Deliverable 1 report

Roadmaps to Assess the Environmental Effects of Pharmaceuticals and Their Degradation Products/Metabolites

Challenge of reference

Challenge 1. Existing drugs for human and animal neglected infections against VBD are scarce, with limited efficacy and toxicity. *Therefore, a collective effort for innovative compounds and prediction tools should be identified to improve the therapeutic properties of the antiparasitic drugs and identify new drugs.*

Challenge 2. The impact of pharmaceutics and their R&D process on the environment is high and it is responsible of huge loss due to contaminated water that affects human and animal health, generate drug resistance problems. *Integrated multidisciplinary efforts (design, synthesis/extraction, in vitro and in vivo biological/animal studies, delivery) should be developed to reduce the drugs impact on the environment at every step of the drug research and development process. This requires the coordinated action of researchers and stakeholders (governmental bodies, patients' organizations, industries and SME).*

Objective of reference (Research Coordination Objective)

1. Coordination and integration of the medicinal chemistry programs by collecting and re-using compounds databases. *In silico* prediction of compounds (biodegradability) behaviors to improve the properties of the antiparasitic drugs.

2. Coordination of the *in vitro* activity of the R&D process and integration of the necessary actions for the reduction/prevention of the drugs impact on the environment.

3. Coordination of the activities to incorporate procedures and assays of the antiparasitic drugs R&D program in the guideline format.

Secondary Objectives

1. Coordination and integration of the medicinal chemistry programs by collecting and re-using large compounds databases available from different sources. Associate the libraries with *in silico* prediction of compounds molecular properties to improve their antiparasitic drugs profile.
2. Coordination of the *in vitro* activity of R&D studies; integration of the activities for reduction/prevention of the drugs impact on the environment. The compounds from different sources (natural, synthetic, from organic waste) will be tested in cell-based assays. Experimental and *in silico* ecotoxicology studies will be coordinated.
3. Coordination of the translation from *in vitro*-to-*in vivo* activities to obtain One Health high quality leads and candidates. Introduction of omics technologies (genomic, proteomics and transcriptomics) and imaging for a limited number of validated leads. Drug delivery of biodegradable nanotechnology and drug targeting tools for pharmacological studies in H&A.
4. Coordination of the activities to incorporate procedures and assays of the antiparasitic drugs R&D program in the guideline format. Coordination of meetings and critical analysis on the activities performed and deliverables achieved. The information and deliverables shared with the stakeholder will be translated in an informed whitepaper with guideline content.

5. To facilitate, through investigations, training schools, workshops, and STSM, an expansion of the currently separated R&D platform for the development of new drugs against H&A. This objective is particularly important for Young Researchers and Innovators and for less research-intensive countries.
6. To cooperate with non-European world-leading experts within each scientific field covered, thereby ensuring mutual benefits and the best possible platform for any research and educational activities within the Action.

Working group of reference:

Working Group 4 (WG4) – Environmental Assessment, Ecotoxicology and Sustainable-by-Design Drug Discovery

WG4 serves as the main reference Working Group for integrating environmental considerations throughout the drug discovery and development process within COST Action CA21111 OneHealthdrugs. Its role is to connect compound design and early computational prediction with experimental environmental fate assessment, ecotoxicology, identification and characterisation of metabolites and degradation products, mechanistic studies, and integrated environmental risk assessment.

The WG4 reference framework is based on a proactive, tiered and integrated approach, moving environmental assessment from a late-stage regulatory activity towards an integral component of drug discovery. Environmental properties are progressively considered from early compound design and lead selection through candidate development, environmental exposure, transformation and risk characterisation.

Core areas of reference

- Early environmental assessment and prediction – integration of physicochemical properties, degradability, persistence, bioaccumulation and predicted ecotoxicity into early compound profiling.
- Environmental fate and exposure – assessment of degradation, transformation, persistence, mobility, environmental compartments and exposure scenarios.
- Ecotoxicology – evaluation of effects on non-target organisms using organism-level, cellular, behavioural, developmental, reproductive, physiological and receptor-based endpoints.
- Metabolites and degradation products – identification, structural characterisation, prioritisation and comparative assessment of environmentally relevant transformation products.
- Mechanistic ecotoxicology – application of biomarkers, receptor-based assays, transcriptomics, proteomics, metabolomics and other omics approaches.
- Adverse Outcome Pathways (AOPs) – mechanistic interpretation linking molecular initiating events and biological responses to adverse outcomes.
- Integrated environmental risk assessment – integration of hazard, exposure, environmental fate, biological effects and uncertainty.
- Sustainable-by-design – translation of environmental findings into medicinal chemistry, candidate prioritisation, structural redesign, mitigation and alternative-candidate selection.

