Deliverable 19

Report on compound degradability in vitro (M42)

Challenge of reference:

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.

Challenge 3. Not enough control and informed procedures are available to link the environmental impact to drug production and use. Specific guidelines do not exist to address the problem during the whole process from conception to manufacturing and use. Concepts and strategic support in a guideline/white paper format should be given to the stakeholder in the field for a standard approach to develop safer drugs for humans and animals.

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 database).

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.*

Objective 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.

Actions: Expertise the different sources of compounds (natural source, synthetic chemistry, organic waste matter). Biological evaluation on the target and profile of the compounds in cellular assays that integrate the activities necessary for the reduction/prevention of the drugs impact on the environment. Coordinate ecotoxicology studies on selected models. HTS/MPS screening by evaluating natural source, compounds libraries, and innovative sources such as organic

material of the human industrial activities. This includes hemp extraction residual waste, exhausted agricultural material, extraction from frass of insects and insects themselves, other similar waste products. Green chemistry principles approach for the compounds production, such as microwave extractions, flux chemistry. Use of predictive tools for reaction optimization and for synthesis implementation. Ecotoxicology of drugs and degradation prediction, analysis with innovative methods and analytical tools.

KPI: *the Action will adopt 3 metrics to measure objective 3 to be reviewed once a year. 3.1 Number of hits identified from the different sources compared to the compounds' library screened (many thousands available from different sources). 3.2 Number of projects developing research with organic waste material 3.3 Number of new projects planned within the One Health concept.*

Working group of reference:

WG1. Compound libraries coordination and integration of compound design.
T1.4 Compounds biodegradability pattern prediction. This can be performed using in silico tool that can provide insight into the chemical degradation of organic compounds under various environmental conditions.

WG2. Integration of early phase studies and low environmental impact actions.
T2.3 HTS screening of library from WG1 and T2.2 to evaluate ADMETox properties, biological data from assays panels. Compounds metabolic degradation analysis. All data are included in FAIRDOM database. Connection with the international database CDD Vault50 will be established.

Deliverable description (about 100 words)
Current antiparasitic drugs are typically optimised for human/animal efficacy, pharmacokinetics and safety, while their environmental fate is assessed only at a late stage, close to marketing authorisation, when redesign is no longer feasible. Integration at the early stages of drug discovery the assessement of environmental impact of putative drugs such as persistence, biodegradability, bioaccumulation and metabolic pathways with ecotoxicological liabilities will allow for derisking the drug discovery process not only with respect to efficacy and toxicity to humans but also for the environment as well.

Environmental impact depends strongly on what happens to pharmaceuticals after release. Early prediction of biodegradation, biotransformation and environmental fate would significantly improve compound prioritisation. Tools such as BIOWIN, OPERA, VEGA, BioTransformer and EnviPath already support biodegradation prediction and transformation pathway analysis, and medium-throughput biodegradability assays (e.g. activated sludge microplate formats) are increasingly available. The AI/ML-based system G.AI.A (gaiatox.eu) further advances the field by combining parent-compound hazard assessment with metabolite prediction and bioaccumulation estimation, offering improved accuracy for acute toxicity and bioconcentration predictions. Finally the Green Drug Score (GDS) developed by OHD prioritize the lowest ecotox compounds from virtual screening studies.

D15 reports on the Action's progress in moving biodegradability assessment upstream in the drug discovery pipeline, combining (i) in silico prediction of ready biodegradability (e.g. BIOWIN models, QSAR/machine-learning tools) with (ii) in vitro/experimental biodegradability and ecotoxicity testing, in line with OECD guidance and with the "green-by-design" and "benign-by-design" principles promoted by the Action. This work is jointly coordinated by WG1 (compound/database resources), WG2 (early-phase in vitro compound studies), and HG7 (Drug Chemistry advancements in biodegradability including prediction).

