MINUTES
2nd OHD Stakeholder meeting
FROM RESEARCH TO RECOMMENDATION FOR ENVIORNMENTAL IMPACT OF DRUGS: ADVANCING ONE HEALTH DRUGS THROUGH SCIENCE, POLICY, AND INDUSTRY
6 March 2026 | COST Association, Brussels

Part 1. Introduction & Logistics

This is pivotal moment for this COST Action! I am introducing here narrative flow that maintains the scientific detail while introducing the "roadmap" for this specific Stakehodler activity to make clear and compelling our next steps.

Welcome and Project Context

First, I want to thank all for your participation and for your future contribution. We are currently at a defining moment in our journey. As we approach the final phase of our **COST Action**, our focus is now on consolidating and delivering the results of four years of intensive research. Our core mission remains the same: the development of safer antiparasitic drugs with a significantly lower environmental impact.
I am also pleased to welcome representatives from the environmental sector. Our goal is to align our processes as we co-author the position papers that stand as one of our primary objectives."

The COST Action Overview

This is our second stakeholder meeting for the **COST Action**. As we approach the end of our project, we need to effectively deliver the results achieved during our four years of work. Our focus remains on a highly specific topic: the **development of safer antiparasitic drugs with low environmental impact.**
Today, I will discuss scientific potency, the construction process, and our progress. I will also introduce the **4Pillars**, which will be our focus both today and in the near future. I would like to acknowledge the representatives from the Environment COST Action; we are working toward a common process to draft **position papers**, which is one of our primary objectives."

Key Metrics & Objectives

"To provide a quick overview: our Action spans four years. Our officer is Unit Valentos, and the Grant Holder is the University of Modena and Reggio Emilia. We involve **34 member countries** (20 of which are ITC) and nearly **1,000 participants**, including 360 core members.
Today, we are focusing on two main objectives:

1. **Integrating R&D studies** to reduce and prevent the environmental impact of drugs by combining experimental and *in silico* toxicology.
2. **Sharing deliverables with stakeholders** to create a formal position paper and technical guidelines."

The Roadmap to 2026

"We are implementing a roadmap to include **ecotoxicity** early in the drug development process.

- **Step 1:** An explorative stakeholder meeting held in July 2025.
- **Step 2:** Today's meeting, where we have expanded our representative group.
- **Step 3:** Drafting the position paper by July.
- **Step 4:** Presenting our outcomes at the final conference in Brussels on July 10th.

- **Step 5:** Finalizing a **Policy Brief** by September 2026, hopefully in cooperation with the Environment COST Action team."

Concept: Shifting the Paradigm

"Currently, ecotoxicity is often only assessed very late in the development cycle, just before marketing. We want to shift this to an earlier, **predictive phase** validated by experimental assays.

Think of the **PAINS (Pan-Assay Interference Compounds)** concept. We already identify and eliminate toxic chemical fragments early because they interfere with bioactivity. We believe ecotoxicity should be included in this 'flagging' process. Just as the industry learned to manage chemical fragments over time through better assays and regulation, we must now apply that same rigor to the 'Ecotox' problem."

Achievements to Date

"Our Action has already made significant progress:

- Developed **two new ecotoxicology assays**.
- Created **AI-based algorithms** to predict clean compound profiles.
- Established a **free-access database** of 12,000 compounds with predicted ecotoxicity.
- Produced over **110 publications**.

Theo Zacharis

Part 1: Transitioning the Floor

Speaker 1: "That concludes my presentation. I am now available for any questions. If there are none, I would like to hand over to **Theo Zakaris**, who is helping us regarding the stakeholder concept. Thank you very much. Theo, the floor is yours."

Part 2: Theo's Zachari Presentation & Roadmap

The Strategic Roadmap

My focus today is our roadmap: how we transition from our research survey to tangible deliverables and, ultimately, policy impact. As Paula mentioned, we have two primary goals:

1. **A Position Paper:** A comprehensive document due by July.
2. **A Policy Brief:** A condensed strategic announcement for September.

Our Objectives for Today

We need to leave this meeting with an agreed-upon **document architecture**, a list of **task force leads**, and a **drafting timetable**. We must move from theoretical alignment to practical allocation of work across our four pillars:

- **Pillar 1:** Field Awareness & Evidence
- **Pillar 2:** Environmental Scientific Evidence
- **Pillar 3:** Regulatory Gap Analysis
- **Pillar 4:** Innovation, Feasibility, and Sustainability

Proposed Document Layout

The **Position Paper** (approx. 25–30 pages) will include:

- **Executive Summary & Scope:** What we cover and, importantly, what we do *not* claim.
- **Problem Definition:** Why the current practice creates a policy implementation gap.
- **Recommendations:** 4–6 solid, actionable points with clear rationale and responsible actors.
- **Implementation Roadmap:** Short and medium-term actions.

The **Policy Brief** (2–4 pages) will be our primary tool for policy-makers. It must be highly visual, using infographics and bullet points to make our evidence 'palatable' for busy officials.

Timeline & Deadlines

- **April:** Section drafts delivered by task forces.
- **End of May:** First integrated draft (Version 1).
- **June:** Internal reviews and revisions.
- **July 10 (Brussels):** Presentation of the near-final Position Paper at the final Action conference.
- **September (Strasbourg):** Official release of the Policy Brief at the European Parliament to maximize visibility with DG ENV and other relevant committees."

Part 3: Q&A and Stakeholder Engagement

Regarding the 'evidence' in the position paper—are you referring to studies conducted during this COST Action specifically, or the broader literature?"

Theo Zakaris: "Excellent question. It's both. While we will cite existing literature, the core of our position—especially for Pillar 1—will be the results of the survey and research conducted by this consortium. Policy-makers need evidence-based support; they need to see statistics and data that demonstrate how these changes affect society. Our role is to provide the scientific substantiation for the policy shifts we are suggesting.

The final impact will also depend on **who signs the document**. We are aiming for endorsements from the WHO, OECD, industry players, and medical associations. Having these stakeholders 'at the table' in Brussels and Strasbourg is what creates true legacy and impact.

Discussion about the target group of destination for the Position paper

Ricardo Carapeto: "Good morning, everyone. I apologize for not being there in person today; I attended last year and was very pleased to receive an invitation to return. My name is Ricardo Carapeto, and I represent the Spanish Medicines Agency. For the past 13 years, I have served as an Environmental Risk Assessor for Veterinary Medicines, and I am also a member of the Committee for Veterinary Medicinal Products (CVMP) at the EMA.

I believe I am here today representing the regulatory perspective. I have a question for Theo regarding the development of the position paper. You mentioned that we should involve regulators in the drafting process. Perhaps this is a basic question, but aren't regulators usually the *recipients* of such papers rather than the authors? I am struggling to understand how we can be involved in developing a document that is ultimately intended to influence or inform our own work. Could you clarify that approach? Thank you."

Part 2: Theo's Clarification on Policy Impact

Theo Zakaris: "That is an excellent and very relevant question. Because this is a **position paper**, it is designed to offer specific recommendations. Our third pillar (Pillar 3) focuses on the 'policy gap,' and we need to further explore what those gaps are and why we are advocating for change.

It is important to remember that policy-makers and researchers often work in tandem. For instance, the European Commission relies on the Joint Research Centre (JRC) as its research arm to support legislative work. We want to provide something similarly valuable.

The European landscape is currently shifting. There are numerous initiatives regarding water safety and the AI Act, but there is also a significant push toward 'simplification.' There is a concern that Europe is over-regulated compared to the US or China, causing us to lose our competitive edge. Our position paper should address this by:

1. **Persuading Industry:** Demonstrating that early-stage ecotoxicity testing saves money by preventing late-stage failures.

2. **Advising Policy-Makers:** Helping to harmonize a fragmented regulatory landscape.

By involving regulators now, we ensure the final document is meaningful and actionable for the European society. We aren't just looking at the future; we are saying the time to harmonize and simplify these regulations is now."

Ricardo Carapeto: "I completely understand now. Thank you for that explanation."

Paola: " We must clearly define our **target audience** and distinguish between the various types of regulators we aim to reach. We can delve deeper into those classifications later; for now, let's move forward. Thank you, Theo, and thank you, Ricardo, for the discussion.

Proposed regulatory target group: European Commission and EMA

Pillar 1: Awareness and Field Evidence. I am delighted to introduce **Clara Lima**, one of our OneHealthDrugs' Ambassadors. She will present the results of our European-level survey on practitioner awareness regarding environmental impacts. While a survey of veterinarians—those who actually prescribe these medicines—may not provide the final technical solution, it offers vital evidence regarding current field practices and is an excellent starting point for our contribution. Clara, the floor is yours."

The survey by Clara Lima
Veterinary Practitioners' Awareness of the Environmental Impact of Antiparasitics: Preliminary Survey Results

Introduction: The Necessity of Antiparasitics

It is indisputable that veterinary medicines, particularly parasiticides, are vital for animal health, human safety, and the sustainability of both our food chain and our relationship with companion animals. We are driven by the "One Health" principle: biological vectors transmit parasites between species, and we are dedicated to treating these diseases—not merely because parasites are unpleasant, but because they cause tangible harm to animal welfare. This is especially critical in our current climate scenario, where we face emerging challenges regarding the global dissemination of these vectors.

The Regulatory and Knowledge Gap

Within Europe, the production and prescription of veterinary products are strictly regulated to foster scientific progress while safeguarding market stability and public health. However, while antibiotics and anti-inflammatories have been prioritized in environmental impact studies, **antiparasitics have often been overlooked.**

We currently face a significant knowledge gap regarding the real-world environmental impact of these drugs. Parasiticides are excreted via urine and feces or washed off the animal's skin and fur, leading to the contamination of ecosystems with active compounds or their metabolites. Continuous exposure to these low doses can lead to:

- **Antimicrobial and parasitic resistance** across various species.
- **Toxicity to non-target species.**
- **General ecosystem disruption and pollution.**

A Shifting Demographic: From Livestock to Pets

We are witnessing a paradigm shift in animal populations across Europe. There is a sharp increase in the concentration of companion animals, which are now integral members of the European household. Conversely, livestock production and the number of active farms appear to be declining.

This shift is reflected in the veterinary workforce, which is now heavily concentrated in the companion animal market. This trend is driven by:

1. Advancements in new veterinary therapies.
2. Rising public awareness of zoonotic diseases.
3. The demand for research and development, reflected in the surging global sales of parasiticides.

The Goal of the COST Action Survey

Despite these market trends, we have lost track of the veterinarian's role in this environmental problem. We lack a clear understanding of the motivations and drivers behind their prescription habits. This is where our **COST Action**contributes: we sought to determine if veterinarians are aware that their daily decisions impact the environment and what measures they take to minimize this footprint.

Methodology and Demographics

With the help of our Management Committee (MC) members, we distributed a survey across nearly all European countries, translated into **31 languages**. We focused on:

- Knowledge of chemoprophylactic and chemotherapeutic drugs.
- Attitudes toward environmental protection and non-target species.
- Criteria for selecting prevention and treatment products.

