of Action.

Achieving this requires coordinated action: researchers educated about environmental consequences and adopting sustainability as a core value; companies accepting early ecotoxicological profiling as standard, supported by updated regulatory guidance; regulators expanding ERA frameworks to encompass chronic sub-lethal endpoints, transgenerational effects, mixture toxicity and realistic exposure; an EU-wide parasiticide surveillance system; strengthened eco-pharmacovigilance; and a coherent framework for manufacturing emissions. The paper situates these within the UN SDGs — SDG 3, 12, 13 and 14 — and calls on policymakers, regulators, researchers and industry to act at source, with prevention rather than compensation as the guiding principle.

3.2 Defining 'Early Integration' — the Minimum Information Package

DEFINITION — The Early Integration Framework
The Early Integration Framework is the systematic consideration of environmental fate and ecotoxicity at the earliest decision points of drug discovery (target identification, hit-to-lead and lead optimisation), so that a molecule's likely environmental behaviour informs its design before major preclinical and clinical investment is committed.
It operates through a defined screening point (the ecotoxicity gate) and a minimal agreed dataset (the Minimum Information Package, MIP). Candidates flagged as higher-risk are redesigned or deprioritised early; those that pass proceed with staged escalation.
It is a decision-support layer for discovery scientists. It does not replace the statutory ERA required at marketing authorisation, does not impose a market ban, and creates no new disclosure obligation unless a candidate proceeds to authorisation.

What it is: an early environmental filter to de-risk candidates (staged escalation plus documentation), applied before major preclinical investment.

What it is not: a replacement for statutory ERA; a basis for blanket bans; or a mechanism for retroactive withdrawal.

Minimum Information Package (MIP) — draft (to finalise): persistence proxy (screen); bioaccumulation proxy (screen); aquatic toxicity proxy (screen); biodegradability screen; documentation template (assumptions and uncertainties). Decision rule (draft): candidates failing one or more MIP thresholds trigger redesign or alternative scaffolds; candidates passing proceed with staged escalation.

3.3 Recommendations (the Core 'Ask')

Each final recommendation should follow the template: title; what (1 sentence); why (anchored to Pillar evidence); who acts; what changes in practice; feasibility note; policy-brief phrasing.

#	Recommendation (working draft)	Primary actor
R1	Introduce an early-stage environmental screening gate with a minimal indicator set (MIP).	R&D teams; industry; funders
R2	Adopt a staged approach: predictive screening first; expanded testing for prioritised candidates.	R&D teams; CROs

R3	Create a simple reporting template to make results comparable across projects.	EG; research community; journals
R4	Align funding calls and R&D governance to require 'Safe-by-Design' environmental data.	Funders; industry sustainability leads
R5	Define feasibility criteria (validation / standardisation / TRL) for acceptable early tools.	Pillar 4 TF; EMA (acknowledge)
R6	Align training and capacity building to the observed gaps (education + tools for vets and researchers).	Educators; professional bodies; COST network
R7	Translate the paper into a 2-page Policy Brief for September visibility.	EG; Chair; Stakeholder Lead

3.4 Implementation Roadmap and 2026–2027 Pilot

HOW THIS ACTUALLY GETS IMPLEMENTED — the mechanism chain

Adoption does not depend on a single legislative act. It advances along a chain of reinforcing mechanisms:

1. Evidence and feasibility (this paper + the 2026–2027 pilot) demonstrate that early screening works and is affordable.
2. Guideline recognition: EMA acknowledges early screening as good practice within ERA-related guidance, lowering the risk of voluntary adoption.
3. Voluntary industry uptake: companies extend the 'fail early, fail cheap' model already used in Animal Health to human PDis discovery, because it reduces their own late-stage risk.
4. Funding conditionality: funders and ESG investors require Safe-by-Design data as a grant or investment condition, reaching academic and SME actors directly.
5. Standardisation: OECD, CEN and the SSbD framework validate and standardise the methods, turning practice into a durable, comparable norm.

Each link makes the next easier. The role of the OHD network is to trigger the chain by supplying the evidence at step 1.