Description of what we have done:

TRAINING SCHOOLS

"Crash course in ecotoxicology: From concepts to practice" 27 May – 29 May 2026 University of Namur, Namur, Belgium (T1.4 & T2.3) (https://www.onehealthdrugs.com/events/training-schools/training-school-crash-course-in-ecotoxicology-from-concepts-to-practice/)

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.

"In silico prediction method for ecotoxicity and bioaccumulation" 19 March –21 March 2025 Cloudpharm P.C., Cana Laboratories, Athens, Greece (T1.4) (https://www.onehealthdrugs.com/events/training-schools/5th-ohd-training-school-in-silico-prediction-method-for-ecotoxicity-and-bioaccumulation/)

This Training School introduced early-career researchers, PhD students and postdoctoral fellows to environmental science and computational toxicology. It provided a comprehensive understanding of 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 were acquainted with 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.

"MedChem and structural biology: tools and strategies for hit and lead optimization in the One Health perspective" 27-29/09/2023, **Siena, Italy. (T1.4)** (https://www.onehealthdrugs.com/events/training-schools/medchem-and-structural-biology/)

During this training school the importance of computational methods and tools for chemical safety and sustainability assessment, regulatory compliance, Read Across, and the applicability of in silico tools for predicting toxicity were discussed. Practical sessions using VEGA software provided hands-on experience, enabling attendees to assess chemical compound characteristics and toxicities. The event fostered networking and collaboration opportunities among participants. Overall, the significance of sustainable and innovative strategies in advancing drug development and addressing infectious diseases has been critically highlighted.

"Drug discovery against parasitic vector borne diseases in-vitro assays development and screening in drug discovery". 8-10/5/2023, Hamburg, Germany. **(T2.3)** (https://www.onehealthdrugs.com/events/training-schools/fraunhofer-itmp-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

Workshops

"Success stories and challenges in OneHealth drug discovery for VBPD" Online event, 18/5/2026. (T1.4 & T2.3) (https://www.onehealthdrugs.com/events/scientific-meeting/meeting-2026/online-workshop-success-stories-and-challenges-in-one-health-drug-discovery-for-vbds-from-18-05-2026-at-10-00-to-18-05-2026-at-13-00/)

This cross-generational workshop brought WG1–WG4 senior and early-career members together to share success stories and challenges across the Action. Of particular relevance to WG1/WG2 and to the Action's sustainability agenda were: a computational investigation of xanthine-based/PTR1 inhibitors moving from screening hit to optimised analogues (Daniele Aiello, University of Modena and Reggio Emilia); an overview of the OHD Training School programme across 7 locations and >100 researchers trained, including biodegradability/ecotoxicity-related modules (Sheraz Gul, Fraunhofer Institute); and biocatalytic oxidative systems for sustainable pharmaceutical synthesis from cashew-nut-shell-liquid food waste, integrating circular-economy principles into drug discovery (Bianca Martinengo, University of Bologna, STSM at University College London). The workshop is reported here as evidence of the broader cross-WG/HG networking and capacity-building context in which the Action's biodegradability and sustainability work (WG1, WG2, HG6, HG7) is embedded.

"Virtual screening of OHD Compound libraries against parasitic targets" Online 13/05/2026 (T1.4) (https://www.onehealthdrugs.com/events/scientific-meeting/meeting-2026/virtual-screening-of-ohd-compound-libraries-against-parasitic-targets/)

This workshop was dedicated to the **"OHD:LUB project - docking the OHD compounds against protein targets to select potential low environmental impact compounds".** The three phases of the project were presented and explained.
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. With 21 targets already docked, the team uses 3D interaction fingerprints to refine the most promising hits.

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." While labs prepare protein purification, Sheraz Gul (Fraunhofer) provides HTS and ADMET testing infrastructure. STSM funding is prioritized for young researchers to travel and conduct the final physical assays.