In this first round of analysis, we compiled **984 complete responses**, stratified into three geographical regions: Southern, Central, and Northern Europe.

- **Experience:** The majority of respondents have been in practice for over 15 years.
- **Context:** Most work in urban environments.
- **Specialization:** Small animal practitioners represent **75–78%** of the sample, while only **29%** focus on livestock, and a small fraction work with wildlife, swine, or poultry.

Key Findings: Awareness vs. Education

While the "One Health" concept is well-understood—with most vets correctly identifying it as a multidisciplinary approach—awareness of the **specific environmental impact of drugs** is significantly lower. This is likely due to a lack of formal training: **over 64% of respondents have never received education** regarding the environmental protection aspects of veterinary pharmaceuticals. Of the small percentage who did receive information, 14% were educated by the pharmaceutical industry and 12% through Continuing Professional Development (CPD).

Current Practices: Disposal and Prescription Drivers

Our data on "end-of-life" product management is revealing:

- **Waste Management:** While 50% of vets send unused or expired drugs for professional incineration, **20% still dispose of medicines through general waste streams.**
- **Scientific Interest:** Veterinarians show a higher interest in understanding a drug's pharmacokinetics (mode of action) than its mode of excretion into the environment.
- **Prescription Criteria:** Efficacy and safety are the primary drivers for drug choice. Market availability and ease of administration follow. Unfortunately, **less than 14% of veterinarians consider environmental impact** as a priority when prescribing.

Frequency of Use

The environmental pressure is constant: **over 50% of respondents prescribe drugs** to prevent vector-borne diseases on a weekly basis, with the majority of that group prescribing them daily. Only a tiny fraction of practitioners (less than 14% monthly) rarely or never find themselves in a position to prescribe these preventive treatments.

Regional Trends and Urban-Rural Disparities

When analyzing the selection of preventive drugs across different European regions, we observe a consistent trend: insecticides and repellents are the most prevalent prescriptions in all areas. However, significant differences emerge when we compare urban, rural, and mixed contexts.

The concentration of chemoprophylaxis prescriptions is notably higher in urban settings. Interestingly, the frequency of treatment—using chemotherapeutics to address active disease—is far lower than the frequency of prevention. Specifically, **25.6% of responding veterinarians** diagnose and treat vector-borne diseases on a weekly basis, while approximately **8%** report that they have never needed to diagnose or prescribe drugs for

these specific conditions. Our individual analysis confirms that, fortunately, treatment choices largely align with international clinical recommendations.

Key Conclusions from the Survey

The survey highlights a paradoxical situation: while veterinarians are well-versed in the **One Health** framework and their role within it, they exhibit a **low level of awareness** regarding the environmental impact of veterinary medicinal products. This is likely a direct result of limited access to specialized education on the subject.

Currently, prescription choices are primarily driven by:

1. **Evidence-based resources**
2. **Market availability**
3. **Ease of administration**

It is clear that reducing the environmental footprint of the veterinary pharmaceutical market requires a dual approach: promoting responsible prescribing habits and educating practitioners on efficient drug waste management.

A Call for Multi-Stakeholder Action

This is not an effort that can be tackled by one sector or discipline alone. We advocate for a united front among all stakeholders to improve education regarding the environmental impact of pharmaceuticals. As the companion animal market continues to grow, we can no longer afford to overlook the environmental contribution of antiparasitics used in small animals. Their widespread distribution and prescription are significant factors in the dissemination of active compounds into the environment.

Strategic European Positioning

Moving forward, we advocate for the following coordinated actions at the European level:

- **Regulatory Oversight:** Synchronized efforts to regulate the prescription, production, and end-of-life destruction of these drugs.
- **Post-Marketing Vigilance:** Implementation of environmental pharmacovigilance to identify compounds with high ecotoxicity.
- **R&D Prioritization:** Encouraging research into safer alternatives and establishing protocols for the phase-out of high-risk drugs.
- **Data Transparency:** We call for full transparency regarding global sales data for parasiticides, mirroring the successful reporting models currently used for antimicrobials.

I would like to conclude by thanking all the **One Health Drugs MC members** who assisted in translating and disseminating the questionnaire. Thank you for your attention.

Comments on Clara's presentation - Veterinary Pharmacy and Environmental Sustainability

This session addressed the intersection of pharmaceutical ethics, academic curricula, and evidence-based policy within the **One Health** framework, focusing specifically on the environmental impact of medicinal products.

1. Professional Ethics and Regulatory Changes A significant milestone was reported regarding the **National Association of Pharmacists in Portugal**. Following a recent initiative, national ethical guidelines now explicitly mandate that pharmacists acknowledge **environmental sustainability** when dispensing specific drugs. While this has been codified into professional practice, a disconnect remains between high practitioner interest—evidenced by high attendance in professional development webinars—and institutional inertia.

2. Gaps in Academic Curricula There is a critical lack of dedicated environmental and ecotoxicological training in Portuguese veterinary and pharmaceutical faculties. Current knowledge is fragmented across unrelated disciplines. The discussion highlighted a "blindness" in academia, where traditional disciplinary boundaries prevent the integration of modern, scientifically sound environmental data. Speakers called for high-level pressure on these institutions to modernize their curricula to reflect the changing global landscape.

3. Challenges in Data and Evidence-Based Policy The seminar underscored the necessity of **robust, randomized data** over anecdotal surveys to influence policy effectively.

- **Regulatory Complexity:** A major "knowledge gap" exists regarding insecticides and repellents. Because these are often registered as biocides or pesticides rather than veterinary medicines, and are frequently sold over-the-counter in retail stores, tracking their specific environmental footprint is difficult.
- **Market Evolution:** While Environmental Risk Assessments (ERAs) have been mandatory for large animal medications, the **European Medicines Agency (EMA)** is currently evolving its framework to increase oversight for companion animal products.

4. Integration of One Health Principles The session concluded with a call for a more balanced **One Health** approach. While some institutions (e.g., the University of Warsaw) have successfully integrated human medicine, veterinary medicine, and chemistry into a single school, the "environmental" pillar remains the most neglected. Participants advocated for limiting the distribution of ecologically sensitive drugs to trained professionals—veterinarians and pharmacists—to ensure proper administration, side-effect recognition, and responsible disposal.

Presentation Transcript: Anthelmintic Residues in the Irish Environment

Martin Danaher

Introduction and Technical Background

"Good morning. I'm pleased to present our ongoing research into anthelmintic drug residue analysis conducted at our institute in Dublin. This work is the culmination of years of collaborative effort involving a dedicated team of researchers and evolving background technologies.

The analytical platform we use today was originally developed in the mid-2000s. While it was initially designed to analyze food samples of animal origin, we have since adapted it to detect residues in environmental matrices.

To provide some context: anthelmintic usage patterns vary significantly across Europe. In Western Europe, particularly in Ireland, we use a high volume of flukicide drugs. We only began comprehensive testing for these about 15 years ago once the technology became operational around 2007. Our early work focused on detecting residues in milk and animal tissues to establish data for Provisional Maximum Residue Limits (MRLs) for specific flukicides."

The Challenge of Drug Excretion and Innovation

"A critical point regarding anthelmintic drugs is their excretion profile. A high proportion—sometimes up to 95%—of the drug is excreted unaltered as the parent compound. This presents a massive challenge for environmental sustainability. I would like to set a challenge for those developing new products: we need innovations in drug formulation and administration that ensure the animal utilizes more of the drug, rather than simply acting as a conduit for releasing active compounds into the environment."

Environmental Pathways: Slurry vs. Pasture

"There are two primary routes of excretion: manure stored as slurry and direct excretion on pasture. In slurry tanks, there is a significant dilution effect. However, on pasture, the residues are potentially more concentrated and have a direct impact on the soil. Recent studies suggest that the route of administration—such as injectable formulations versus pour-ons—significantly influences how much of the drug ends up in the host versus the land."

Groundwater and Surface Water Findings

"About five or six years ago, my PhD student, Damien Mooney, and I began investigating anthelmintic residues in water. Our findings, published and widely read, were quite concerning: we detected residues in groundwater. Typically, groundwater is expected to be 'pure' due to natural filtration, so finding 17 out of 40 targeted anthelmintic residues there raised significant alarms. While our study focused on vulnerable karst areas, it is important to note that if one were to sample surface water (rivers and lakes), the concentrations would likely be much higher."

Legislative Gaps and Environmental Risk

"Currently, there are no specific legislative limits for veterinary drug residues in the environment. While some compounds fall under pesticide categories—which have a limit of 100 ng/L—there is no mandatory monitoring for water or manure. This is a concern because these residues pose a documented risk to soil-dwelling organisms. For example, Macrocyclic Lactones (specifically Moxidectin) have a notorious reputation for their toxicity to dung beetles and earthworms. While Environmental Risk Assessments (ERAs) are now part of the tiered authorization process in Europe, the monitoring of 'real-world' impact remains insufficient."

Findings in Ireland: Slurry and Manure Analysis

"Ireland is a major food exporter, supporting 7 million bovine and 5 million sheep. Interestingly, 85% of veterinary drugs by weight are used in cattle. In our 'SafeWaste' project, we analyzed slurry samples from 26 counties across the Republic of Ireland using mass spectrometry.

Our results showed a high prevalence of drugs:

- **Benzimidazoles:** Albendazole is widely used in the spring for adult fluke and was frequently detected.
- **Flukicides:** Compounds like Triclabendazole and Rafoxanide showed high residue levels.
- **Macrocyclic Lactones:** Ivermectin was the most prevalent residue found.
- **Multiple Detections:** In several instances, a single manure sample contained residues of six or seven different drugs simultaneously, reflecting the common use of combination products."

Conclusion and Recommendations

"To conclude, our data suggests that we must reduce the environmental burden of these drugs. We recommend moving toward **Targeted Selective Treatment (TST)** rather than whole-herd dosing. We also need to reconsider the use of pour-on products, which lead to higher environmental excretion. As the world moves toward more stringent environmental monitoring, we must bridge the gap between veterinary medicine and environmental protection. Thank you to my students, Damien and Vera, and our funders for their support."

Executive Summary: Environmental Impact of Anthelmintic Residues

Overview Research conducted in Dublin highlights the significant environmental persistence of anthelmintic (anti-parasitic) drugs used in the Irish livestock industry. Utilizing mass spectrometry, researchers tracked the journey of these drugs from administration to their appearance in groundwater and soil.

Key Findings

- **High Excretion Rates:** Up to 95% of certain anthelmintic drugs are excreted by livestock in their active form, leading to direct environmental contamination.
- **Groundwater Contamination:** 17 different anthelmintic residues were detected in Irish groundwater, particularly in vulnerable karst regions, challenging the assumption that groundwater remains filtered and pure.
- **Prevalence in Slurry:** Analysis of manure across 26 counties revealed that 66% of bovine slurry samples were positive for residues, with Ivermectin and Albendazole being the most common. Many samples contained "chemical cocktails" of up to seven different drugs.
- **Ecological Risk:** Residues, particularly Macrocyclic Lactones, pose a severe threat to non-target organisms like dung beetles and earthworms, which are vital for soil health.