Governance: Editorial Group (integration, version control) plus four Pillar Task Forces (content) plus stakeholder reviewers (comment-based review). The 2026 timetable runs March (structure) → April (drafts) → May (integration) → June (review) → July (Brussels consolidation + Policy Brief) → September (policy moment). A realistic pilot can be tested within the OHD network in 2026–2027 without new regulatory instruments:

1. **In silico baseline screen (months 1–3):** 3–5 active PDis programmes apply a standardised QSAR screen (VEGA, EPI Suite, enviPath) for persistence, bioaccumulation and aquatic toxicity; outputs documented in the MIP template. Cost negligible.
2. **Experimental validation (months 4–9):** flagged high-risk candidates undergo a targeted assay (OECD TG 301F biodegradability or TG 202 Daphnia), comparing measured to predicted values to validate tool performance on PDis scaffolds.
3. **Cross-programme comparison (months 10–12):** participating programmes share MIP documentation (not raw structures) to test the reporting template in practice.
4. **Report and iterate (months 13–18):** findings reported to the network and submitted as a short methods paper; the MIP template and tool recommendations refined.

3.5 Limitations and Risk Management

Table — Stakeholder tensions and how the paper addresses them

Tension point	The concern	How the paper responds
Industry vs environmental NGOs	Industry fears added cost and constrained innovation; NGOs press for stricter, faster environmental controls.	Frames early screening as a shared interest: cheaper de-risking for industry, earlier hazard identification for environmental goals; positions it as decision-support, not prohibition.
Regulator hesitation	Regulators may be cautious about endorsing non-validated early-screening methods.	Recommends acknowledgement as best practice rather than mandate; separates validated tools from those needing validation (see tool hierarchy).
Funding constraints	Smaller academic and SME groups lack resources for new requirements.	Prioritises low-cost in silico and NAM screens, shared infrastructure, and a minimal template-based MIP; leverages tiered SSbD implementation for SMEs.
Data-sharing reluctance	Companies are wary of disclosing early-stage environmental data.	Early data are internal decision-support; no disclosure obligation arises unless a candidate proceeds to marketing authorisation.

This paper is evidence-informed and feasibility-driven; it does not claim full regulatory endorsement of early-stage tools, and separates what is validated from what remains predictive. It avoids overreach by keeping long-term coalition governance out of scope and focusing on deliverable construction and near-term adoption. Data confidentiality is handled by using category-level tool descriptions unless explicit permission is given to name proprietary elements.

4. Who Should Act — Stakeholder Map and Calls to Action

Table 4.1 — Stakeholder calls to action

Stakeholder	Why this paper matters to them	Specific ask
European Medicines Agency (EMA)	The new Pharma Package strengthens ERA and makes environmental risk a possible refusal ground; the 2024 ERA guideline is already in force.	Recognise early-stage screening as best practice that de-risks the ERA EMA will require; reference it in implementation guidance.
European Commission (DG SANTE, DG ENV)	The UWWTD already imposes €1.2bn/yr in polluter-pays costs; >90% of micro-pollutants are pharma/cosmetic.	Support early environmental design as the lowest-cost way to reduce micro-pollutant load at source; connect Pharma Package and SSbD implementation.
Industry R&D leadership	Bringing a drug to market costs ~$2.3bn; ~90% of clinical candidates fail; environmental risk can now gate authorisation.	Adopt early environmental screening as internal decision-support; 'fail early, fail cheap' as in Animal Health.
ESG investors / funders	ESG assets are projected at ~$33.9tn by 2026; ESMA's 80% fund-naming rule pushes capital toward demonstrably sustainable assets.	Treat environmentally-screened pipelines as a factor in investment assessment; require environmental data for safe-by-design assessment in grant conditions (R4, R6).
Academic / SME discovery teams	Most groups are small with limited ecotox capacity; SSbD now offers tiered, SME-friendly implementation.	Apply low-cost in silico screening and the shared MIP template; participate in the 2026–2027 pilot.
Veterinary & research educators	62% of vets never received environmental training; the prescribing gap is an education gap.	Embed environmental stewardship in curricula and CPD.

5. The Economic and ESG Case

5.1 The cost-of-failure case ('fail early, fail cheap')

The economics of drug development make a powerful argument for acting early. Bringing a single medicine to market is widely estimated to cost in the region of 2.3 billion US dollars, and the Tufts Center for the Study of Drug Development has put the average cost to approval at roughly 2.6 billion dollars once the cost of capital and failed candidates is included. Attrition is severe: of the candidates that enter clinical testing, only around one in ten is ultimately approved, and roughly half of all Phase III trials fail, depending on therapeutic area. Industry analyses place the cost of a single failed late-stage trial between 800 million and 1.4 billion dollars. Against this backdrop, any property that can cause a candidate to fail, including an environmental liability, is far cheaper to detect during early discovery than during late development. An environmental red flag identified at Phase III could destroy years of investment; the same flag identified at hit-to-lead costs little more than a screening assay. Under the reformed EU pharmaceutical legislation, where environmental risk can now contribute to a refusal of marketing authorisation, the case for early detection is stronger still.