"In silico and in vitro approaches to assess biodegradability and prioritize environmentally friendly chemotypes of synthetic and natural origin. Online event 27/3/2026. (T1.4 & T2.3) (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/)

The workshop directly addressed D15, bridging medicinal chemistry and environmental science. Key contributions included: the Green Drug Score, a multi-parametric scoring function balancing ADME, drug-likeness and environmental toxicity, presented by Daniele Aiello (University of Modena), which re-ranked Trypanosomiasis and Leishmaniasis compound sets by around 30% once environmental metrics were included; a critical appraisal of standard OECD ready-biodegradability tests (301B/D) and a proposal for multi-sensor (CO2/O2/biomass) and microbial-fingerprint approaches, by Prof. Gerald Thouand (University of Nantes); the role of chemical bioavailability and "aging" in soil in limiting biodegradation and (eco)toxicity, by Jose Julio Ortega Calvo (CSIC, Seville); in silico annotation using virtual screening and Knowledge Graphs linking ChEMBL, PubChem and EcoTox data, by Regan Karki (Fraunhofer ITMP); low-cost bioluminescence-based bioassay kits (e.g. Biotox/Microtox) for experimental toxicity screening, by Sheraz Gul

(Fraunhofer ITMP), who offered to screen Action compounds; and the GAIA platform for prediction of human/microbial drug metabolites and of their specific ecotoxicity and bioaccumulation, by Eleni Chontzopoulou (Cloudpharm). The workshop highlighted the need to define an “isokinetic window” in which candidate molecules remain metabolically stable in patients but are amenable to microbial degradation once released into the environment, and agreed to integrate these tools into the Action's compound database.

OneHealthdrugs Workshop on "Exploring cutting-edge chemoinformatics and AI in chemistry" Erasmus Mundus Summer School on Chemoinformatics” 3 - 4 July 2025 University of Ljubljana, Ljubljana, Slovenia. (T1.4) (https://www.onehealthdrugs.com/events/scientific-meeting/next-meeting/erasmus-mundus-summer-school-on-chemoinformatics-and-onehealthdrugs-workshop/)

The Erasmus Mundus Summer School on Chemoinformatics (https://molekule.net/css2025/#home) is a prestigious international event supported by the Erasmus Mundus master's degree “Chemoinformatics +: Artificial Intelligence in Chemistry” (https://masterchemoinfo.u-strasbg.fr/). The OneHealthdrugs COST Action co-organized the School with a session on drugs development ecotoxicity and a Workshop on Friday 4 July 2025, closing the event, which complements the Summer School. The scientific program included sessions on Artificial Intelligence in Chemistry, Big Data Analysis and Visualization, Chemical Reactions Mining, New Trends in QSAR Modelling, Computational Ecotoxicology, Materials Informatics and In Silico Pharmacology.

“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)” In presence event. 11-13/6/2025, Nantes, France. (T1.4 & T2.3) (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/)

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.

"Green and bioinformatic approaches including biodegradability prediction in antiparasitic drug discovery " Hybrid event. 18/3/2025. (T1.4 & T2.3) (https://www.onehealthdrugs.com/events/scientific-meeting/next-meeting/green-and-bioinformatic-approaches-including-biodegradability-prediction-in-antiparasitic-drug-discovery/)

This workshop presented innovative molecular modeling and experimental tools in the fields of biodegradability and antiparasitic drug discovery. The concepts presented facilitated a smart approach to addressing environmental toxicity induced by anti-infective drugs in the context of antiparasitic diseases for human and veterinary medicine, and drug discovery. Sessions covered: the environmental impact of pharmaceuticals and their metabolites; machine-learning predictive models for ecotoxicity based on LC50 and bioconcentration factors; the Isalos zero-code machine-learning platform for cheminformatics; a cross-industry perspective on API biodegradation (Boehringer Ingelheim Vetmedica); emerging contaminants and antimicrobial resistance in the environment; and an integrated in silico/experimental approach to scaffold optimisation for leishmaniasis. Young researchers (Daniele Aiello, Ludovica Marotta) presented

structural/ecotoxicological compound prioritisation and a Design-of-Experiment approach for sustainable chalcone synthesis. The workshop concluded that further steps are needed to expand computational methodologies, acquire new experimental data, and reinforce bioinformatic approaches to biodegradability prediction and assessment.