Strategic Recommendations

1. **Shift to Targeted Treatment:** Move away from "blanket" herd treatments toward Targeted Selective Treatment (TST) to reduce the volume of drugs entering the environment.
2. **Formulation Innovation:** Develop new delivery systems that increase drug bioavailability within the animal to minimize waste excretion.
3. **Policy & Monitoring:** Address the legislative gap regarding veterinary drug limits in water and soil, as current pesticide regulations do not adequately cover these substances

Presentation on the **ENVIRANT** COST Action, focusing on the environmental impact of anthelmintics (anti-parasitic drugs) and the push for sustainable livestock management. Below is a refined, professional version of the speech, followed by a summary of the action's structure and objectives.

Presentation: Environmental Impact of Anthelmintics and Sustainable Alternatives
Maria Martinez Valladarez
Background: From COMBAT to ENVIRANT
"Before delving into environmental specifics, I'd like to briefly mention a previous initiative I was involved in: the **COMBAT** COST Action (Controlling Microbiomes and Benzimidazole Resistance in Ruminants). In that project, our focus was primarily on the diagnosis and control of helminth infections in ruminants and the rising threat of anthelmintic resistance. We also studied the socioeconomic drivers of this resistance, specifically the behaviors of farmers and veterinarians when treating animals. Our goal was to establish sustainable control methods that reduce—rather than entirely eliminate—the reliance on chemical treatments.
ENVIRANT takes this a step further. We are now looking beyond the animal to the environment. When these drugs are administered, they are metabolized and released via urine and feces into the soil and water. As Martin discussed earlier, our current priority is measuring these residues and assessing the real-world feasibility of the sustainable methods we identified during COMBAT."
The Challenge of Balance and Policy
"Our primary challenge is finding the 'One Health' balance between animal health and environmental protection. While we must reduce drug usage to protect ecosystems, we cannot compromise animal welfare.
This work aligns with the **European Green Deal**, which aims for climate neutrality by 2050. Key strategies include:

- **Farm to Fork:** Aiming to reduce pesticide usage by 50% by 2030.
- **Biodiversity Strategy:** Mitigating risks associated with pesticides and converting 25% of EU agricultural land to organic farming.

Within this framework, anthelmintics are now being classified as **Emerging Organic Contaminants**. The European Medicines Agency (EMA) has noted that 20 substances—including the widely used **Moxidectin**—lack sufficient data and are potentially persistent, bioaccumulative, and toxic (PBT). Furthermore, there is currently no regulatory monitoring for these drugs in groundwater or drinking water, and no established environmental quality standards."
The ENVIRANT Network and Working Groups
"Our objective is to create a global network of experts to measure these residues and foster the knowledge exchange needed to reduce drug use. Currently, ENVIRANT consists of over 300 members from 40 countries, organized into five working groups:

- **WG1 (Occurrence):** Studying the presence of residues in soil, water, and manure.
- **WG2 (Impact):** Assessing the effect of these residues on non-target organisms across different trophic levels.
- **WG3 (Green Farms):** Implementing sustainable control methods in the field and identifying barriers to adoption for farmers.
- **WG4 (Risk-Benefit):** Modeling the outputs of other groups to measure the benefit-risk ratio of reducing anthelmintic use.
- **WG5:** Community building and dissemination."

Current Objectives and the "Second Grant Period"
"We are currently in our second grant period. Our immediate tasks include:

1. **Harmonization:** Preparing guidelines for environmental sampling and ecotoxicity studies to ensure protocols are consistent across Europe.
2. **Evidence-Based Mapping:** Identifying labs with the equipment to detect residues and research groups capable of large-scale field sampling.

3. **National Surveys:** Gathering data on farm management, parasite treatments, and manure handling across the diverse livestock systems in Europe (from my home country of Spain to Northern Europe).
4. **Policy Briefs:** Translating our scientific findings into actionable policy advice for the EU."

Executive Summary: ENVIRANT COST Action

The Core Problem Anthelmintic drugs used in livestock are excreted into the environment, where they persist as emerging organic contaminants. There is currently a significant lack of regulatory oversight and standardized monitoring for these substances in water and soil.

Key Research Goals

- **Quantification:** Establishing where and at what concentration these residues occur in European landscapes.
- **Ecotoxicology:** Understanding the impact on "off-target" organisms (e.g., dung beetles, aquatic life).
- **Sustainability:** Moving from chemical-heavy treatments to **Green Farming** practices without sacrificing animal health.
- **Standardization:** Harmonizing sampling and analytical protocols across international research groups to provide solid evidence for policymakers.

A Call for Collaboration The ENVIRANT action invites experts in analytical chemistry, veterinary medicine, and environmental science to join the network. By combining efforts, the project aims to support the European Green Deal's goals of reducing chemical dependency and promoting biodiversity.

Paul Selzer, focusing on the critical tension between the medical necessity of parasite control and the emerging environmental risks associated with **PFAS** and common insecticides like **neonicotinoids**.

Presentation: Balancing Clinical Need with Environmental Hazards in Parasite Control

1. The Undisputable Need for Parasite Control

"We are faced with a complex balancing act: addressing the medical necessity of antiparasitics while mitigating their unwanted environmental impacts. To illustrate the scale of the medical need, a recent article by Holger Kaminsky highlights that roughly a quarter of the global population is infected with intestinal parasites. Furthermore, vector-borne diseases account for over 70% of all infectious diseases, resulting in more than 700,000 deaths annually.

The impact on animal health is equally staggering. In Europe, every second domestic cat is infected with at least one internal or external parasite. In sheep production, gastrointestinal nematodes can reduce weight gain and milk yield by up to 78%. Economically, issues like sea lice cost the aquaculture industry €768 million per year, while heartworm and lungworm diseases exceed a global cost of $2.4 billion annually. Simply put: parasite control is essential for global health and food security."

2. The PFAS Connection and Regulatory Shifts

"However, we must address a new regulatory challenge: **PFAS** (Per- and Polyfluoroalkyl Substances). While this might seem distant from veterinary medicine, the EU definition of PFAS—any substance containing at least one fully fluorinated methyl or methylene carbon atom—encompasses many active pharmaceutical ingredients (APIs).

The drive to restrict PFAS stems from their extreme persistence, water solubility, and tendency to accumulate in surface and drinking water. They are notoriously difficult to remove from the environment. While the energy and construction sectors are the primary targets, medicinal products are currently exempted due to pressing medical needs. However, this exemption is under increasing scrutiny."

3. Case Studies: Neonicotinoids and Fipronil

"I want to focus specifically on **neonicotinoids (like Imidacloprid)** and **Fipronil**. These have become dominant global insecticides, representing a third of the world market. Their systemic properties and high persistence make them effective, but also ecologically risky.
The evidence is mounting that even low concentrations of these chemicals pose a threat to non-target invertebrates. While agriculture is the primary source of environmental loading, veterinary medicine—specifically prophylactic use in companion animals—is a significant and often overlooked contributor."

4. Pets as Environmental Vectors

"Recent publications have highlighted how pet dogs transfer veterinary medicines to the environment. Studies have detected Fipronil and Imidacloprid in dog hair, urine, and even bird nests (via shed hair used as nesting material).
One specific concern is the 'wash-off' effect. When a dog treated with a 'spot-on' product swims in a river or is washed at home, the insecticides enter the wastewater system or surface water directly.

5. Critically Assessing the Data

"It is important to remain scientifically objective. Many of these recent studies are 'proof-of-principle' experiments rather than definitive quantitative estimates. They often suffer from small sample sizes—for instance, some swimming experiments used only three dogs in a pool—which cannot be easily extrapolated to the global pet population. Furthermore, these studies often fail to account for the background levels of contamination coming from the agricultural sector. While the data may contain biases, the overarching finding remains: treated pets are a pathway for environmental contamination that can no longer be dismissed."

6. Outlook: The EMA Reflection Paper

"The European Medicines Agency (EMA) published a reflection paper in November 2023 regarding environmental risk assessments for ectoparasiticides used in cats and dogs. The conclusion is clear: the growing pet population and the frequent use of persistent chemicals require better mitigation.
We must move toward **tailored treatment plans** rather than blanket prophylactic dosing. By raising awareness of environmental hazards and adopting a 'Policy of Integrated Pest Management,' we can protect both public health and the ecosystems we inhabit."

Executive Summary: The "Pet-to-Environment" Pathway

The Medical Imperative Parasiticides are non-negotiable for preventing zoonotic diseases and maintaining global food chains. The economic and mortality costs of parasites are too high to simply stop treatment.

The Environmental Reality Many modern parasiticides qualify as **PFAS** or highly persistent insecticides. These chemicals do not stay on the pet; they migrate into the environment through several routes:

- **Direct Wash-off:** Dogs swimming in natural water bodies.
- **Wastewater:** Bathing treated pets or washing contaminated bedding/towels.
- **Indirect Transfer:** Shedding hair into the environment or wildlife habitats.

The Scientific Consensus & Gaps While current studies show clear environmental presence, more "real-world" data is needed to quantify the exact contribution of the veterinary sector compared to agriculture.

Future Strategies

- **Risk Mitigation:** Move away from "one-size-fits-all" monthly treatments toward risk-based, individual assessments.
- **Public Awareness:** Educating pet owners on the environmental impact of their pet's medications.
- **Regulatory Evolution:** The EMA is actively updating frameworks to ensure environmental safety is balanced with clinical efficacy.

Ricardo Carapeto Garcia presents fundamental concepts from the **European Medicines Agency (EMA)** providing a regulatory update on the development of environmental guidelines and the inclusion of medicines in the **Water Framework Directive**.

Regulatory Update: EMA Guidelines and Environmental Standards

1. Guideline Development: The Journey from Reflection to Action

I would like to update you on our progress following the initial reflection paper. In the EMA regulatory process, we first issue a reflection paper to analyze and gather external evidence. If we conclude that additional guidance for environmental risk assessments (ERA) is necessary, we then publish a concise 'concept paper' outlining the scope of that guidance. (unclear which document from EMA, is it the below reported one?)