Table 5.1 — Cost of late-stage failure

Figure	Value	Source (retrieved Jun 2026)
Cost to bring one drug to market (2022)	~$2.3 billion	Multiple; widely cited
Tufts CSDD average cost to approval	~$2.6bn (~$1.4bn out-of-pocket + $1.1bn time)	Tufts CSDD via Pharmaceutical Technology
Likelihood of approval from Phase I	~9.6% (≈1 in 10)	BIO via Clinical Leader
Phase III trial failure rate	~50%	Parexel via Pharmaceutical Technology
Cost of a single failed clinical trial	$800m – $1.4bn	Clinical Leader
Overall drug-translation failure rate	~90%	ScienceDirect (2022)

5.2 he ESG and sustainable-finance case

Environmental performance is increasingly material to how pharmaceutical companies are financed. PwC projected in 2022 that global assets under management linked to environmental, social and governance (ESG) criteria could reach around 33.9 trillion US dollars by 2026, and Morningstar data indicate that sustainable fund assets stood at roughly 3.7 to 3.9 trillion dollars at the end of 2025. Regulatory expectations are tightening in parallel: under the European Securities and Markets Authority's fund-naming guidelines, funds that use ESG or sustainability terms must invest at least 80 per cent of their assets in line with those characteristics, and the Corporate Sustainability Reporting Directive extends mandatory sustainability disclosure across large companies. The direction of travel is clear: environmental performance is moving beyond reputational positioning and is increasingly becoming part of how companies are assessed by sustainability-oriented investors. In this context, pharmaceutical pipelines that can demonstrate environmentally informed design may be better positioned to meet investor expectations and regulatory scrutiny.

Table 5.2 — ESG and sustainable finance

Figure	Value	Source (retrieved Jun 2026)
Global ESG AUM, projected 2026	~$33.9 trillion (up 84% from $18.4tn in 2021)	PwC (2022) via EJMEB (2025)
Global sustainable fund assets, end-2025	~$3.7–3.9 trillion	Morningstar/Robeco via EcoVadis (2026)
EU ESMA fund-naming rule	≥80% of investments must match ESG terms	Skadden (2025); EcoVadis (2026)

5.3 The green-chemistry and efficiency case

Designing greener molecules and synthetic routes also supports cost efficiency in many cases. The pharmaceutical sector's environmental factor, the mass of waste generated per kilogram of active ingredient, is high, commonly cited in the range of 25 to 100 and sometimes far higher; a study by Roschangar and colleagues of 97 commercial-scale syntheses reported an average complete environmental factor of 182. Solvents typically account for 80 to 90 per cent of the mass used in synthesis, so reducing solvent use and waste at the design stage cuts both environmental burden and manufacturing cost directly. The revised Safe and Sustainable by Design framework explicitly links early application of SSbD principles to greater cost efficiency and improved readiness for current and anticipated regulatory requirements.

Table 5.3 — Savings by design

Figure	Value	Source (retrieved Jun 2026)
Pharmaceutical E-factor (waste per kg API)	25–100 (up to ~200)	Sheldon; Syrris; DrugPatentWatch
Average cEF of 97 commercial API syntheses	182 (range 35–503)	Roschangar et al. (2021)
Solvent share of synthesis mass	80–90%	DrugPatentWatch (2026)
Illustrative saving from PMI improvement of 110	~$770 per kg API	DrugPatentWatch worked example (2026)

The same logic that links greener design to lower cost applies directly to ecotoxicity testing. The cost of an ecotoxicity assay depends heavily on when it is done and how. Traditional animal-based ecotoxicity studies are typically performed at an advanced stage of development, are resource-intensive, and are comparatively expensive. New Approach Methods (NAMs), which use cell-based and in silico assays rather than whole animals, can be applied much earlier and at a fraction of the cost, while also aligning with the 3Rs principle of replacement, reduction and refinement of animal use (Mittal et al., 2022; and the wider NAM literature).

Reported estimates illustrate the scale of the difference: traditional animal-based ecotoxicity testing is cited in the range of roughly 15,000 to over 100,000 US dollars per chemical, often requiring 100 or more animals and around eight weeks, whereas NAM-based in vitro screening is cited at roughly 2,600 US dollars per chemical, with few or no animals and around four weeks. The figures vary with the endpoint, the organism and whether testing is in-house or outsourced, and should be treated as indicative benchmarks. The strategic point holds regardless of the exact numbers: an inexpensive, non-animal ecotoxicity screen applied during early hit-to-lead, where many compounds are tested, costs little per compound and can identify a deal-breaking environmental profile before significant capital is committed. Set against total development costs that can exceed one billion dollars, an early screen of a few thousand dollars per candidate is a prudent de-risking investment, not a burden.