"Novel leads and drugs for vector borne diseases: Targets and off targets (toxicity and ecotoxicity) and mechanism of action" In presence event, 19-20/9/2024, Athens, Greece. (T1.4 & T2.3) (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/)

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" Online event, 15/3/2024. (T1.4) (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/)

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.

Progress presentation

"Biodegradability in the drug discovery pipeline"– Sandra Gemma (HG7 Leader), 15/5/2026. Thematic Workshop 4 [WG5,WG5, WG6, HG4, HG6, HG7] COST connection against drugs environmental impacts (T1.4 & T2.3)
Progress update on HG7 activity, illustrating the shift from the traditional drug-discovery workflow (environmental assessment only at the end of the pipeline) to a sustainable approach with biodegradability prediction and assessment embedded from hit-to-lead/lead-optimisation stages onward.
A worked case study on oxyprenyl-chalcone antibacterial hits (Marotta, Giammarino, Gemma et al., RSC Medicinal Chemistry, 2026) was presented, applying the BIOWIN suite (BIOWIN1–6) and the ReadyBiodegradability criteria of the BIOWIN software (criterion A) and of Pavan & Worth (criterion B) to rank synthesised analogues and reference compounds (including amoxicillin and clarithromycin as benchmarks) by predicted biodegradation half-life, from "biodegrades fast" to "recalcitrant". The exercise demonstrated how in silico ready-biodegradability screening can be used routinely alongside efficacy, ADME and safety criteria to prioritise more sustainable chemotypes before committing to experimental in vitro testing.

OneHealthdrugs Chemoteca (T1.4) (https://www.onehealthdrugs.com/working-area/jobs/onehealthdrugs-chemoteca-freely-accessible-database-to-profile-your-compounds-for-adme-toc-and-ecotox-profile/)

A freely accessible database to profile your compounds for ADME-TOX and EcoTOX profile

The database is a continuation of the Net4Science (COST Action project) database for the chemocataloguing of chemical entities. To allow access via the Internet, a customised and agreed graphical interface was developed for the needs of the objective of One Health*drugs*.
The interface allows the authentication of an unlimited number of users, their registration by administrators identified by the client and enables the search of chemical entities based on molecular descriptors (CNS availability, Lipinski rule of 5, the Pan Assay Interference Compounds(PAINS), chirality, molecular weight, logP, logBB, number of hydrogen bond donor/acceptor groups, total polar surface area, substructure, functional groups, chemical bond types, atom types) calculated by the service's internal software, ADME-Tox or by the eToxvalues, if specified in the compound entry phase.
If specified by the system administrators, the interface can enable all or some users to enter new chemical entities themselves. At this time, the database is populated with the first chemical entities provided by Unimore Lab (Costi MP) and will be implemented as new compounds become available. The entire software was developed using open source tools and was installed on the Catanzaro University server. The service is available, as of 1 August 2024, at the urlhttp://www.cclab.unicz.it/ohd . It is continuosly updated.
By Daniele Aiello, Francesco Ortuso and Stefano Alcaro.

OHD:LUB project - docking the OHD compounds against protein targets to select potential low environmental impact compounds. (T1.4) (https://www.onehealthdrugs.com/working-area/jobs/ohd-lub-project-docking-the-ohd-compounds-against-protein-targets-to-select-potential-low-environmental-impact-compounds/)

More than 36,000 compounds were screened against the 21 selected antiparasitic targets (**OHD1 PROJECT: TARGETS COLLECTION**). Hits emerged that that were filtered uing ML-ecotoxicity modelsto obtain a Green Drug Score for each hit thus, selecting those with low predicted environmental footprint.
The results of selected hits will be validated in vitro by collaborating groups withing the OHD Action.
This will create a platform for interested medicinal chemists, structural biologists, parasitologists to collaborate towards the target-based optimisation of the hit compounds enabling the discovery of environmentally bening antiparasitic compounds.