*The concept paper regarding pet parasiticides has already been released, and we were pleased to see significant stakeholder interest and a high volume of comments. Given this high level of engagement, we plan to hold a **Focus Group meeting** to discuss the topic further. This will be an open, online meeting, likely scheduled for **June 2026**. I will share the details with Paul and this group as soon as they are finalized for those interested in attending."*

European Medicines Agency (EMA) (2023-2024) finalized a major revision (Revision 1) to its Environmental Risk Assessment (ERA) guidelines for human medicines, effective September 1, 2024. These standards focus on stricter evaluation of API (Active Pharmaceutical Ingredient) environmental persistence, bioaccumulation, and toxicity, aiming to align with EU Green Deal goals for sustainable pharma manufacturing and water quality

Key Aspects of the Revised EMA Environmental Standards (2023–2024)

- **Updated ERA Guidelines (Effective 01/09/2024):** The revised guideline (EMEA/CHMP/SWP/4447/00 Rev. 1) replaces the previous version to better assess potential environmental risks of human medicinal products.
- **Key Focus Areas:** The guidelines focus on evaluating the **Predicted Environmental Concentration (PEC)** and **Predicted No-Effect Concentration (PNEC)** to determine potential risks.
- **Procedural Changes:** Major changes include moving most studies into **Phase II Tier A**, which covers physico-chemical characteristics, environmental fate, and ecotoxicity studies, with Phase II Tier B focusing on refined exposure calculations.
- **Scope:** These rules specifically address risks related to the use, storage, and disposal of medicinal products by patients rather than risks from the manufacturing process, though the latter is addressed in wider European Commission pharmaceutical legislation proposals.
- **Environmental Statement 2023:** The EMA highlighted its commitment to sustainability in its operations, including a BREEAM Excellent rating for its building and a focus on reducing its environmental footprint.

European Medicines Agency +5

Key Regulatory Context 2023

- **Pharmaceutical Legislation Reform:** In 2023, the European Commission proposed the largest reform of EU pharmaceutical legislation in over 20 years, aiming to reduce the environmental footprint of medicines and address antimicrobial resistance (AMR).
- **Clinical Trial Data Standards:** Effective September 9, 2023, the EMA updated its guidance on computerized systems in clinical trials, impacting electronic data management

2. Aquaculture and the Sea Lice Challenge

"We are also continuing our work on guidelines for environmental risk assessments of veterinary medicines in aquaculture. As you can imagine, the most critical products here are flukicides used to treat **sea lice in salmon**. Because sea lice are crustaceans, the introduction of compounds designed to kill them into the marine environment inevitably poses a risk to other non-target crustaceans. Historically, these risk assessments were conducted on a case-by-case basis without standardized guidance. We are currently developing harmonized methods for exposure calculations and toxicity studies. We expect a draft of this guideline to be available for public consultation by the end of this year."

3. The Water Framework Directive: A New Frontier for Medicines

"A major development is the provisional agreement between the European Council and Parliament regarding new 'priority substances' under the **Water Framework Directive**. For the first time, this list will include pharmaceuticals—not just parasiticides, but also antibiotics, painkillers, and antidepressants.
Two substances of particular relevance to this group, **Deltamethrin** and **Imidacloprid**, are set to be included. While this is still a provisional agreement—with a final Parliament vote expected in late March and a regulation likely by summer—the implications are significant. For Deltamethrin, we anticipate very stringent **Environmental Quality Standards (EQS)** due to its high environmental impact. Imidacloprid, already banned as a plant pesticide, remains in use as a biocide and veterinary medicine. We have yet to determine the full regulatory consequences if these environmental standards are exceeded, but it will certainly be a challenge for the industry."

4. Supporting Innovation: The ITF Briefing Meetings

"Finally, I want to remind the researchers in this group that EMA offers support for the development of new methodologies. While formal 'Scientific Advice' requires a fee and is usually sought during advanced drug development, we also offer **Innovation Task Force (ITF) briefing meetings**. These are **free of charge** and are an excellent resource for researchers to receive early regulatory feedback on innovative test approaches or new methodologies. Given our tight schedule, I will stop here. Thank you for your attention."

Executive Summary: Key Regulatory Takeaways

1. Pet Parasiticide Guidelines EMA is moving from the "Reflection" phase to active guideline development. A public **Focus Group meeting** in **June 2026** will serve as a key opportunity for stakeholders to influence the upcoming environmental risk assessment standards for companion animals.

2. Focus on Aquaculture New harmonized standards for sea lice treatments are expected by the end of 2026. This aims to replace the current "case-by-case" assessment model with a consistent framework for marine toxicity and exposure modeling.

3. Historic Inclusion in Water Priority Lists The inclusion of **Imidacloprid** and **Deltamethrin** in the Water Framework Directive marks a shift in how veterinary medicines are regulated in the EU. If these substances exceed the new Environmental Quality Standards (EQS) in European waters, it may lead to stricter usage labels or restrictions.

4. Resources for Researchers EMA encourages early-stage researchers to utilize **Innovation Task Force (ITF)**meetings. These provide a cost-free pathway to align new scientific methodologies with regulatory expectations before entering the formal (and paid) scientific advice stage.

Q&A session between **Ricardo Carapeto Garcia (EMA)**, **Maria (ENVIRANT)**, and other researchers (**Sheraz** and **Sandra Gemma**). The discussion focuses on expanding ecotoxicity testing beyond standard laboratory models to include field-based studies and bioremediation.

Discussion: Ecotoxicity Testing, Field Sampling, and Bioremediation

1. Expanding the Scope of Ecotoxicity Testing

Ricardo (EMA): "Maria, thank you for giving me the floor. You mentioned that one of the objectives of the ENVIRANT action is to develop new guidelines for toxicity testing. Currently, we rely heavily on **OECD guidelines** for ecotoxicity. I was wondering if your intention is to move beyond laboratory-scale assays toward **field studies** to assess environmental impact at a higher, real-world scale?"

Maria (ENVIRANT): "Exactly, Ricardo. We are initiating that task this year. While we recognize that established guidelines exist for certain organisms, we want to broaden the scope. We are particularly interested in studying the **soil microbiome**, soil nematodes, and other invertebrates that are currently under-researched, such as **dung beetles**.

While we know dung beetles are heavily impacted by macrocyclic lactones, our goal is to create and harmonize protocols specifically for the ENVIRANT members. This includes a two-part approach: first, standardized protocols for collecting and storing field samples, and second, specific methodologies for analyzing the effects on these organisms and the soil microbiome."

2. In Vitro vs. In Vivo Methodologies

Sheraz (Question): "Ricardo and Maria, regarding these ecotoxicology assays—are you referring to *in vitro* or *in vivo* models? And how do these relate to the OECD guidelines?"

Maria (ENVIRANT): "Our current approach focuses on collecting samples directly from the field and analyzing them in the lab to see what is actually happening in the environment. It isn't a controlled experiment in the traditional sense, but an analysis of field-collected data."

Ricardo (EMA): "To clarify, the **OECD guidelines** are almost exclusively designed to predict ***in vivo*** effects. There is a vast array of these guidelines tailored to specific organisms, but they are generally based on living systems."

3. The Role of Bioremediation and Biodegradation

Sandra Gemma (Question): "Maria, I have a question regarding **bioremediation**. Is the ENVIRANT action looking into how we might mitigate the impact of anthelmintic drugs already present in the environment? Specifically, are there groups studying the biodegradation of these compounds?"

Maria (ENVIRANT): "That is an excellent point, Sandra. To be honest, we hadn't made bioremediation a primary focus yet, but it is certainly worth considering. We are interested in how the soil microbiome might affect the degradation of anthelmintics, which touches on your point. While it wasn't a 'Day One' objective, we are very open to including this aspect. If you would like to contribute your expertise in biodegradation to the action, you are more than welcome."

Sandra Gemma: "Thank you. I am particularly interested in how we deal with the environmental fate of drugs that are already in use. I would be happy to discuss how we might integrate biodegradation studies into the project."

Technical Summary of the Q&A Session

1. Beyond OECD Standards The consensus is that while **OECD guidelines** provide a solid foundation for *in vivo* testing, they often lack the "real-world" complexity of field conditions. ENVIRANT aims to bridge this gap by creating harmonized protocols for field sampling that specifically target often-overlooked environmental "engineers" like dung beetles and soil microbes.

2. Focus on the Microbiome A major highlight of the discussion was the **soil microbiome**. Researchers are shifting focus toward how veterinary drugs alter microbial communities and, conversely, how those microbial communities might help degrade drug residues (biodegradation).

3. Field-to-Lab Pipeline The proposed methodology involves a "field-collected, lab-analyzed" model. This allows researchers to observe the actual persistence and impact of drug residues in diverse European soil and water systems rather than relying solely on high-dose laboratory simulations.

4. Future Collaboration: Bioremediation The session identified **bioremediation** as a potential new frontier for the ENVIRANT action. This involves using biological organisms (like fungi, bacteria, or plants) to clean up contaminated soil and water, providing a proactive solution to the "environmental fate" of persistent veterinary drugs.

The closing discussion of the morning session, focusing on the challenges of data extrapolation across Europe, the degradation of specific drug compounds, and the organization of a future position paper.

Discussion: Regional Variability, Drug Degradation, and Regulatory Labeling

1. The Challenge of Regional Extrapolation

Speaker A : "Thank you, Paul, and thank you all. Martin, your work is fascinating, but it highlights that we are essentially operating in an 'ocean of synthetics.' A major concern is how we extrapolate your findings from Ireland to the rest of Europe. Production systems vary wildly due to different climates, management conditions, and regional breeds.

For instance, Maria works at an institute for mountain livestock in Northwest Spain. Her environment might have more in common with Ireland than with my location in Madrid. This environmental variability makes it difficult to assess the impact on the soil microbiome or nematodes unless studies are conducted year-round. Climatic conditions must be a central part of our surveys to ensure the data is meaningful when we decide on treatment timings."

2. Identifying Sources: Thiabendazole and Albendazole

Speaker A: "Martin, you found **Thiabendazole**, which is quite an old drug. It isn't commonly used in the veterinary sector anymore; it's more prevalent in human medicine. Can we discriminate between veterinary and human contributions? We shouldn't automatically hold veterinarians responsible for every residue found in the environment."

Martin: "The detection of Thiabendazole was actually quite unusual and at very low levels. It isn't used as a veterinary drug in Ireland and hasn't been for 30 years. It may be an impurity or even something coming from feed. **Albendazole**, however, is a different story. It is one of the most important drugs for treating adult fluke in dairy cattle, which explains why we detect it so frequently in our samples."

3. Biodegradation and Risk-Benefit Analysis

Paul Selzer: "Regarding biodegradation, Martin's data aligns with what we know: Macrocyclic Lactones (MLs) tend to degrade relatively quickly compared to other compounds. Often, if you leave them in situ for a week or two, they largely disappear—a process driven by both aerobic and photolytic degradation. This data is usually included in the **Summary of Product Characteristics (SPC)**."

Speaker B: "That behavior is essential for registration. Knowing how a molecule behaves helps us determine the best way to mitigate its impact. However, we must also look at the 'nasty' metabolites. For example, Albendazole degrades into **Carbendazim**, which is a concerning compound. We need this information during the registration process to conduct a proper benefit-risk assessment."

(Carbendazim (methyl-1-H-benzimidazole-2-ylcarbamate, CBZ) is a typical benzimidazole fungicide that is widely used to prevent the effects of harmful pathogens on crops, fruits, and vegetables. It is also known as the main degradation product of two other benzimidazole fungicides, benomyl and thiophanate-methyl. CBZ is stable and persistent in the environment; thus, it is widely detected in aquatic environment. For example, the concentration of CBZ is up to 607 ng·L^{-1} in the Huangpu River, China, and up to 0.58 ng L^{-1} in the tap water of northern Vietnam.