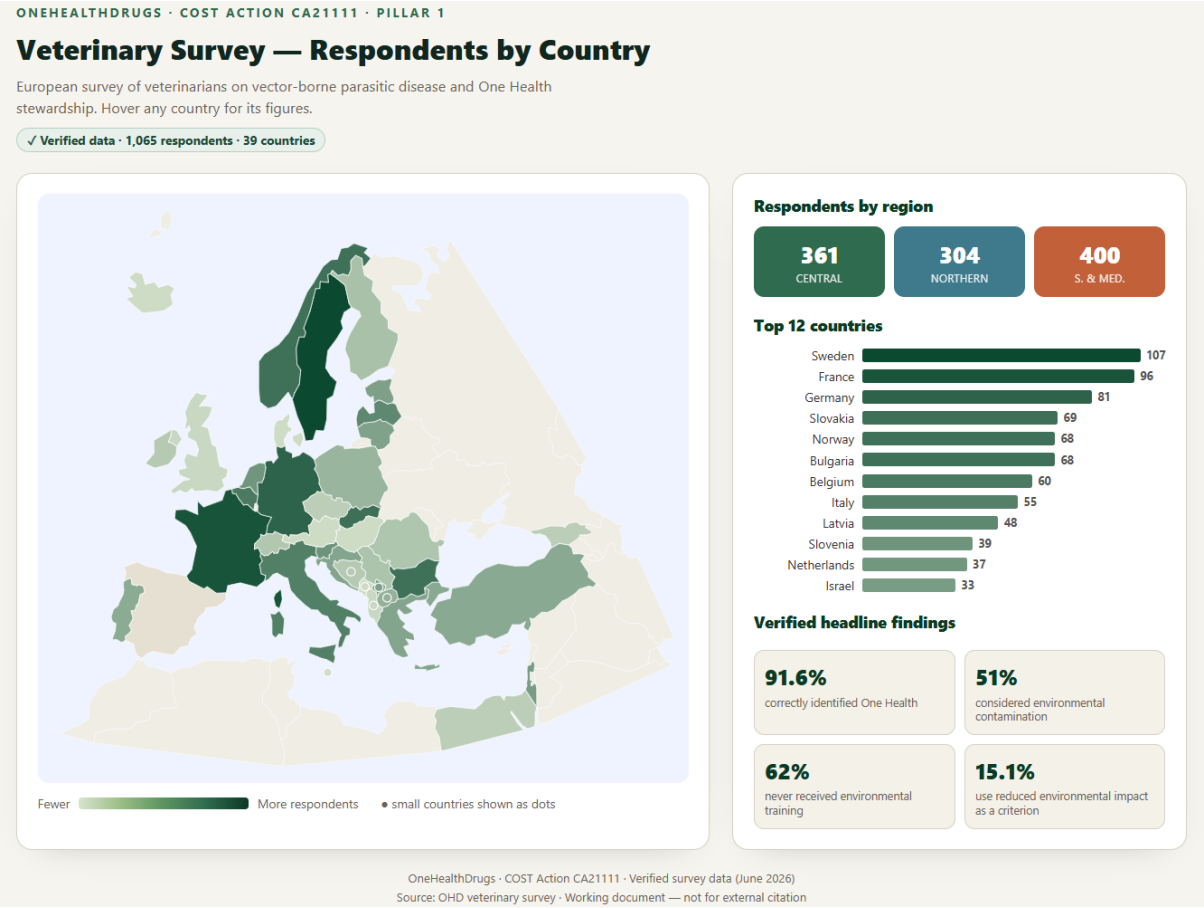
Table 5.4— Indicative cost of ecotoxicity testing: traditional vs New Approach Methods

Method type	Estimated cost per chemical	Resource intensity	Typical speed
Traditional (animal-based)	~$15,000 to $100,000+	High (often 100+ animals)	~8 weeks
New Approach Methods (in vitro / in silico)	~$2,600	Low (few or no animals)	~4 weeks

6. Annexes

Annex A — Survey Snapshot

The veterinary survey results are available as an interactive, country-level map at https://gss.cost-action.eu/OHD_Survey_Map_by_Country.html. The map presents all 1,065 respondents across 39 countries, with per-country figures on hover, a regional breakdown (Central Europe 361, Northern Europe 304, Southern Europe and the Mediterranean 400), the top twelve countries by response, and the verified headline findings: 91.6% correctly identified One Health, 51% had considered environmental contamination, 62% had never received environmental training, and 15.1% factor reduced environmental impact into prescribing.
While the survey was distributed across all targeted European regions, participation was uneven, and in some countries national data-sharing policies and institutional constraints limited or precluded responses; the resulting distribution should therefore be read as indicative of engaged practitioners rather than as a complete European census.