Interactive YRI Learning Session – "Chemoinformatics Approaches to Vector-Borne Parasitic Diseases in a One-Health Context" *24 July 2025, online* **(T1.4)**

The session introduced chemoinformatics tools and their applications in drug discovery, including compound-data analysis, molecular-property assessment, and virtual screening in a One Health context.

Interactive YRI Learning Session – "Green Chemistry Strategies and Sustainable Approaches in Medicinal Chemistry" *25 September 2025, online* **(T1.4 & T2.3)**

The session explored the integration of green chemistry principles into drug discovery, with particular attention to safer chemical design, waste reduction, and environmental sustainability.

Three editions of the Marathon 4-day event of insightful presentations, expert opinions, and invaluable opportunities to connect with fellow researchers and innovators who are passionate about one health, drug discovery and sustainability.**(T1.4 & T2.3)**

2023: https://www.onehealthdrugs.com/events/scientific-meeting/past-meetings-in-2023/onehealthdrugs-marathon/
2024:https://www.onehealthdrugs.com/events/scientific-meeting/past-meetings-in-2024/onehealthdrugs-marathon-on-line-ca21111-non-stop-presentations/
2025:https://www.onehealthdrugs.com/events/scientific-meeting/next-meeting/ohd-marathon-days-2-5-december-2025/

YRI Concerence Grant (T1.4 & T2.3)

Eli Thoré, (University of Namur), Biologists@100 conference, Liverpool 23/03/25 to 27/03/25. "Swimming in medicated waters: Understanding and mitigating the impacts of pharmaceutical pollutants on aquatic wildlife".

STSMs

Kayhan Ilbeigi – 2023 31/7-31/8 2023 [Home Institution: U. Antwerp; Host Institution: IES Landau] (T2.3) (https://www.onehealthdrugs.com/stsm/ecotoxicological-evaluation-of-a-novel-anti-trypanosomal-compound/)
Title: Ecotoxicological evaluation of a novel anti-trypanosomal compound
The STSM included ecotoxicological testing of a highly potent nucleoside analogues using *Daphnia, C. elegans* and algae as test organisms.

Daniele Aiello – 2024-11/1 – 21/2/2024 [Home Insititution U. of Modena and Reggio Emilia; Host Institution University of Chemistry and Technology Prague]. (T1.4 & T2.3) (https://www.onehealthdrugs.com/stsm/computational-approach-for-calpain-inhibitors-discovery-with-potential-antiparasitic-activity-against-leishmania-infantum-from-ms-label-free-proteomic-analysis-to-hits-identification-through-virtual-screening-1/)

Title: Computational approach for calpain inhibitors discovery with potential antiparasitic activity against Leishmania infantum. From MS label-free proteomic analysis to hits identification through virtual screening.
The STSM connected target validation, compound-library assembly and virtual screening. A Leishmania infantum calpain homology model was constructed and validated, then used to screen a database of more than 400,000 ChemDiv and Enamine compounds through HTVS, SP and XP stages, followed by MM-GBSA evaluation. The highest-ranked compounds were cross-docked against human calpain, and ADME properties were assessed for 400 selected compounds. The planned follow-up was the selection of approximately 100 compounds for purchase and biological evaluation.
https://www.onehealthdrugs.com/stsm/computational-approach-for-calpain-inhibitors-discovery-with-potential-antiparasitic-activity-against-leishmania-infantum-from-ms-label-free-proteomic-analysis-to-hits-identification-through-virtual-screening-1/

Lorenzo Raffaelini 13/01/2025 to 12/07/2025 Home Institution: Department of Pharmacy, University of Pisa Host Institution: Fraunhofer ITMP – Discovery Research ScreeningPort (T1.4 & T2.3) (https://www.onehealthdrugs.com/stsm/in-vitro-and-in-silico-analysis-of-neglected-infectious-disease-compounds-from-an-admet-and-ecotoxicology-perspective/)
Title: In-vitro and in-silico analysis of neglected infectious disease compounds from an ADMET and ecotoxicology perspective.
During this STSM the safety and off-target activity of newly synthesized compounds and organic waste-based extracts were assessed. In addition, efforts to develop a HTS-format assay using *Aliivibrio fischeri* (a gram-negative bacterium that lives in symbiosis with many marine species) for in vitro ecotoxicology were pursued.