Reference framework

The WG4 approach follows the integrated sequence:

DESIGN → PREDICT → PRIORITISE → TEST → IDENTIFY → CHARACTERISE → UNDERSTAND → INTEGRATE → PREVENT → VALIDATE → MONITOR → FEEDBACK

This framework ensures that environmental information is not used only to reject problematic candidates, but also to guide the development of safer and environmentally sustainable pharmaceutical candidates.

Interaction with other Working Groups
WG4 operates as an integrative environmental interface within the Action:
WG1 – compound design, compound libraries and degradability prediction
WG2 – lead optimisation and sustainable-by-design considerations
WG3 – advanced lead/candidate characterisation and experimental ecotoxicology
WG4 – environmental fate, transformation products, environmental risk assessment and integration of environmental evidence
The document therefore establishes WG4 as a cross-cutting reference point for environmental assessment, while recognising that effective One Health drug development requires coordinated contributions from WG1, WG2, WG3 and WG4.

Key reference principle

Environmental assessment should encompass the entire chemical life cycle of the active substance, from molecular design through use, excretion, environmental transformation and degradation.
Accordingly, WG4 provides the framework for translating environmental and ecotoxicological knowledge into environmentally informed drug discovery and development, supporting a better balance between therapeutic efficacy, human and animal health, environmental protection and societal benefit.

Deliverable description.

The current therapeutic modalities for parasitic vector-borne diseases are limited and old and suffer from a variety of problems. Thus, new drugs for these diseases are urgently needed, de-risked for environmental toxicity. Novel sustainable sources of hits and leads including natural products or from valorisation of organic waste material from human activity industries may provide new drug candidates for VBDs. Novel technologies are developing continuously to recover and recycle valuable compounds and nutrients from waste materials. This new field helps in the circular economy and can contribute to the identification of novel substances for VBDs. Furthermore, green synthetic methods promote sustainability and reduce environmental impact. Integrating the green chemistry principles (such a waste reduction, use of safe solvents, energy efficient methods (microwave or ultrasound or flow synthesis) and catalysis) in drug synthesis makes it more cost-effective and environmentally responsible. These concepts and medicinal chemistry approaches are emphasized in the context of OneHealth Drugs towards the discovery and development of new drugs for VBDs.

Description of what we have done.

1. Roadmap development

Three complementary roadmaps were developed:

- Roadmap 1: assessment of the environmental effects of the parent pharmaceutical;
- Roadmap 2: assessment of degradation products and metabolites;
- Roadmap 3: an integrated drug-discovery-to-environment workflow connecting compound design, environmental assessment and feedback into drug development.

2. Development of technical workflows and decision tools

The work resulted in practical technical diagrams and decision frameworks describing:

Design → Predict → Prioritise → Test → Identify → Characterise → Understand → Integrate → Prevent → Validate → Monitor → Feedback

The framework includes a tiered testing strategy ranging from computational screening (Tier 0) through environmental fate, targeted ecotoxicology and mechanistic assessment to integrated environmental risk assessment (Tier 4). A dedicated decision tree was also developed for environmentally relevant degradation products, including their identification, prioritisation, comparison with the parent pharmaceutical, ecotoxicological assessment and subsequent risk management or redesign.

3. Integration of environmental fate, ecotoxicology and mechanistic approaches

This provides a mechanistic bridge between chemical exposure, molecular initiating events, biological responses and ecological consequences.

4. Minimum dataset and implementation framework

An implementation strategy was proposed covering short-, medium- and long-term actions, including harmonisation of terminology and endpoints, experimental validation, standardisation of ecotoxicology assays, metabolite/degradation-product workflows, integration of omics and AOPs, predictive modelling and development of sustainable-by-design criteria.

5. Meetings, workshops, Training Schools and STSMs

The Action has established meetings, workshops, Training Schools and Short-Term Scientific Missions (STSMs) as networking and capacity-building mechanisms.