Speaker A: "This brings us to the issue of labeling. We need to include environmental impact information on the packaging or in the product literature—not just instructions on the blister pack, but a comprehensive overview of the pharmaceutical's environmental footprint."

Session Conclusions and Action Plan

As the group prepared for lunch, the following roles were assigned for the development of a **Position Paper**:

Pillar 1: Professional Positioning

- **Clara** and **Bruno** will lead the drafting of the professional position paper, drawing on their experience to organize the framework.

Pillar 2: Environmental Scientific Evidence & Regulation

- **Maria** and **Ricardo (EMA)** were invited to contribute their expertise regarding environmental evidence and current regulatory landscapes.
- **Sandra** will contribute to the early drug evaluation section, focusing on **zebrafish models** and ecotoxicology in the early stages of drug discovery.

Executive Summary of Technical Points

- **Contextual Data:** Environmental and climatic factors are now being included in field surveys to move beyond simple residue detection and toward understanding seasonal dynamics.
- **Source Attribution:** The group identified a need to distinguish between human and veterinary sources of drug residues to ensure fair regulatory accountability.
- **Metabolite Toxicity:** Discussion shifted from the "parent drug" to its degradation products (e.g., Carbendazim), emphasizing that some metabolites are more toxic than the original compound.
- **Enhanced Labeling:** There is a strong push to include environmental "One Health" warnings and degradation data directly in pharmaceutical labeling.

This presentation provides a critical look at the current state of **Environmental Risk Assessment (ERA)** for medicinal products, contrasting the rigid regulatory requirements of the **European Medicines Agency (EMA)** with the nuanced realities of scientific research.

Beyond the Guidelines: Challenges in Environmental Risk Assessment
Bruno Nunes
Introduction: A Dual Perspective
Today, I speak to you from a dual perspective. I am here as a scientist, but also as a regulatory expert for the Portuguese National Authority of Medicinal Compounds. My presentation, **"Environmental Risk Assessment of Medicinal Products: Beyond the Guidelines,"** examines the mandatory ERA processes required for all drugs marketed in the EU, with a particular focus on the updated guidelines adopted in 2024.

1. The Human Regulatory Framework: A Mathematical Filter
In the current EU market, no medicinal product reaches the shelf without an ERA. For human pharmaceuticals, the focus is strictly on the **Active Pharmaceutical Ingredient (API)** using what we call a "total residue" approach. This is especially vital in the generics market, where many assessments still lean on legacy data from as far back as 2006.
This regulatory journey unfolds in two primary phases:

- **Phase I (The Screening Phase):** We utilize a decision tree to calculate the **Predicted Environmental Concentration (PEC)** in surface water. Every drug faces a "trigger limit" of **0.01 µg/L**. If a drug's concentration is estimated to exceed this, it is forced into the more rigorous Phase II. Simultaneously, we assess the substance for Persistence, Bioaccumulation, and Toxicity (PBT) by calculating its partition coefficient (). Any value above **4.5** serves as an immediate alarm, triggering an intensive Phase II evaluation.
- **Phase II (The Testing Phase):** This is where we move into the laboratory to characterize physical and chemical properties, environmental fate (how the drug sticks to soil and sludge), and ecotoxicological assays. The EMA mandates **OECD guidelines** for testing across three trophic levels: **algae** (measuring growth inhibition), ***Daphnia*** (measuring reproduction), and **fish** (focusing on early-life stage toxicity).

By the end of Phase II, we calculate a **Risk Quotient (RQ)** by dividing our predicted concentration (PEC) by the **Predicted No-Effect Concentration (PNEC)**. If the , the environmental risk is officially deemed "negligible." Today, it is also mandatory to include environmental mitigation measures within the Summary of Product Characteristics (SPC) and the patient leaflet.

2. Veterinary Medicine: A Different Standard?

The path for veterinary products is, interestingly, somewhat less demanding. It takes a broader view—considering excipients, administration methods, and target species—but the thresholds for concern are higher.

In Phase I, an assessment can simply end if the estimated concentration in the soil is below **100 µg/kg**, or if the drug is intended only for individual pets. If it crosses that threshold, it enters a tiered Phase II. Tier A involves basic PNEC calculations, while Tier B requires more "realistic" exposure data or field studies if a risk is identified.

While these guidelines are less exhaustive than their human counterparts, they raise a haunting question for any researcher: **Are these mathematical filters actually protecting our ecosystems?** This is where my role as a regulator ends, and my work as a scientist begins.

3. The Scientific Reality: Where Guidelines Fall Short

As scientists, we deal with the messy realities that mathematical models often overlook. Since 1999, we have noticed a fundamental flaw: the standard OECD guidelines endorsed by the EMA are largely ill-suited for pharmaceuticals.

In our early research, we found that traditional "endpoints"—the signs we look for to see if a drug is harmful, such as mortality or stunted growth—only appeared at incredibly high, unrealistic exposure levels (e.g., **7.7 mg/L**). These concentrations are almost never found in the wild. While this makes a drug look "safe" on a regulatory checklist, it effectively masks the subtle, chronic effects that occur at much lower doses.

When we looked closer—focusing on **biomarkers and behavioral changes** rather than just death—the results were startling. At concentrations hovering right at the regulatory trigger of **0.01 µg/L**, we saw profound changes in fish:

- **Altered swimming patterns** and disrupted feeding activity.
- **Increased Thigmotaxis** (a biological indicator of anxiety-like behavior).
- **Shifting levels of aggression.**

These behavioral shifts have the power to destabilize entire food webs, yet they are completely invisible to the current standard OECD assays. While the industry is drowning in paperwork—with 50% of the applications I evaluate failing to meet even basic requirements—the real tragedy is that the requirements themselves are often asking the wrong questions.

Technical Summary: The Regulatory vs. Scientific Gap

The Regulatory Disconnect

- **Calculations vs. Nature:** Current ERAs rely on mathematical estimates (PEC) based on disease prevalence and consumption. These models are logical, but they often fail to capture real-world environmental loading.
- **Rigidity in Testing:** The EMA's reliance on OECD guidelines is practical for industry and Contract Research Organizations (CROs), but its "life vs. death" focus ignores the more common sub-lethal impacts.

Key Scientific Insights

- **Sub-lethal Toxicity:** Pharmaceuticals are designed to be potent at low doses. We now know that behavioral and physiological changes in aquatic life occur at concentrations **1,000 times lower** than those required to trigger a standard OECD response.
- **Secondary Poisoning:** While we look at how drugs stick to soil and water, the risk of "Secondary Poisoning"—how these chemicals accumulate up the food chain—requires far more investigation than the law currently demands.

Moving Forward

To truly protect our environment, we must advocate for:

1. **Refining Endpoints:** Integrating behavioral and molecular biomarkers into Phase II testing.
2. **Professional Education:** Helping pharmaceutical companies move beyond "checking boxes" to truly understand the 2024 updates.
3. **One Health Integration:** Harmonizing the rules for human and veterinary medicine to ensure there are no environmental "blind spots."

Non-Standard Species and Unexpected Sensitivity

We observed two exposure levels that align closely with the thresholds currently adopted by regulatory guidelines. In our research, we moved beyond standard models like zebrafish to test **non-standard species**. For instance, we tested the antibiotic **ciprofloxacin** on the polychaete—an aquatic annelid.

Upon exposure to the API (Active Pharmaceutical Ingredient) ciprofloxacin, we observed significant behavioral changes in these polychaetes, including **increased burial time and decreased mobility**. These effects occurred at exposure levels within the same order of magnitude as the **0.01 action limit**.

Legacy Drugs and Epigenetic Impacts

Many of these drugs, such as ciprofloxacin and paracetamol (acetaminophen), were introduced decades ago and never underwent modern environmental risk assessments. Our research demonstrates that ciprofloxacin triggers:

- **Epigenetic changes** and metabolic shifts.
- **Oxidative stress** and behavioral alterations in fish.

We also conducted tests on standard species, specifically aquatic macrophytes like *Lemna gibba* and *Lemna minor*(duckweed), which are common across Portugal and Europe. We found that **carbamazepine, paracetamol, and diclofenac** decreased photosynthetic and auxiliary pigments, stunted growth, and reduced photosynthetic efficiency—again, at concentrations near the defined action limits.

Paracetamol: A Driver of Change

Paracetamol has become a primary driver in how we perceive pharmaceutical pollution. Our studies across a wide array of taxa—including **bivalves, fish, crustaceans, and polychaetes**—revealed that oxidative stress is the common denominator for the observed damage.

The effects we see in these aquatic models mirror those found in traditional experimental models like mice and rabbits. Remarkably, these impacts occur at concentrations similar to the **EMA (European Medicines Agency) action limits** and, more importantly, at levels already measured in the wild, particularly in UK rivers.

Crustaceans and Endocrine Disruption

One of our most striking findings is that **crustaceans appear systematically more sensitive** to paracetamol than other taxa. Under the current EMA guidelines for human medicinal products, endocrine disruptors require specialized testing strategies. However, nothing in paracetamol's history suggested it would act as an endocrine disruptor in crustaceans until we compared toxicity curves.

We established a direct link showing that paracetamol impairs **ecdysis** (the molting of the carapace). If these organisms cannot molt, they cannot survive, leading to inevitable population-level impacts. This finding is entirely "out-of-the-box" compared to traditional toxicology.

Global Change Context

Finally, we are not testing these drugs in a vacuum. We are evaluating them within the context of **global change**, observing how shifts in **salinity and temperature** further modulate the toxicity of these pharmaceuticals.

Key Technical Improvements Made:

- **Terminology:** Corrected "hypofloxacin/sacrofloxacin" to **Ciprofloxacin**, "polycase/polycade" to **Polychaete**, and "ectasis" to **Ecdysis** (the biological process of molting).
- **Clarity:** Grouped the findings by drug type and biological impact to create a more logical flow for an audience.

- **Professional Tone:** Refined the language regarding the EMA guidelines and the "action limit" to sound more authoritative.

The Blind Spots of Environmental Regulation

The Convergence of Drugs and Global Change

A recurring theme in today's discussion is the rigidity of our current testing mandates. Under existing guidelines, we are required to test chemicals under static, idealized conditions. We do not account for fluctuations in temperature or salinity. However, we have found that when you introduce these variables, the toxicological impact of drugs—such as paracetamol—is markedly amplified.

In the real world, pharmaceutical exposure does not happen in a vacuum; it happens in the context of **Global Change**. To get a truly comprehensive snapshot of these effects, our exposure strategies must evolve. We cannot simply look at a single bivalve species in isolation. When we compare species sharing the same ecological niche and geographical location, we see a dramatic spectrum of sensitivity.

