Deliverable 12

Report on integration of ecotox studies from WG1–WG3 and perspective for benefits upon such integration (M42)

Challenges 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)

Objective 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 behaviours (e.g. molecular and chemioinformatic properties, metabolic and chemical degradation, ADME-tox properties of metabolites) to improve the properties of the antiparasitic drugs. Actions: Increase the number of compounds to screen in a coordinated approach (from virtual or phenotypic approaches). Coordination of the compounds' libraries available and usable for screening and repurposing studies by the participants. The compounds libraries that are IP free (with no intellectual protection), discovered previously or/and during the 4 years of the Action, will be made available to all participants. Compounds degradation prediction. Collection of the information in an open access database repository dedicated to OneHealthdrug, such as FAIRDOM database (FAIRDOM is open-source database52). KPI: the Action will adopt 3 metrics to measure objective 1.1 activities to be updated, at least every 6 months 1.2 Number of compounds identified belonging to different libraries >10000. 1.3 Number of in silico studies including metabolic (enzyme assisted) and chemical degradation, antiparasitic drug R&D process, from early compound discovery and prioritisation through medicinal chemistry, biological validation and experimental assessment, towards environmentally informed decision-making and practical recommendations.

Working group of reference:

WG4. Integration of R&D process-environmental studies for the translation in informed white paper. (Challenge 4)

Objectives: Coordination of the R&D programs innovative strategies and compliance with the overall environmental impact to provide a sharable guideline-like document. This may inform the compounds probability of exposure, an information derived from a more detailed understanding on the substances environmental fate. The validation against the ecological interpretation of selected indicators (see below) is important to properly inform drug designer and managers of environmental risks compared to societal benefits.

T4.1 Identify the most relevant ecotox aspects emerged from WG1-WG3 activities, identify the life cycle principles included in the whole discovery & development design for the responsible pharmaceutical use and disposal, improved environmental monitoring and risk assessment of the drugs (D4.1).

Deliverable description.

Year 1 – 2023: establishing the environmental dimension

During 2023, the Action established the conceptual basis for integrating environmental considerations into drug discovery and development. The activities explicitly addressed environmental impact of pharmaceuticals, ecotoxicology in drug-product development, environmental impact assessment, biomarkers and ecotoxicological screening. These activities were important because they framed environmental effects as a component of the One Health problem rather than as a separate downstream issue.

The 2023 Training School on *in-vitro* ADME-Tox profiling while maintaining low environmental impact and the STSM devoted to ecotoxicological evaluation of a novel anti-trypanosomal compound provided practical examples of connecting conventional drug-development activities with environmental considerations.

Year 2 – 2024: expanding the methodological framework

In 2024, the environmental dimension was broadened considerably. The Action connected ecotoxicology with green chemistry, alternative experimental systems, omics, formulation, toxicity and ecotoxicity, and adverse outcome pathways. This was an important transition because it moved the discussion from the general recognition of environmental risk towards a broader methodological framework for understanding, predicting and reducing environmental effects.

Particularly relevant were activities addressing green chemistry and innovative drug delivery, environmentally friendly alternatives to classical animal models, omics technologies in ecotoxicology, formulation approaches aimed at reducing dose and environmental impact, and toxicity/ecotoxicity of targets and off-targets. The AOP workshop further contributed a mechanistic framework for connecting molecular initiating events and subsequent biological outcomes.

Year 3 – 2025: moving towards predictive and experimental integration

Year 3 represents a significant step towards operationalising environmental considerations. Activities increasingly addressed biodegradability, ecotoxicity and bioaccumulation prediction, together with the relationship between ADMETox and ecotoxicology. Training and STSM activities provided practical exposure to *in-silico* and *in-vitro* environmental assessment, while computational and chemoinformatics activities created opportunities to introduce environmental properties into early-stage screening and prioritisation.

The importance of this stage is that prediction can reduce the need to wait for late-stage environmental testing. If sufficiently validated, computational approaches can be used to identify compounds requiring closer assessment, while experimental ecotoxicology can be focused on candidates and endpoints that are most informative for decision-making.

Year 4 – 2026: from assessment towards environmentally informed drug discovery

Year 4 is particularly important for D13 because the environmental dimension becomes more closely connected to practical drug-discovery decisions. Activities addressed the integration of green and greener approaches into medicinal chemistry, *in-silico* and *in-vitro* biodegradability assessment, prioritisation of environmentally friendly chemotypes, practical ecotoxicology training and stakeholder-oriented recommendations.

A particularly illustrative development is the OHD:LUB virtual-screening workflow and Green Drug Score. The activity demonstrates how machine-learning-based ecotoxicity information can be incorporated into the filtering of virtual-screening hits, thereby moving environmental considerations towards the front end of compound prioritisation rather than leaving them exclusively to later-stage assessment.

Year 4 also strengthened the translation dimension. The Research to Recommendation activity connected environmental-impact evidence with stakeholder discussion, while the final Forward Look activities provided an opportunity to consolidate the scientific lessons of the Action and identify future directions.

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.

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.

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.

Interested stakeholders

- Experts in medicinal chemistry, parasitology, and environmental toxicology who focus on drug discovery.
- Computational chemists and biologists involved in *in silico* prediction modeling.
- Organizations seeking innovative antiparasitic compounds for drug development pipelines.
- Stakeholders in pharmaceutical R&D emphasizing environmentally sustainable practices.
- Agencies interested in setting standards and policies for sustainable drug development with low environmental impact. Researchers participating in “OneHealthdrugs” initiatives or similar global programs aiming at interdisciplinary solutions for health challenges.