5.1. Training schools

Crash course in ecotoxicology: From concepts to practice (https://www.onehealthdrugs.com/events/training-schools/training-school-crash-course-in-ecotoxicology-from-concepts-to-practice/), 27-29/5/2026, Namur, Belgium. This 3-day training school introduced early-career researchers, Ph.D. students, and postdoctoral fellows to the fundamentals of ecotoxicology. Through a combination of lectures, interactive sessions featuring case studies, and hands-on laboratory work, participants explored how chemicals affect organisms and the ecosystems they inhabit. The participants gained an overview of the main classes of chemical pollutants, how these substances enter and move through the environment, the effects they can have on wildlife, and approaches to measuring and mitigating their impact. The program also covered the principles of dose–response testing, experimental design, and data interpretation, and included a practical session running a standard toxicity assay. Emphasis was placed on linking laboratory findings to ecological relevance and environmental safety. The course was designed for participants with no prior background in ecotoxicology and was opened to trainees from a wide range of disciplines.

OneHealthdrugs Workshop on "Exploring cutting-edge chemoinformatics and AI in chemistry" Erasmus Mundus Summer School on Chemoinformatics (https://www.onehealthdrugs.com/events/scientific-meeting/next-meeting/erasmus-mundus-summer-school-on-chemoinformatics-and-onehealthdrugs-workshop/), **3-4/7/2025, Ljubljana, Slovenia.** This inspiring event brought together leading European experts, whose lectures offered deep insights into the power and versatility of cheminformatics—spanning applications from forensic science to pharmaceutical innovation and even ecological implications.

***In silico* prediction method for ecotoxicity and bioaccumulation (https://www.onehealthdrugs.com/events/training-schools/5th-ohd-training-school-in-silico-prediction-method-for-ecotoxicity-and-bioaccumulation/), 19-21/3/2025, Iraklio, Greece.** This Training School aimed to provide participants with a comprehensive understanding of *in silico* (computer based) methods used to predict the ecotoxicity and bioaccumulation potential of chemicals. Through a series

of lectures, hands-on workshops, and case studies, attendees learnt the principles, tools, and applications of computational techniques in environmental risk assessment. The training covered key aspects such as predictive toxicology models, bioaccumulation forecasting, and the integration of *in silico* methods into environmental protection strategies. This event was designed for researchers and students seeking to enhance their knowledge in the field of environmental science and computational toxicology.

Drug discovery against parasitic vector borne diseases *in-vitro* assays development and screening in drug discovery (https://www.onehealthdrugs.com/events/training-schools/fraunhofer-itmp-hamburg-germany/), 8-10/5/2023, Hamburg, Germany. The initial aim of drug discovery is to develop compounds that exhibit appropriate safety and efficacy profiles which can be progressed to clinical evaluation. The focus of this Training School was to explore the principles underlying target identification, biochemical and cell-based assay development, small molecule screening and *in-vitro* ADME-Tox profiling to produce compounds ready for clinical studies, whilst maintaining low environmental impact.

5.2. Workshops

Scientific Achievements and Pathways for the Future (https://www.onehealthdrugs.com/events/scientific-meeting/meeting-2026/online-workshop-onehealthdrugs-and-the-ecotox-paradigm-shift-towards-better-drugs-in-the-pipeline/), Hybrid event, 2/9/2026, Valletta, Malta. The workshop focused on the scientific achievements of COST Action CA21111 and future pathways for sustainable antiparasitic drug development. Emphasis was placed on the integration of green chemistry and ecotoxicological considerations into early-stage drug discovery, including environmentally benign molecular design, safer synthesis, reduced waste, and improved environmental degradation of drug candidates.

Compounds from natural sources and organic waste for VBDs (https://www.onehealthdrugs.com/events/scientific-meeting/meeting-2026/workshop-online-compounds-from-natural-sources-and-organic-waste-for-vbds/), Online event, 25/6/2026. The workshop covered activities related to sustainable drug discovery for VBDs using natural sources and valorisation of organic waste. Various secondary metabolites from plants and other organisms have achieved regulatory approval for treating infectious diseases. In addition, valorisation of agro-food by-products and organic waste into valuable precursors towards the synthesis of new drugs against VBDs merges circular economy with sustainable drug discovery leading to the development of eco friendly, cost-effective antiparasitic drugs. The workshop provided insights on the recent trends in natural products research for VBDs, exploring the therapeutic potential of natural products along with sustainable methods for extraction, isolation and synthesis.