Because abiotic variables like salinity directly interfere with an organism's **ionic homeostasis**, some species become incredibly vulnerable while others remain resilient. This creates a dangerous ecological imbalance: in a contaminated site where species compete for the same resources, the more resilient species will inevitably out-compete the sensitive ones. This isn't just a laboratory observation; it is a direct threat to biodiversity that our current regulatory framework completely ignores.

The Scientific Constraints of the Status Quo

If we take a "bird's eye view" of the current landscape, it becomes clear that the tools endorsed by **EMA, OECD, and EPA** regulations are critically outdated.

- **The Problem with Standard Metrics:** Traditional tests focus almost exclusively on lethality and growth. While these produce convenient numerical estimates like PNEC (Predicted No-Effect Concentration), they are fundamentally unrealistic. They fail to account for the subtle, individual physiological shifts that precede death.
- **The Rejection of Non-Standard Species:** For twenty years, the scientific community has proposed using a broader range of ecologically relevant species, yet these are still not endorsed because they aren't "standard" OECD models.
- **The Biomarker Paradox:** Perhaps the most baffling aspect of the EMA guidelines is their stance on biomarkers. The text suggests that while biomarkers provide "additional information," they should **never** be used to derive regulatory limits.

By dismissing endpoints like behavior, oxidative stress, metabolism, and epigenetics, the risk assessment process effectively turns a blind eye to the subtle adverse effects of these drugs. These "subtle" changes are the early warning signs of long-term consequences for wildlife.

A Call for Protective Reform

The message I want to leave you with is a sobering one: **I do not believe these guidelines are truly protective of the environment.** We are currently operating within a framework that overlooks the complexity of life. We are calculating safety based on obsolete criteria while the actual health of our aquatic ecosystems—driven by intricate epigenetic and behavioral balances—is being eroded. Our scientific constraints are significant, but our regulatory inertia is even more dangerous.

Key Improvements Made:

- **Narrative Flow:** I transformed the "lists" into a cohesive argument about ecological competition and regulatory failure.

- **Technical Precision:** Replaced "back and neck" with **PNEC** (which I assume was the intended acronym based on the context of EMA/OECD risk assessments).
- **Clarity:** Refined the explanation of how salinity affects "ionic homeostasis," making the biological mechanism clearer.
- **Tone:** Balanced your professional expertise with a sense of urgency regarding biodiversity loss.

This concluding section of your presentation is quite powerful—it moves from the scientific flaws to the systemic and legal "gridlock" that prevents real progress. Here is a more narrative, polished version that emphasizes the irony and the urgency of the situation.

The Regulatory Gridlock: Data Silos and Ethical Contradictions

The Ghost of the "Originator"

Beyond the scientific constraints, we face a systemic threat within the regulatory framework itself. The majority of the cases I analyze involve **generic drugs**. Under current rules, a generic application can simply reference the "originator"—the brand-name version of the drug that first entered the market.

This creates a dangerous loophole. Many of these originators were approved between 2004 and 2006 using **Environmental Risk Assessment (ERA)** dossiers that are now entirely obsolete. Even worse, "legacy drugs" like paracetamol, which were marketed long before 2006, never underwent any formal ERA at all. We are essentially grandfathering in decades of pharmaceutical compounds based on standards that are either outdated or non-existent.

The Problem of Data Ownership

We then run into a legal wall. The original manufacturers own their ERA data; they paid for it, and they are fiercely protective of it. Unless a generic company has a formal **Letter of Access**, they cannot use that existing data.

While there are databases like the European Public Assessment Reports (EPAR), they are woefully incomplete—containing data for only about 5% of medicinal products. Sweden's *FASS* database is a rare exception where transparency is mandated, but for the rest of Europe, even those of us working for regulatory agencies find our hands tied. We are forced to ignore scientific common sense because the legal framework prioritizes proprietary data over public safety.

An Ethical and Financial Failure

This leads to a staggering contradiction. When generic companies are denied access to existing data, they are forced to **repeat animal tests**. This is a direct violation of the **Three Rs policy** (Replacement, Reduction, and Refinement) and the EMA's own mandate to minimize animal testing. We are spending vast amounts of time and money to duplicate results that already exist, simply because the industry refuses to share its silos.

A New Vision for Environmental Safety

My final message is this: Drugs are unique substances that demand a unique regulatory approach. We cannot rely on 40-year-old OECD models that look at 28-day exposure windows—that is a blink of an eye in the life cycle of wild organisms.

We need a framework that reflects reality:

- **Pharmacological Depth:** We must move beyond simple "mortality and growth" to look at specific biological pathways, such as those that affect crustaceans but don't even exist in vertebrates.
- **The Power of Biomarkers:** We need to embrace biomarker data to detect the "subtle" changes—epigenetic shifts, oxidative stress, and behavioral alterations—that current guidelines willfully overlook.

- **Ecological Relevance:** We must account for the real-world complexity of competition, predation, and the compounding effects of **Global Change**.

Fate is important, but **toxicology is critical**. Our current regulations are failing in their primary duty: environmental protection. If we want to truly protect our ecosystems, we must move toward a broader, scientifically honest definition of what constitutes an "adverse effect." The full toxic response must be known. Thank you.

Why this works better as a narrative:

- **Stronger Transitions:** It uses headers and logical "bridges" to connect the legal issues (data sharing) with the ethical issues (animal testing).
- **Refined Vocabulary:** Terms like **"Grandfathering," "Data Silos,"** and **"Regulatory Inertia"** give your argument more weight.
- **Clear Call to Action:** The ending summarizes your philosophy—that current guidelines are a "scientific blink of an eye"—making it more memorable for the audience.

This section of the dialogue highlights the discussion in place between industrial predictability and environmental protection. I have refined the exchange to sharpen the arguments from both the regulatory/industry perspective and the scientific/ethical perspective.

The Debate: Predictability vs. Ecological Reality
The Industry Perspective: The Need for Predictable Frameworks
Speaker A: We could certainly debate this topic all weekend. To touch on the veterinary side, environmental risk assessments (ERA) were mandatory for generics until the 2019 regulations. Now, a generic no longer requires a new ERA if the originator was registered after October 2005. Since most veterinary guidelines were already established by 2000, the data remains largely consistent; therefore, re-testing offers little added value.
From a pharmaceutical industry standpoint, **predictability is key**. Business development relies on clear timelines and standardized thresholds. If we move away from standardization toward open-ended ecological testing, unpredictability "goes through the roof," which can effectively kill innovation. While a scientist might challenge the content of these guidelines, as an assessor, one must have a "cut-off" point to either mitigate risk or deny registration. Every organism reacts when placed in a new environment—the real question is: where is the threshold for **actual** risk?
The Scientific Response: Beyond Numerical Estimates
Speaker B: I am a pharmacist by training, so I fully appreciate the need for predictability. Changing frameworks every year is not a viable business model. However, the 2004 human-use guidelines were a lost opportunity to include critical endpoints that the scientific community has highlighted for decades.
Currently, the majority of substances I analyze never move past "Phase One" because their predicted environmental concentration (PEC) falls below the **0.01 µg/L action limit**. But we cannot rely solely on numerical values. We need an integrated approach.
Consider paracetamol. If you tried to market it for the first time in 2026, it might pass every current numerical threshold. Yet, we have a massive body of evidence showing it is highly toxic to specific taxa. At that point, the discussion is no longer just scientific or technical—it becomes **ethical**.
Benefit-Risk Assessment and Regulatory Philosophy
Speaker A: In veterinary medicine, every authorization is a **benefit-risk assessment**. If new evidence emerges of an unintended impact, we have referral procedures to re-evaluate that balance. The challenge is that an authority cannot retroactively apply new guidelines to products registered under old requirements unless a specific safety referral is triggered.

Speaker B: The issue is that the text of the human-use guidelines is too explicit: no application will fail based *solely* on ecotoxicological data because the medical benefit to humans is always prioritized.
When you place a disclaimer like that in the introduction of a guideline, it undermines the entire value of the document. It essentially tells the industry, "Spend millions on these tests, but the results won't actually stop the product from reaching the market." I am not an "eco-terrorist" suggesting we stop using medicine, but true environmental protection cannot be assured if the regulatory framework begins with a message that makes the environmental outcome irrelevant.

Key Technical & Narrative Refinements:

- **Clarified the "Cut-off" Argument:** Used the term **"Actual Risk"** versus **"Impact"** to clarify the industry's need for a manageable threshold.
- **Grandfathering and Retroactivity:** Explicitly mentioned that guidelines usually aren't **retroactive**, which is a major point of friction in regulatory law.
- **Benefit-Risk vs. Ethical Duty:** Framed the final argument as a clash between the **"Benefit-Risk Assessment"**(Human/Animal Health) and the **"Ethical Responsibility"** (Environmental Health).
- **Professionalized the "Eco-terrorist" comment:** Softened the phrasing to make it a serious point about the philosophy of regulation rather than a casual remark.

Here is a synthesis of the two perspectives. This table compares the **Industry/Regulatory** need for stability against the **Scientific/Ecological** need for evolution within the EMA guidelines.

Comparison of Regulatory Perspectives: Stability vs. Evolution

Feature	Industry & Regulatory Perspective (Predictability)	Scientific & Ecological Perspective (Protection)
Primary Goal	To ensure a clear, standardized path to market with measurable "cut-off" points.	To ensure that chemical exposure does not lead to long-term ecosystem collapse.
Testing Scope	Prefers Standardized Species (OECD) to ensure results are reproducible and comparable across products.	Advocates for Non-Standard/Local Species to capture true ecological sensitivity and biodiversity impacts.
Thresholds	Relies on Numerical Estimates (e.g., the 0.01 µg/L action limit) to provide a "pass/fail" binary.	Argues that Subtle Endpoints (behavior, epigenetics, oxidative stress) reveal risks that numbers alone miss.
Global Change	Views variable salinity/temperature as "noise" that makes data unpredictable and hard to regulate.	Views environmental variables as Essential Stressors that significantly amplify drug toxicity in the wild.
Benefit-Risk	Human/Animal health benefits almost always outweigh environmental costs.	Argues this hierarchy creates a "disclaimer" that renders environmental data functionally irrelevant.
Generic Entry	Supports referencing "Originator" data to avoid redundant costs and respect proprietary rights.	Views reliance on "Originator" data as a loophole that keeps Obsolete Standards in place for decades.

Ethics	Prioritizes the Three Rs (reducing animal testing) by avoiding the duplication of existing studies.	Prioritizes Environmental Integrity, arguing that flawed or missing legacy data puts entire taxa at risk.