Annex B — Glossary and Definitions

Term	Definition
ERA	Environmental Risk Assessment — formal regulatory process assessing environmental impact; required for EU marketing authorisation.
PBT	Persistent, Bioaccumulative and Toxic — EU classification for substances meeting threshold criteria.
PNEC / PEC	Predicted No-Effect Concentration / Predicted Environmental Concentration — benchmarks used in ERA.
PDis	Parasitic diseases (human and veterinary) — the paper's shorthand.

TRL	Technology Readiness Level (1–9) — maturity of a technology.
MIP	Minimum Information Package — defined early-stage environmental data required at the screening gate.
QSAR	Quantitative Structure–Activity Relationship — computational prediction of activity from structure.
SSbD	Safe and Sustainable by Design — European Commission framework for designing out hazard from the outset.
ESG / SFDR	Environmental, Social and Governance criteria / Sustainable Finance Disclosure Regulation.
One Health	Integrated approach balancing the health of people, animals and ecosystems (WHO/FAO/UNEP/WOAH, 2021).
OECD TG	OECD Test Guideline — standardised environmental testing protocols recognised by regulators.

Annex C — Environmental Classification / 'Shelf Labelling' Examples

Illustrative precedent for decision-support and communication (not an EU-wide pack label): Sweden's FASS system, requiring voluntary environmental disclosure (persistence, bioaccumulation, toxicity) for prescription medicines, displayed for prescribers and pharmacists; PBT criteria used as early structural-alert criteria; and Nordic pharmacy shelf-labelling pilots enabling environmentally informed choice at dispensing.

7. Survey Methodology

The findings presented in Pillar 1 draw on two complementary surveys conducted within the OneHealthDrugs network during the Action. The first targeted practising veterinarians across Europe and received 1,065 valid responses from 39 countries; the second targeted researchers working on parasitic and vector-borne diseases. Both were distributed as structured online questionnaires through the Action's professional and academic networks and through partner veterinary and research associations, with participation voluntary and responses anonymised. Responses were grouped into three regions — Central Europe, Northern Europe, and Southern Europe and the Mediterranean — to allow regional comparison while preserving respondent numbers per group. The veterinary instrument covered practice profile, familiarity with One Health, awareness of the environmental impact of veterinary medicinal products, prescribing criteria, and prior environmental training; the research instrument covered group profile, research priorities, and the extent to which environmental and ecotoxicological considerations are integrated into early discovery. Detailed country-level figures for all 39 countries are available in the interactive survey map (Annex A).

8. Governance, Contributions, and Funding

Author contributions: All listed contributors participated in drafting and review of their respective sections. A detailed contribution statement will accompany the final version.

Data availability: Survey data underlying this paper are held by the Action and available on reasonable request.

Competing interests: Contributors will declare any competing interests in the final version.

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References: A consolidated reference list accompanies the final version, drawing together the citations in the environmental-evidence, regulatory, feasibility, policy-landscape and economic sections.

The four-pillar architecture is complete, and each pillar has substantive content drawn from the contributor files. No fifth pillar is needed; the paper's logic (practice reality → environmental evidence → regulatory gap → feasibility) is sound and self-contained. The following items are genuinely outstanding, in priority order. This list reflects only what is verifiably absent from or unconfirmed in the current files.

Dissemination and Publication Strategy

This Position Paper is developed as a COST Action CA21111 output with a dual dissemination pathway. First, it will be disseminated as a policy-facing document through stakeholder meetings, the European regulatory ecosystem, and targeted policy briefings. Second, it will be translated into a structured Policy Brief and supporting communication materials (slide deck and evidence snapshot) for institutional engagement in September 2026.

In parallel, the scientific content is intended to be adapted for submission to peer-reviewed journals in environmental health, regulatory science, or One Health domains. In this case, the manuscript will be reformatted according to journal-specific citation and structural requirements (e.g., Vancouver or APA style), ensuring full traceability of sources and methodological transparency. The Position Paper itself remains a stakeholder co-created COST Action output and may be cited as grey literature unless formally published in a journal format.

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