Virtual screening of OHD Compound libraries against parasitic targets (https://www.onehealthdrugs.com/events/scientific-meeting/meeting-2026/virtual-screening-of-ohd-compound-libraries-against-parasitic-targets/), Online event, 13/5/2026. The OHD:LUB Project is the OneHealthdrugs COST Action's premier success story, showcasing how interdisciplinary synergy can fast-track drug discovery on a budget. Its workflow bridges the gap from supercomputing to sustainable therapy through three key phases: Phase I: High-Velocity Virtual Screening – Leveraging the Vega HPC system, the team (led by Podlipnik and Jukić) has screened 36,000+ compounds against 22 targets. Phase II: The "Green" Triage – In a pioneering move, the project uses ML-driven ecotoxicity models (in collaboration with Daniele Aiello) to filter hits. This creates a "Green Drug Score," ensuring candidates are both potent and environmentally benign from the outset. Phase III: Experimental Validation – With a deadline of October 2026, the project has launched a "call to action."

***In silico* and *in vitro* approaches to assess biodegradability and prioritize environmentally friendly chemotypes of synthetic and natural origin (https://www.onehealthdrugs.com/events/scientific-meeting/meeting-2026/workshop-online-in-silico-and-in-vitro-approaches-to-assess-biodegradability-and-prioritize-environmentally-friendly-**

chemotypes-of-synthetic-and-natural-origin/), **Online event, 27/3/2026.** The workshop covered innovative models (*in silico* and experimental) at the interface of drug discovery for VBDs and (eco)toxicology including biodegradability. This collaborative event provided a platform for scientists, academics, young researchers and industry professionals to share insights, methodologies, advancements, a pipeline and portfolio of approaches in the pursuit of environmentally conscious antiparasitic drug discovery.

Integration of green and greener actions into medicinal chemistry programs (https://www.onehealthdrugs.com/events/scientific-meeting/meeting-2026/workshop-integration-of-green-and-greener-actions-into-medicinal-chemistry-programs-23-03-2026-14-30-16-30-cet-online/), Online event, 23/3/2026. The workshop brought together innovative perspectives across four carefully curated sessions: 1) Green Frontiers in Medicinal Chemistry (Exploring how sustainable strategies are redefining drug discovery and development); 2) From Molecule to Medicine: Property Prediction in Action (Translating molecular insights into real therapeutic potential); 3) One Health: Bridging Medicine, Animals, and Environment (Addressing health challenges through a truly interconnected, holistic approach); 4) From Omics Data to Drug Breakthroughs (Turning complex biological data into next-generation medicines).

Advanced Technologies Integration into Medicinal Chemistry Programs (https://www.onehealthdrugs.com/events/scientific-meeting/next-meeting/online-workshop-advanced-technologies-integration-into-medicinal-chemistry-programs-june-30th-2025-online-from-14-00-to-16-30-cet/), Online event, 30/6/2025. This workshop aimed to showcase how advanced technologies—such as AI-driven drug design, high-throughput screening, and omics integration—can be strategically applied in medicinal chemistry pipelines. Emphasis was placed on supporting the OneHealthdrugs mission: coordinating the discovery of drugs that effectively combat vector-borne infections in both human and veterinary medicine, while adhering to optimal efficacy profiles across species. Participants explored tools that enhance target specificity, accelerate development, and reduce environmental impact, fostering cross-disciplinary collaboration aligned with One Health principles.

Novel leads and drugs for vector borne diseases: Targets and off targets (toxicity and ecotoxicity) and mechanism of action (https://www.onehealthdrugs.com/events/scientific-meeting/past-meetings-in-2024/novel-leads-and-drugs-for-vector-borne-diseases-targets-and-off-targets-toxicity-and-ecotoxicity-and-mechanism-of-action/), 19-20/9/2024, Athens, Greece. The workshop provided several insights on strategies and tools for sustainable drug discovery for vector borne diseases (VBDs). Biodegradability and toxicity aspects were also pinpointed with application of specific software and QSAR model for (eco)toxicity and persistence prediction.

Green chemistry approaches and innovative drug delivery systems towards reducing environmental impact in antiparasitic drug discovery (https://www.onehealthdrugs.com/events/scientific-meeting/past-meetings-in-2024/green-chemistry-approaches-and-innovative-drug-delivery-systems-towards-reducing-environmental-impact-in-antiparasitic-drug-discovery/), Online event, 15/3/2024. The workshop explored sustainable practices that reduce the environmental impact focusing on green chemistry and innovative drug delivery systems and their application in antiparasitic drug discovery. During the discussion the concept of developing predictive models able to describe the overall environmental risks to be used to facilitate regulatory decision making clearly emerged.