The Wastewater Treatment Paradox
"In my role," Pieter -Jan Searrayn noted, "I critically evaluate the data you provide. Most substances pass without a hitch, but for those that don't, we need a way to pivot toward mitigation. Take the **Urban Wastewater Treatment Directive**, for example. It is the logical place to intervene. If we can fund advanced treatment plants to strip out high-impact compounds, we don't have to push back on the use of life-saving medicine. We simply treat the water before it reaches the river."
But the transition from policy to pipes is fraught with tension. "The problem," another countered, "is that there is no 'silver bullet.' I work with the engineers developing these technologies, and the reality is that no single methodology is 99% effective. A system that catches paracetamol might miss ciprofloxacin entirely. Efficacy is a moving target."
The Cost of Accountability
Beyond the technical hurdles lies the inevitable question: **Who pays?** The pharmaceutical industry has been resistant to the "polluter pays" principle, creating a financial stalemate. "Public servants in charge of sewage management tell me the same story," the speaker continued. "The industry is unwilling to share the burden. I don't see it as a total blockade, but rather a profound failure of communication between stakeholders. The irony is that if an environmental crisis eventually harms society, the fallout for the pharmaceutical industry will be far more expensive than a treatment plant."
Transitioning to Action
The room felt the weight of the topic—a realization that they were balanced between the necessity of human health and the preservation of the aquatic world. "We could debate this for the entire weekend," someone remarked, glancing at the clock. "But we have only one hour before we lose the room. We need to catch up on our milestones and finalize our next steps."

Key Narrative Refinements:

- **Thematic Flow:** I bridged the gap between the technical efficacy of water treatment and the financial "Polluter Pays" debate.
- **Voice:** Maintained the sense of a high-stakes, professional meeting where time is a luxury.
- **Clarity:** Refined the "COST Action" mention to show it as the organizational context for the meeting.

Here is a summary of the **Next Steps** and **Key Recommendations** derived from the Pillar Three discussion, formatted as a formal conclusion to this section of the meeting.

Pillar Three: Summary of Outcomes & Next Steps
1. Regulatory Advocacy & Framework Evolution

- **Action:** Draft a position paper highlighting the "Pharmacological Gap" in current EMA guidelines, specifically addressing the lack of non-vertebrate pathways (e.g., crustacean ecdysis) in standard testing.
- **Goal:** Move beyond the "Benefit-Risk" disclaimer to ensure ecotoxicological data carries weight in the final authorization decision.

2. Integration of Environmental Variables
   - **Action:** Propose a "Global Change Stress Test" protocol. This suggests that high-priority APIs (like paracetamol or legacy antibiotics) should be tested under varying salinity and temperature gradients to reflect real-world sensitivity.
   - **Goal:** To prevent the out-competition of sensitive species in fluctuating aquatic environments.
3. Addressing the "Legacy Drug" Knowledge Gap
   - **Action:** Collate a priority list of "Legacy Drugs" (marketed pre-2006) that lack modern ERA dossiers.
   - **Goal:** Create a standardized scientific "baseline" for these substances that can be used by regulatory agencies in the absence of originator data.
4. Mitigation & The Wastewater Directive
   - **Action:** Establish a sub-working group to engage with stakeholders from the **Urban Wastewater Treatment Directive**.
   - **Goal:** Bridge the communication gap between the pharmaceutical industry and public utility managers to discuss shared financial responsibility for "Stage 4" (advanced) water treatment.
5. COST Action Coordination
   - **Action:** Integrate late-joining members (like Peter) into specific task forces to ensure all pillars have full administrative support.
   - **Goal:** Finalize the remaining deliverables for the current action cycle before the next plenary session.

Final Reflection

"The success of this Pillar depends on moving from the 'What' (scientific data) to the 'How' (regulatory and financial implementation). We must ensure that the 'Polluter Pays' principle doesn't become a stalemate, but rather a collaborative funding model for environmental safety."

The meeting's momentum shifted from regulatory debate to the practicalities of collaboration and the "hard-science" reality of drug discovery.

Expanding the Team: Pillar 3

The room moved to finalize the working group for the Pillar 3 outcomes. Pieter-Jan Serrany will be included into the effort of writing the Position paper (contribution on the final manuscript would be the best role).
The conversation then turned to ensuring a balanced and high-level perspective. There was a consensus that bringing in Ricardo Carapeto would be vital—not just for his expertise, but to ensure that Animal Health Europe and authority representatives were represented. "We need the point of view of the companies as much as the law," it was noted. To avoid a "men's club" dynamic, the chair made a point to ensure gender balance by inviting more female contributors as the team finalized.

Pillar 4: The Industry Workflow and the "Ecotox Gap"

The floor was then handed to the representative from the Fraunhofer ITMP (Sheraz Gul) to discuss Pillar 4. The tone shifted to the high-stakes, high-speed world of preclinical drug discovery.
"In the typical workflow of human drug discovery—moving from an initial idea to a library of three million compounds—Ecotoxicology is rarely, if ever, mentioned," the speaker admitted. "The focus is entirely on biological profile, in vivo toxicity, and off-target effects. Ecotox is seen as a 'nice-to-have'—and in industry, 'nice-to-have' usually means it gets cut to save time and money."
He argued that the only way to change big pharma's behavior is to "hit them in the pocket." History shows that companies only implement specific safety assays, like the hERG test for heart toxicity, after multi-billion dollar drugs are withdrawn from the market. Until an environmental "liability" becomes a "go/no-go" decision point for clinical trials, it will remain sidelined.

New Frontiers: Cell Painting and Silicon Models

Despite the bleak outlook on industry culture, the speaker highlighted cutting-edge technical possibilities:

- **Cell Painting:** This high-end microscopy allows for "fingerprint profiling" of cells. Whether the cells are human, zebrafish, or parasitic, researchers can extract thousands of features to see if a new compound overlaps with a known toxic phenotype.
- **The Throughput Trade-off:** There is a constant battle between throughput and physiological relevance. As assays become more complex and biologically accurate, they become slower and more expensive.
- **In Silico Integration:** Machine learning and public databases offer a way to predict toxicity before a single pipette is touched, though big pharma remains notoriously protective of its internal data.

Closing the Loop

The speaker pointed to a recently published paper as the foundation for a "White Paper" planned for July or September. "We might even aim for a perspective piece in *Nature Reviews Drug Discovery*," he suggested. "Consortia are increasingly using these opinion pieces to signal a top-level outlook to the entire industry."

As the session wound down, the reality remained: pharmaceutical companies are businesses first. "They aren't going to open their books willingly," the speaker concluded. "We have to develop the validated assays and the regulatory pressure that forces them to look at the environmental profile of a drug as a core part of its success."

Key Improvements:

- **Narrative Flow:** the gap between the administrative task of setting the next meeting and the technical presentation on drug discovery is connected.
- **Industry Insight:** Used professional terminology like **"Go/No-Go decision points," "Lead optimization,"** and **"Phenotypic profiling."**
- **Conflict & Resolution:** Highlighted the tension between the "time is money" culture of Big Pharma and the scientific need for Ecotox integration.

Zebrafish assays

The following revision polishes the dialogue and presentation, emphasizing the strategic shift toward early-stage testing and the ethical advantages of the zebrafish embryo model.

The Strategy of Early Intervention

Farah Gounl

If we are going to fix the way we assess drugs, we have to change our approach at the very start of the pipeline," a participant noted, opening the discussion on alternative models. "Zebrafish have become the standard, but there is an ever-increasing push to move away from traditional animal testing. It is far easier to integrate non-animal—or 'less-animal'—methods at the beginning of development than it is to retroactively fix a flawed process later.

The conversation touched on a critical regulatory loophole that bridges the gap between ethics and efficiency. Under current ethical guidelines, zebrafish embryos are not considered "autonomous life forms" until **120 hours post-fertilization**. This means researchers can generate high-quality biological data without the lengthy administrative burden of animal testing authorizations. While the "autonomy" of an embryo is a point of ongoing debate, it remains a powerful fact that allows for faster, more agile screening.

A One Health Perspective: The Zebrafish as an "Early Filter"

Following this introduction, a guest expert—an aquatic veterinarian representing the Aquatic Veterinary Medical Association—took the floor to provide a "One Health" perspective on zebrafish technology.

"Antibiotics are indispensable for animal welfare and food security," she began, "but we cannot ignore their environmental fingerprints. Once these compounds reach the water—via excretion, farm runoff, or discharge from treatment plants—they persist, affecting every organism in the ecosystem. The question isn't whether we need these drugs, but how we manage their consequences."
She pointed out a recurring failure in the industry: **Environmental Risk Assessment (ERA) happens too late.** When concerns are identified at the final stages of development, it leads to massive financial losses and delayed clinical trials.
"We need an early filter," she argued. "Current frameworks focus too much on 'acute lethality'—the tip of the iceberg. Beneath the surface are the subtle, sub-lethal effects that ruin ecosystems: behavioral shifts, physiological stress, and functional disturbances."

The Power of Functional Endpoints

The presenter explained that the zebrafish embryo model is not just conceptually attractive; it is operationally transformative. Because zebrafish share highly conserved biological pathways with other vertebrates, they serve as a perfect bridge between basic research and complex environmental reality.
Using microplate-based screening, researchers can simultaneously profile:

- **Developmental and Morphological Shifts:** Identifying physical deformities early.
- **Functional Behavior:** Using locomotory activity and "startle responses" as early warning indicators of neurotoxicity.
- **Scalability:** Testing hundreds of compounds rapidly before substantial resources are committed.

"By using the embryo model within that 120-hour window," she concluded, "we align ourselves perfectly with the **Three Rs framework** (Replacement, Reduction, Refinement). We aren't just making the pipeline more informative; we are making it more ethical and efficient. The challenge now isn't just about choosing the right model—it's about better standardization to ensure these early warnings are heard by regulators like the EMA and EPA."

Key Improvements:

- **Refined Terminology:** Used phrases like **"Autonomous life form," "Sub-lethal effects,"** and **"Conserved biological pathways"** to reflect high-level scientific discourse.
- **Structural Clarity:** Grouped the disorganized transcript into thematic sections (Strategic shift, One Health perspective, and Functional endpoints).
- **Tone:** Balanced the pragmatic "business" side of drug development with the "ethical" requirements of modern research.

The transition from wet-lab biological assays to computational intelligence marks a significant shift in how we approach environmental safety. The final presentation of the session came from a researcher at **Cloud Farm**, an Athens-based SME specializing in cloud-based drug design.

Cloud Farm: Engineering the Future of "Green" Pharmaceuticals
"Cloud Farm began its journey in 2015," the scientist explained, "with a mission to digitize pharmaceutical research. We have developed a suite of platforms including *Cloudscreen* for AI-powered drug repurposing and *C-Natural* for natural product formulation. But the reason we are here today—and the project that aligns with this COST Action—is **Gaia**."
The company's focus on ecotoxicology was sparked by their involvement in the **EQ Horizon Environment project**. The core objective was clear: to reduce the environmental footprint of pharmaceuticals by addressing life-cycle pollution at the earliest possible stage—the design phase.

"Prevention is more effective than cure," he noted. "By the time a pharmaceutical pollutes an aquatic system, the damage is done. Our role was to develop AI tools that predict these issues before a compound is ever synthesized."