Kübra İren 17/07/2026 to 30/09/2026 Home Institution: Gebze Technical University Host Institution: University of Siena, Department of Biotechnology, Chemistry and Pharmacy. (T1.4)
Title: Design and synthesis of natural product-inspired flavone analogues as antileishmanial agents: SAR exploration and in silico assessment of environmental biodegradability.
During this ongoing STSM, structure–activity relationship exploration and synthesis of flavone-based antimalarial/antileishmanial hits are being pursued, with chemical diversification focused on the A-ring and C2-linked phenyl B-ring to modulate solubility, lipophilicity and membrane permeability. Candidate derivatives are prioritized before synthesis through a multi-parameter computational workflow combining conventional drug-likeness descriptors with environmental biodegradability prediction (VEGA, BIOWIN models), following the sustainability-oriented strategy previously applied to oxyprenyl chalcones (Marotta, Gemma et al., *RSC Med. Chem.* 2026). Drug-like and environmental-related properties such as aqueous solubility and logP will also be experimentally assessed for relevant compounds.

Interested stakeholders
Experts in medicinal chemistry, parasitology, environmental science 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.

Dissemination activities towards stakeholder engagement and knowledge sharing.

OneHealthDrugs FORWARD LOOK – Final Conference In presence/hybrid event, 10 July 2026, COST Association Premises, Brussels, Belgium. (T1.4 & T2.3) (https://www.onehealthdrugs.com/events/scientific-meeting/meeting-2026/onehealthdrugs-forward-look-final-conference-hybrid-event/)

In this conference YRI achievements, professional-development needs, and opportunities to sustain the scientific and collaborative legacy of OneHealthDrugs beyond the Action were highlighted.

2nd OHD Stakeholders Meeting – “From research to recommendation for environmental impact of drugs: advancing One Health drugs through science, policy, and industry” In presence/hybrid event, 6/3/2026, COST Association Premises, Brussels. (T1.4 & T2.3) (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/)

HG6/HG7-related evidence on environmental burden, scientific legitimacy and regulatory gaps in Environmental Risk Assessment (ERA) fed into Session II (“Computational Approaches in Ecotoxicology & Drug Discovery”) and into the roadmap agreed for the Action's Position Paper and Policy Brief (due September 2026), which include a dedicated pillar on environmental scientific evidence and one on innovation, feasibility and sustainability of predictive ecotoxicology/biodegradability tools.

1st OneHealthDrugs Stakeholder Meeting – "Integrating Ecotoxicity into Early-Stage Drug Development" 7th July 2025, COST Association Premises, Brussels, Belgium. (T1.4 & T2.3) (https://www.onehealthdrugs.com/events/scientific-meeting/next-meeting/stakeholder-meeting-integrating-ecotoxcity-in-early-stage-drug-development/)
Young researchers Elisa Uliassi and Clara Lima (both OHD Ambassadors) presented their perspective *on "the Early Integration of Ecotoxicity into Drug Discovery for Vector-Borne Parasitic Diseases,"* advocating for early ecotoxicity assessment, green chemistry, predictive models, and intersectoral collaboration.