Innovative sustainable approaches in antiparasitic drug discovery: towards a one Health approach (https://www.onehealthdrugs.com/events/scientific-meeting/past-meetings-in-2023/innovative-sustainable-approaches-in-antiparasitic-drug-discovery-towards-a-one-health-approach/), Online event. 22/06/2023. The workshop interrogated how sustainability principles can be embedded in antiparasitic drug discovery under ongoing and future programs. Natural products, sustainable drug design, greener synthetic methods for drug synthesis, and waste

valorisation strategies were discussed. Round table discussion addressed the criteria that define a drug discovery process sustainable, which steps of the drug discovery process are considered more critical for sustainability and the connection between One Health and sustainability. The workshop was inspirational and emphasized our vision for sustainability towards the future.

5.3. Conferences

OneHealthdrugs FORWARD LOOK - Final conference (https://www.onehealthdrugs.com/events/scientific-meeting/meeting-2026/onehealthdrugs-forward-look-final-conference-hybrid-event/). Hybrid event. 10/7/2026, Brussels, Belgium. The OneHealthdrugs Forward Look Conference marked the culmination of COST Action CA21111 and brought together researchers, regulators, industry representatives, policy stakeholders and young researchers to discuss the future of sustainable antiparasitic drug discovery within a One Health framework. The conference highlighted the importance of integrating environmental and ecotoxicological considerations into the early stages of drug discovery, supported by computational tools, predictive models and innovative screening approaches. Key outcomes included the establishment of an interdisciplinary European network, development of new digital and scientific resources, extensive training and career-development activities, and the formulation of recommendations for safer and more sustainable medicines. The participants also emphasized the importance of continued collaboration with initiatives such as ENVIRANT, further development of the OneHealthdrugs Position Paper, and the integration of sustainability and ecotoxicology into future research, education and regulatory frameworks.

33rd Annual GP2A Conference, XIVth Paul Ehrlich MedChem Euro-PhD Network Meeting & COST Action One Health drugs against parasitic vector borne diseases in Europe and beyond (OneHealthdrugs) (https://www.onehealthdrugs.com/events/scientific-meeting/next-meeting/33rd%E8%81%BDannual-gp2a-conference-xivth%E8%81%BDpaul-ehrlich-medchem-euro-phd-network-meeting%E8%81%BD-cost-action-one-health-drugs-against-parasitic-vector-borne-diseases-in-europe-and-beyond-onehealthdrugs/). 11-13/6/2025, Nantes, France. In this OHD COST Action & GP2A & PaulEhrlich joint event medicinal chemistry programs were presented by young researchers and innovators promoting antiparasitic drug research while, emphasizing the concept of the environmental impact of drugs.

OHD 2025 Annual Conference "Strategies for breaking the chain between the parasite reservoir in animals and infections in humans" (https://www.onehealthdrugs.com/events/scientific-meeting/next-meeting/ohd-2025-annual-conference-strategies-for-breaking-the-chain-between-the-parasite-reservoir-in-animals-and-infections-in-humans/). 4-6/6/2025, Antwerp, Belgium. The OneHealthdrugs COST Action network brought together experts to advance the discovery of innovative drugs and therapeutic targets aimed at combating vector-borne infections in both human and veterinary medicine. By adhering to the principles of an optimal drug profile, our approach enhances treatment effectiveness while minimizing environmental impact.

5.4. STSMs

Comparative Study of Conventional *vs.* Eco-Friendly Routes for *N*-Heterocyclic Drug Candidates (https://www.onehealthdrugs.com/stsm/comparative-study-of-conventional-vs-eco-friendly-routes-for-n-heterocyclic-drug-candidates/). **Gunel Aliyeva. University of Bari, Italy, 13/2-31/3/2026.** The primary objective of the STSM was to integrate green chemistry approaches into heterocyclic synthesis by combining conventional organic methods with environmentally friendly cross-coupling techniques. In particular, Suzuki–Miyaura reactions were performed in green media such as water and deep eutectic solvents (DES), significantly reducing the environmental footprint of the processes.