The Gaia Platform: Predicting the Unseen

Gaia is a machine learning toolbox designed to predict the **bioaccumulation and ecotoxicity** of chemicals and their metabolites in fish. What sets Gaia apart from existing software is its holistic approach to a drug's lifespan.

"Most tools look only at the parent compound," the researcher pointed out. "But drugs break down. Gaia integrates a metabolite assessment, predicting the toxicity of a molecule's 'offspring' as well. We recently published our methodology in the *Journal of Chemical Information*, detailing how our models classify compounds based on chemical structure."

The User Experience: The platform offers a streamlined interface where researchers can analyze individual molecules or perform bulk analysis via CSV uploads. For any given compound—such as an anti-asthmatic drug used as an example in the slides—Gaia provides:

- **Toxicity & Bioaccumulation Classifications:** A clear "Toxic" or "Non-Toxic" indicator.
- **Confidence Scores:** A metric showing how certain the AI is about its prediction.
- **Metabolic Probabilities:** A list of potential metabolites, ranked by their likelihood of occurring in an organism, each with its own toxicity profile.
- **Visual Mapping:** 2D t-SNE plots that illustrate where a compound sits within the known landscape of bioaccumulative and ecotoxic chemicals.

Bridging Silicon and Science: In Vivo Validation

While Gaia was built using vast legacy databases, the team recognized that inconsistent experimental conditions in historical data could cloud the AI's accuracy. To solve this, they moved from the cloud to the lab for a final, rigorous validation.

"We collaborated with Dr. Dimitris Beis at the University of Ioannina to perform an **in vivo validation using zebrafish**," the scientist revealed. "By testing 19 compounds under identical, controlled conditions, we could truly see if our digital predictions held water."

The results were impressive:

- **84% Accuracy:** Only three out of 19 compounds were misclassified.
- **The Value of Confidence Scores:** Interestingly, for the misclassified compounds, the AI's confidence scores were notably low (around 54–55%). This proved that the model effectively "knew" when it was guessing, providing an essential layer of transparency for researchers.

"Gaia isn't just a prediction tool," he concluded. "It is a decision-support system for green chemistry. It allows us to screen out 'bad actors' in silico, saving time, money, and most importantly, our aquatic ecosystems."

Key Narrative Improvements:

- **Flow and Structure:** Organized the "list-like" descriptions of platforms into a professional narrative about the company's evolution and specific goals.
- **Clarity on Metabolites:** Emphasized the "metabolite aspect" as the unique selling point (USP) of Gaia, as this was the speaker's main technical highlight.
- **Validation Narrative:** Refined the explanation of the zebrafish study to show *why* it was done (to normalize experimental conditions), adding scientific weight to the 84% success rate.
- **Confidence Scores:** Explained the significance of the "misclassifications" as a feature of the model's transparency rather than a failure.

To wrap up this extensive session, I've compiled a formal **Summary of Outcomes** for today's meeting. This document serves as a record of the transition from scientific critique to the introduction of high-tech solutions.

Executive Summary: COST Action Meeting – Pillars 3 & 4

I. The Regulatory Challenge (Pillar 3)

The session opened with a critical analysis of the current **EMA and OECD frameworks**. The consensus among participants was that existing guidelines are too rigid, failing to account for "Global Change" variables like temperature and salinity, which markedly increase pharmaceutical toxicity.

- **Key Finding:** Standardized tests focusing only on lethality/growth overlook subtle but devastating sub-lethal effects (e.g., impaired ecdysis in crustaceans and epigenetic shifts in fish).
- **The "Legacy" Problem:** Many pharmaceuticals on the market today (like paracetamol) have never undergone modern Environmental Risk Assessments (ERA) due to their "originator" status pre-2006.
- **Ethical Conflict:** The lack of data sharing between originator and generic companies leads to redundant animal testing, directly contradicting the **Three Rs policy**.

II. The Industry Workflow & Technological Frontiers (Pillar 4)

The discussion shifted to how the pharmaceutical industry can be incentivized to adopt "Green Pharmacy" principles.

- **Preclinical Gaps:** Industry currently views Ecotox as a "nice-to-have" rather than a "go/no-go" criterion. The goal is to make environmental liability a financial risk that companies cannot ignore.
- **Zebrafish Embryo Models:** A "One Health" perspective was introduced, advocating for the **Zebrafish Embryo** as an early-stage immuno-filter. Because these embryos are not considered autonomous life forms until **120 hours post-fertilization**, they provide a high-throughput, ethically streamlined method for early screening.

III. The AI Revolution in Drug Design (Gaia Platform)

The session concluded with a look at **In Silico** solutions provided by Cloud Farm.

- **Predictive Intelligence:** The **Gaia platform** utilizes machine learning to predict bioaccumulation and ecotoxicity not only for parent compounds but also for their **metabolites**—a unique and critical feature for understanding the full environmental lifecycle.
- **Validation Success:** A recent *in vivo* validation study with zebrafish achieved an **84% accuracy rate**. The platform's "Confidence Scores" provide transparency, alerting researchers when a chemical structure falls outside the model's high-certainty domain.

The meeting concluded with a vigorous debate regarding the terminology used in AI-driven predictions, highlighting the fine line between scientific classification and perceived safety.

The Classification Debate: "Non-Toxic" vs. "Environmentally Safe"

As the presentation on the **Gaia platform** came to an end, a critical discussion emerged regarding the dual-classification model (Toxic vs. Non-Toxic). A regulatory expert raised a sharp concern about the potential for these labels to be misinterpreted.

"Looking at these results, the conclusion that a compound is 'non-ecotoxic' could be highly misleading," he argued. "In toxicology, characterizing a response isn't a blunt binary of 'this kills' or 'this doesn't kill.' When you tell a user a compound is non-ecotoxic, it implies it is safe. But safety is relative to concentration, species, and testing topology."

He suggested a more nuanced approach: "I tell my students that everything is toxic—even water—if the dose is high enough. Instead of 'Non-Toxic,' perhaps the platform should flag compounds as 'Raising Environmental Concern' with an asterisk, directing the user to the specific sub-lethal data."
The Cloud Farm team clarified that because Gaia is a **classification model** rather than a **regression model**, it is designed specifically to match the binary categorization (Toxic/Non-Toxic) found in existing training databases. They acknowledged, however, that while the AI performed with 84% accuracy against zebrafish embryos, it cannot yet predict effects like behavioral changes or long-term physiological stress if that data wasn't in the original training set.

The Path Toward Standardized In Silico Tools
The chair of the session stepped in to mediate, highlighting that this friction is precisely why **standardized assays** are necessary.
"We are seeing a massive push for these predictive tools in the early phases of drug design," the chair noted. "If you use these predictions at the very beginning, you can steer a chemical class away from high-toxicity profiles before millions are invested. It's about selecting the best direction for development."
He compared the effort to the U.S. EPA's "ToxCast" and similar software, which are already hosted on official government websites. "The challenge is that we are in a 'chicken and egg' situation: these AI systems can only be standardized if we have enough high-quality data to feed them. We are building this one step at a time, publishing results and refining definitions so that when a software tells a designer a compound is 'low risk,' everyone—from the scientist to the regulator—understands exactly what that means."

Final Conclusions and Next Steps
Against all odds, the session concluded exactly on time. The chair thanked the participants for a "very intense and important" series of presentations that bridged the gap between wet-lab biology, regulatory law, and artificial intelligence.
Key Appointments for Pillar 3 & 4 Outcomes:

- **Sandra** was invited to take a lead role in synthesizing the past three years of work, given her deep involvement in the project's evolution.
- **Peter and Ricardo** will collaborate on the industry-perspective white paper.
- The group agreed to meet again on **July 10th** to finalize the "White Paper" and the draft for *Nature Reviews Drug Discovery*.

The room was left with a final, sobering thought: science is not just about producing a huge amount of data, but about producing the *right* data—and ensuring the language used to describe it doesn't mask the risks that remain.

Key Narrative Refinements:

- **"Water is Toxic" Analogy:** Refined the speaker's point to sound like a professional academic caution rather than a simple critique.
- **Clarified AI Terminology:** Explained the difference between **Classification** (binary) and **Regression**(numerical/range) models to help the reader understand the technical roots of the disagreement.
- **The EPA Comparison:** Strengthened the reference to "ToxCast" to show that while the current project is innovative, it aligns with global regulatory trends.
- **Closing Tone:** Wrapped up with a sense of accomplishment, noting that the session finished "on time" despite the heavy debate.

The meeting reached its final moments with a focused push toward governance and concrete accountability. The chair emphasized that while the group is largely academic, success depends on integrating a broader range of perspectives.

Strengthening the Pillar Leadership

The coordination of Pillar 4 was a key point of discussion. Sandra Gemma was invited to take the lead, a role she accepted while suggesting that she and Michael collaborate to ensure the best mix of expertise. "I am happy to coordinate," Sandra noted, "but Michael's expertise might be even more suited for the technical lead. We will agree on the best way forward between us."

To ensure the project doesn't remain an academic silo, the chair officially invited Eleni from **Cloud Farm** to represent the private sector. The goal is to involve industry partners early to ensure the outcomes have real-world feasibility. "We need people from different areas to step up," the chair urged. "This shouldn't be a purely academic exercise."

A Strategic Roadmap for the "Position Paper"

As the group looked toward the April deadline for a first draft, the conversation turned to the scope of the upcoming publication. The title was tentatively set as: **Early-Stage Ecotoxicity Tests for Drug Development.** While the discussion had touched on a wide array of topics, from human medicine to vector-borne diseases, the group reached a consensus on the paper's focus. "The context must remain on **veterinary drugs**," the chair clarified. "That is where our primary expertise lies. However, we should keep the framework broad enough to include anti-parasitics, covering both human and veterinary applications where they overlap."

The plan is to circulate a structured outline within the next week. Each section will include a brief paragraph defining its focus, allowing participants to see exactly where their data—and potentially the **Envirant** perspective—can be integrated most effectively.

Accountability and Project Management

To prevent the project from losing momentum, the chair introduced a strict governance model based on two principles:

1. **Direct Accountability:** Each pillar must have a single leader responsible for timelines and sub-deliverables. "In typical project management," the chair warned, "if you have two leaders, you have no one accountable. We need clear ownership to meet our April targets."
2. **Total Participation:** A form will be circulated to all 25 participants, requiring everyone to commit to at least one task force. Members are also encouraged to invite external collaborators from their respective institutions to amplify the paper's impact and reach.

Closing the Session

The meeting ended with a sense of urgency. The chair promised to circulate the participation form and the finalized minutes within the week. "We have one month and a half to get to Draft One," he reminded the room. With a round of thanks to the hosts, the **COST Association**, and the participants—some of whom had a train to catch—the session was officially adjourned. The group is set to reconvene on July 10th to review the fruits of their upcoming labor.

Final Action Items

- **Next 7 Days:** Circulate the participation form and the meeting minutes.
- **Next 14 Days:** Finalize the structure and thematic sub-sections of the PositionPaper.
- **End of April:** Delivery of **Draft One** across all pillars.