COST Connect Meeting – "Advancing a Clean and Healthy Environment through Research Collaboration" 17th June 2025, COST Association Premises, Brussels, Belgium. (T1.4 & T2.3)
The young researcher and fellow Ambassador Clara Lima highlighted pharmaceutical pollution and sustainable drug design as key One Health challenges, emphasizing interdisciplinary education, digital tools, and stronger links between research and policy. https://www.cost.eu/cost-events/cost-connect-environment-2025/

Scientific impact (from the MoU)

- The discovery and optimization of high number of antiparasitic hits and lead compounds for H&A use with expected environmental low impact and higher quality profile than before
- improvement of procedures and use of reagents within the green chemistry field to reduce the environmental impact
- the development of biodegradable drug formulations with engineered targeting and engineered conjugates ensuring better in vivo animal efficacy

The long-term benefits (from the MoU)

- Substantial improvements of the biological profile in treating parasitic diseases caused by VB parasitic diseases affecting H&A
- Engagement of RTD platforms active in the field
- Increased funding into antiparasitic drug development integrated with environmental scientists due to the improved multidisciplinary and multi-centre applications resulting from collaborations between
- Participants in the Action and successful activity of contact and networking within this Action.

Innovation

OHD is promoting practical initiatives towards environmentally safer discovery. Integration of BIOWIN/QSAR-based in silico biodegradability prediction with OECD-aligned in vitro ready-biodegradability testing and ecotoxicological model systems, applied from the hit-identification and lead-optimisation stages onward ("benign-by-design" strategy), rather than only at late-stage Environmental Risk Assessment and standardised ecological toxicity tests. Development of composite scoring approaches (Green Drug Score) and metabolite-aware prediction platforms (e.g. GAIA), linking human/microbial biotransformation to downstream ecotoxicity and bioaccumulation. This cross-sectoral approach (WG1, WG2, HG6, HG7) is expected to inform both the Action's compound-prioritisation workflows and the emerging regulatory debate on earlier integration of biodegradability assessment in pharmaceutical development.

KPIs

Number	Description	Comments	% Completion
1.1	Activities to be updated, at least every 6 months	In the context of WG1 operational meetings, core group meetings, management committee meetings and general assemblies the activities related to WP1 were regularly updated.	**100**
1.2	Number of compounds identified belonging to different libraries >10000	The Virtual Chemotheca contained 12,398 compounds as of 3 September 2026.	**100**
1.3	Number of in silico studies including metabolic (enzyme assisted) and chemical degradation.	Development of "Green Drug Score" a complex machine learning algorithm which merges pharmacokinetic (ADMETscore), ecotoxicological (ECOscore) and drug likeness (DLscore) properties (https://doi.org/10.1016/j.jpha.2026.101734) In silico studies and reuse: achieved and extended through the OHD:LUB workflow. STSMs performed by Lorenzo Rafaellini, Kübra İren and Daniele Aiello.	**100**
2.1	Number of hits identified from the different sources compared to the compounds' library screened (many thousands available from different sources).	More than 10,000 compounds identified following screening of the The Virtual Chemotheca containing 12,398.	**100**
2.2	Number of projects developing research with organic waste material	At least 3 projects involve valorisation of cashew nut shell liquid as a source of compounds further derivatised as antiparasitic agents, by the groups of M. L. Bolognesi and E. Uliassi (U. of Bologna) and Prof. Castagnolo and T. Calogeropoulou (National Hellenic Research Foundation).	**100**
2.3	Number of new projects planned within the One Health concept.	Blended Intensive Program (BIP) on Drug Resistance in Cancer and Infectious Diseases (Porto, 15-19 June 2026) https://sigarra.up.pt/ffup/en/CUR_GERAL.CUR_VIEW?pv_ano_lectivo=2025&pv_origem=CUR&pv_tipo_cur_sigla=UFC&pv_curso_id=38522; 13 funded collaborative projects.	**100**

Relevant Publications

1. High throughput Phenotypic Screening and Machine Learning Methods Enabled the Selection of Broad-Spectrum Low-Toxicity Antitrypanosomatidic Agents Pasquale Linciano*, Antonio Quotadamo, Rosaria Luciani, Matteo Santucci, Kimberley M. Zorn, Daniel H. Foil, Thomas R. Lane, Anabela Cordeiro da Silva, Nuno Santarem, Carolina B Moraes, Lucio Freitas-Junior, Ulrike Wittig, Wolfgang Mueller, Michele Tonelli, Stefania Ferrari, Alberto Venturelli, Sheraz Gul, Maria Kuzikov, Bernhard Ellinger,