Determination of *in vitro* ADME-Tox properties of newly optimized pyrimido[5,4 d]pyrimidines with antileishmanial activity (https://www.onehealthdrugs.com/file/Home/visual-composer-foto/915/Report-COST-STSM-CA21111-OneHealthdrugsAndreLopes.pdf). **André Manuel Gomes Lopes. Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Germany, 29/4-28/7/2026.** The main goal of the STSM was to profile the 352 compound library from the grantee's research group to identify and confirm high-quality candidates for the next step in his PhD which is the in vivo assays. This work complemented and aligned perfectly with his PhD and the OneHealthDrugs principals as it reduced animal testing and only allow the best and safer compounds to advance to the next stage of pre-clinical drug development.

***In-vitro* and *in-silico* analysis of neglected infectious disease compounds from an ADMET and ecotoxicology perspective** (https://www.onehealthdrugs.com/stsm/in-vitro-and-in-silico-analysis-of-neglected-infectious-disease-compounds-from-an-admet-and-ecotoxicology-perspective/). **Lorenzo Raffellini. Fraunhofer ITMP – Discovery Research ScreeningPort, Germany, 13/01-12/07/2025.** This STSM was built on an ongoing collaboration between the applicant's institution, where various compound series have been designed, and Fraunhofer ITMP, where he conducted *in vitro* and *in silico* profiling of novel compounds and extracts. The goal was to identify safe, effective candidates with low off-target activity.

Revealing the Mechanism of action and the toxicity of the innovative antileishmanial agent H80, leveraging MS omics tools combined with ADME/Tox chemoinformatics (https://www.onehealthdrugs.com/file/Home/visual-composer-foto/735/Report-COST-STSM-CA2111-oneHealthDrugsLorenzoTagliazucchi.pdf). **Lorenzo Tagliazucchi. National Hellenic Research Foundation (NHRF), Greece, 02/04-14/06/2024.** The aim of this STSM was the characterization of *L. infantum* promastigotes metabolomic response to H80 in comparison with miltefosine, and its integration with MS Proteomics results to obtain a multi-omics biochemical asset leading to the evaluation of metabolome modulation.

Ecotoxicological evaluation of a novel anti-trypanosomal compound (https://www.onehealthdrugs.com/stsm/ecotoxicological-evaluation-of-a-novel-anti-trypanosomal-compound/). **Kayhan Ilbeigi. iES Landau, Institute for Environmental Sciences, RPTU Kaiserslautern-Landau, Germany, 31/7-31/8/2023.** Being patented as promising drug candidates for the treatment of late-stage sleeping sickness and animal African trypanosomiasis, two nucleoside analogues (FH7429-D & FH15967) were evaluated for ecotoxicity. The STSM aimed to conduct ecotoxicological tests on these two compounds using *Daphnia magna* and green algae (*Desmodesmus subspicatus*) as test organisms.

ADMET studies on novel thiazolidinone derivatives with pr omising in vitro anti-Leishmanial activity (https://www.onehealthdrugs.com/stsm/admet-studies-on-novel-thiazolidinone-derivatives-with-promising-in-vitro-anti-leishmanial-activity/). **Sara Luelmo Moya, Institute of Chemical Biology at the National Hellenic Research Foundation (NHRF), Greece, 2023.** The goals of this STSM proposal were to perform *in vitro* ADMET and pharmacokinetic studies (PK) on selected thiazolidinone derivatives. Five derivatives will be evaluated for microsomal stability and CYP enzyme inhibition to select the most appropriate for SNAP-PK evaluation. This STSM also promoted the career development and scientific upbringing of the applicant through the contact with different aspects of preclinical development associated to *in vitro* ADMET experiments. This included the possibility for hands-on application of new techniques and analytical methods and the use of state-of-the-art instrumentation [UPLC-MSn Orbitrap Velos mass spectrometer (Thermo Scientific) and Lionheart FX (BioTek) plate reader.]

Sustainable biocatalytic derivatization of antiparasitic natural lipids and cashew nut-shell liquid (CNSL) derivatives using unspecific peroxygenase (UPOs) enzymes (https://www.onehealthdrugs.com/file/Home/visual-composer-foto/647/SummarywebsiteCA21111BiancaMartinengo.pdf). **Bianca Martinengo. University College London (UCL), United Kingdom, 2023.** The goal of this STSM was the derivatization of lipids, CNSL derivatives, and drug building blocks

exploiting UPOs enzymes, with the aim of identifying and synthesising compounds with potential improved antiparasitic activity.