Stakeholder meetings

From Research to Recommendation for environmental impact of drugs: Advancing One Health Drugs through Science, Policy and Industry (https://www.onehealthdrugs.com/events/scientific-meeting/meeting-2026/stakholder-meeting-from-research-to-recommendation-for-environmental-impact-of-drugs-advancing-one-health-drugs-through-science-policy-and-industry/), 6/3/2026, Brussels, Belgium. The meeting focused on translating the scientific outcomes of the COST Action OneHealthDrugs into concrete regulatory and policy recommendations aimed at reducing the environmental impact of antiparasitic drugs. Emphasis was placed on integrating ecotoxicity assessment into the early stages of drug development, strengthening environmental risk assessment and regulatory frameworks, and promoting innovative experimental and *in silico* approaches. The participants also agreed on the structure, responsibilities, and timeline for the development of the Position Paper and subsequent Policy Brief, with contributions from scientific, regulatory, and industry stakeholders.

Integrating ecotoxcity in early-stage drug development (https://www.onehealthdrugs.com/events/scientific-meeting/next-meeting/stakeholder-meeting-integrating-ecotoxcity-in-early-stage-drug-development/), 7/7/2025, Brussels, Belgium. The 1st meeting joined OneHealthdrugs COST Action members, Pharma company and regulatory experts, United Nations representatives and environmental science experts.

Scientific impact

1. INTEGRATION OF KNOWLEDGE
WG1 – discovery & prioritisation
WG2 – chemistry & development
WG3 – biological/ecotoxicological evidence
WG4 – integration & translation
→ Scientific significance: environmental considerations connected with the complete antiparasitic drug R&D pathway.

2. ADVANCEMENT OF SCIENTIFIC METHODS
Ecotoxicity • bioaccumulation • biodegradability • biomarkers • receptor-based assays • omics • AOPs • alternative models
→ Scientific significance: broader methodological toolbox for understanding, predicting and assessing environmental effects.

3. PREDICTIVE + EXPERIMENTAL INTEGRATION
In-silico prediction + *in-vitro*/experimental assessment + ADMETox
→ Scientific significance: environmental properties can be considered earlier and experimentally validated where necessary.

4. NEW SCIENTIFIC KNOWLEDGE
Biodegradation • environmental fate • metabolites/degradation products • ecotoxicological endpoints • mechanistic effects • computational approaches
→ Scientific significance: improved understanding of environmental consequences of antiparasitic pharmaceuticals.

5. ENVIRONMENTALLY INFORMED DRUG DISCOVERY
Green chemistry • environmentally friendly chemotypes • compound prioritisation • Green Drug Score
→ Scientific significance: environmental properties become an additional consideration in hit/lead selection and optimisation rather than only a downstream assessment.

6. TRANSLATION AND LONG-TERM SCIENTIFIC VALUE
Training Schools • STSMs • publications • stakeholder activities • recommendations • guideline-like framework
→ Scientific significance: creation of a transferable scientific basis for environmentally responsible One Health drug development.

FROM ENVIRONMENTAL ASSESSMENT AS A DOWNSTREAM ACTIVITY → TOWARDS ENVIRONMENTALLY INFORMED DRUG DISCOVERY AND DEVELOPMENT

The long-term benefits

1. SUSTAINABLE DRUG DISCOVERY
Environmental considerations become a lasting component of antiparasitic drug discovery and development.

2. ENVIRONMENTALLY INFORMED PRIORITISATION
Environmental properties can be incorporated into future hit/lead selection and optimisation.

3. REUSABLE SCIENTIFIC TOOLBOX
Computational models, experimental approaches, biomarkers, omics and AOP-based methods provide a basis for continued research.

4. HARMONISED ASSESSMENT
Common descriptors, reporting practices and tiered assessment can facilitate more consistent environmental evaluation.
5. KNOWLEDGE & CAPACITY
Training, STSMs, workshops, publications and networking strengthen a multidisciplinary community able to continue this research beyond the Action.
6. TRANSLATION INTO GUIDANCE
Accumulated evidence can support practical recommendations for medicinal chemists, computational scientists, ecotoxicologists, developers and risk managers.

From a COST Action–based research network → towards a lasting framework for environmentally responsible One Health drug development.

Innovation

1. ENVIRONMENTAL CRITERIA IN DRUG DISCOVERY
Moving environmental properties from downstream assessment towards early hit/lead prioritisation.

2. INTEGRATION OF PREDICTIVE AND EXPERIMENTAL APPROACHES
Combining *in-silico* prediction with targeted experimental ecotoxicology, biodegradability and bioaccumulation assessment.

3. GREENER MEDICINAL CHEMISTRY
Introducing environmental considerations into chemical optimisation, synthesis and the selection of environmentally friendly chemotypes.

4. MULTI-METHOD ECOTOXICOLOGY
Connecting alternative models, biomarkers, receptor-based assays, omics and AOPs for mechanistic environmental assessment.

5. COMPUTATIONAL ENVIRONMENTAL FILTERING
OHD:LUB / **Green Drug Score** illustrates how machine-learning-based ecotoxicity information can be incorporated into virtual-screening hit filtering and compound prioritisation.

INNOVATION: FROM CONVENTIONAL DRUG DISCOVERY TO ENVIRONMENTALLY INFORMED DRUG DESIGN

Integrating environmental prediction, experimental evidence and greener chemistry into the drug-discovery process enables environmental properties to become an active criterion for compound prioritisation and optimisation.