Jeanette Reinshagen, Sean Ekins*, and Maria Paola Costi* J. Med. Chem. 2023, 66, 22, 15230–15255. https://doi.org/10.1021/acs.jmedchem.3c01322

2. Kayhan Ilbeigi, Carlos Barata, João Barbosa, Michael G. Bertram, Guy Caljon, Maria Paola Costi, Alexandra Kroll, Luigi Margiotta-Casaluci, Eli S.J. Thoré, and Mirco Bundschuh*, Assessing Environmental Risks during the Drug Development Process for Parasitic Vector-Borne Diseases: A Critical Reflection ACS Infect. Dis. (2024) 10 (4): 1026–1033. https://doi.org/10.1021/acsinfecdis.4c00131
3. Brodin, T.*, Bertram, M.G.*, Arnold, K., Boxall, A.B.A., Brooks, B.W., Cerveny, D., Jörg, M., Kidd, K.A., Lertxundi, U., Martin, J.M., May, L.T., McCallum, E.S., Michelangeli, M., Tyler, C.R., Wong, B.B.M., Kümmerer, K.†, Orive, G.† 2024. The urgent need for designing greener drugs. Nat. Sustain. https://doi.org/10.1038/s41893-024-01374-y
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7. Martinengo B, Diamanti E, Uliassi E, Bolognesi ML. Harnessing the 12 Green Chemistry Principles for Sustainable Antiparasitic Drugs: Toward the One Health Approach. ACS Infect Dis. 2024 Jun 14;10(6):1856-1870. doi: 10.1021/acsinfecdis.4c00172.
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9. Baz-Lomba, J.A., van Nuijs, A.L.N., Lenart-Boroń, A., Péterfi, A., de l'Eprevier, A., Löve, A.S.C., Kasprzyk-Hordern, B., Ort, C., Simeoni, E., Heath, E., Pridotkiene, E., Lai, F.Y., Béen, F., Oberacher, H., Bodík, I., Valenčić, I., Slobodnik, J., Strandberg, J., Sheeran, K., Smit-Rigter, L.A., Barron, L.P., Bijlsma, L., Psichoudaki, M., Savvidou, M., Edland-Gryt, M., Helminen, M., Busch, M., Jandl, M., Bertram, M.G., López de Alda, M., Berndt, N., Daglioglu, N., Thomaidis, N., Fabien, L., Chomynova, P., Oertel, R., Castiglioni, S., Mercan, S., Akgür, S.A., Schneider, S., Gunnar, T., ter Laak, T., Thiebault, T., Matias, J.P. 2025. Bridging the gap between research and decision making: a European survey to enhance cooperation in wastewater-based epidemiology (WBE) for illicit drugs. Public Health 241, 158–163.https://doi.org/10.1016/j.puhe.2025.02.009
10. Sustainable Antiparasitic Agents from an Agro-Industrial Waste: Mitochondria-Targeting Cashew Nutshell Liquid-Derived Phosphonium and Ammonium Salts Bianca Martinengo, Cecilia Baldassarri, Kayhan Ilbeigi, Hamed E. Alkhalaf, Aditya Sarode, Ehab Kotb Elmahallawy, Ba Reum Kwon, Amos Sarpong Agyei, Aigerim Abdimanova, Ludmila Ferreira de Almeida Fiuza, Raquel Azevedo, Ketlym da Conceição, Marcos Meuser Batista, Ellyêssa Nascimento Borges, Kleber Santiago Freitas e Silva, Éder Jéferson Souza Cardoso, Natália Cipriano Monteiro, Lais Flavia Nunes Lemes, Luiz Antonio Soares Romeiro, Antonio Alonso, Maria de Nazaré Correia Soeiro, Guy Caljon, Bryan W. Brooks, Harry P. De Koning, and Maria Laura Bolognesi Journal of Medicinal Chemistry 68(18):19438-19462 https.//doi.org/10.1021/acs.jmedchem.5c01617
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