Scientific impact

- **Integrated environmental assessment into drug discovery** by connecting chemical design, computational prediction, environmental fate, ecotoxicology and risk assessment within a single framework.
- **Advanced the assessment beyond the parent pharmaceutical** by systematically incorporating metabolites and environmental degradation products, including their persistence, mobility, biological activity and potential toxicity.
- **Established a tiered and resource-efficient testing strategy**, progressing from in silico screening to environmental fate studies, targeted ecotoxicology, mechanistic assessment and integrated environmental risk characterisation.
- **Strengthened mechanistic ecotoxicology** through the integration of biomarkers, receptor-based assays, omics technologies and Adverse Outcome Pathways (AOPs), enabling links between molecular initiating events and adverse ecological outcomes.
- **Established the scientific basis for sustainable-by-design drug development**, enabling environmental findings to feed back into compound prioritisation, medicinal chemistry, candidate selection, redesign and mitigation.

Overall impact

The work shifts pharmaceutical environmental assessment from a late-stage hazard evaluation towards a proactive, integrated and predictive component of drug discovery, supporting the development of effective antiparasitic medicines with reduced environmental impact.

The long-term benefits

1. Environmentally informed drug discovery
Environmental properties will become an integral criterion in drug design, lead prioritisation and candidate selection, rather than being assessed only at late stages of development.

2. Safer and more sustainable pharmaceutical candidates
The framework will support the identification, mitigation or redesign of compounds with undesirable environmental profiles, contributing to the development of effective antiparasitic medicines with lower environmental impact.

3. Improved prediction and prevention of environmental risks
Integration of computational prediction, environmental fate, exposure assessment and ecotoxicology will enable earlier identification of environmental liabilities and more efficient prevention of environmental risks.

4. Better understanding of transformation products
Systematic consideration of metabolites and degradation products will improve understanding of the complete environmental life cycle of pharmaceuticals and help identify persistent, bioactive or potentially more hazardous transformation products.

5. Standardised and transferable assessment approaches
The proposed minimum dataset, tiered testing strategy, technical workflows and decision frameworks provide a basis for harmonising environmental assessment across compounds, laboratories and future drug-development programmes.

6. Stronger predictive and mechanistic science
The integration of biomarkers, receptor-based assays, omics and AOPs will strengthen mechanistic understanding and support the development of predictive approaches for environmental effects.

7. Long-term cross-disciplinary collaboration
The framework creates a durable interface between medicinal chemistry, computational science, pharmacology, ecotoxicology and environmental science.

8. Contribution to the One Health concept
In the long term, the framework will support a better balance between **therapeutic efficacy, human health, animal health and environmental protection**, strengthening the practical implementation of the One Health approach.

Long-term vision

From environmental assessment of existing drug candidates → to environmentally informed, predictive and sustainable-by-design drug discovery.
The ultimate benefit is a **circular drug-development model** in which environmental evidence continuously feeds back into compound design, candidate optimisation, risk management and future drug development.

Innovation

1. Environmental assessment embedded in drug discovery
Environmental considerations are introduced **from the early stages of drug design and lead selection**, rather than being treated primarily as a late-stage regulatory requirement.
2. Assessment of the complete chemical life cycle
The framework moves beyond assessment of the parent pharmaceutical by systematically considering **metabolites and environmental degradation/transformation products** and their potentially different environmental properties and effects.
3. A tiered, adaptive assessment strategy
A **Tier 0–4 framework** progressively combines computational screening, environmental fate assessment, targeted ecotoxicology, mechanistic studies and integrated risk assessment, allowing scientific effort to be focused where evidence indicates the greatest need.
4. Integration of prediction and experimentation
Computational predictions are used to **prioritise experimental testing**, while experimental results can validate and improve predictive models, creating an iterative evidence-generation process.
5. Mechanistic ecotoxicology through omics and AOPs
The framework combines **biomarkers, receptor-based assays, transcriptomics, proteomics, metabolomics and Adverse Outcome Pathways (AOPs)** to connect molecular initiating events with biological and ecological outcomes.
6. Sustainable-by-design feedback loop
Environmental assessment is transformed from a **"pass/fail" endpoint into a design criterion**. Environmental evidence can trigger medicinal-chemistry optimisation, candidate prioritisation, structural redesign, mitigation or selection of alternative compounds.

The key innovation is the transformation of environmental assessment from a late-stage risk-evaluation step into an integrated, predictive and iterative component of pharmaceutical discovery, enabling environmental evidence to actively shape the design of safer and more sustainable antiparasitic candidates.

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