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NEWSLETTER No 2

enviromed

Welcome to our second newsletter!

In this edition, we're diving into groundbreaking initiatives, exciting collaborations, and the latest research driving innovation in environmental science and green pharmaceuticals. Here's a glimpse of what's inside:

• **Pioneering Computational Tools:** Learn about a cutting-edge platform designed to predict the potential toxic effects of drugs on the aquatic environment, offering a novel approach to safeguarding our ecosystems.

• **Fieldwork Insights:** Updates on the environmental monitoring campaigns being conducted in Greece and Italy.

• **Collaborative Advances:** Highlights from the ENVIROMED project's collaborative site visits, setting the ground for successful validation and deployment of our novel monitoring analysers.

• **Key Events:** heads up for the Annual Meeting on Horizon Europe Green Pharmaceuticals Projects in Brussels, Belgium, where global experts will gather to exchange ideas and strategies on Green Pharmaceuticals.

• **Research Spotlight:** We're thrilled to announce the publication of a new research article, showcasing our team's contributions to advancing sustainable pharmaceutical practices.

Dive in and explore what's happening in the ENVIROMED project.

Thank you for being part of our community-we're thrilled to share this journey with you!

Enjoy reading!

Platform predicting the potential toxic effects of drugs on the aquatic environment

Medical science has advanced rapidly, creating drugs that treat diseases and help us live longer, healthier lives. However, these benefits come with a downside: significant amounts of pharmaceutical substances are now found in the environment, especially in water. Human medications get into the environment mainly through wastewater from hospitals, homes, and the pharmaceutical industry, carrying unused and unmetabolised drugs. Veterinary drugs, used for farm animals and pets, enter the environment through animal waste. These drugs often pass through animals unmetabolised and are released through excretion. This waste can then leach into water systems, run off from fields treated with contaminated manure, or come directly from aquaculture. As a result, these pharmaceutical contaminants in the environment can harm ecosystems.

For all these reasons, it is essential to minimise the environmental impact of pharmaceuticals. To this end, our consortium partner Cloudpharm PC is currently developing within ENVIROMED a platform that predicts the potential toxic effects of drugs on the aquatic environment. This platform assesses the potential of pharmaceuticals to accumulate in aquatic organisms by utilizing the Bioconcentration Factor (BCF), a crucial metric for this process. It also evaluates the toxicity of pharmaceuticals to aquatic organisms using the Lethal Concentration 50% (LC50), which is a key metric for this approach. However, the experimental determination of BCF and LC50 are of high experimental cost and requires a large number of vertebrate animals to perform the assays. This platform is essential for addressing these challenges, as it offers a viable way to ethically reduce or replace animal testing and assess the environmental risk

of numerous pharmaceuticals. By leveraging Machine Learning (ML) and Artificial Intelligence (AI) predictive models, these effective tools can help eliminate unsuitable candidates early in the drug discovery process, promoting the development of future compounds with green-by-design principles in mind.

Precisely forecasting the bioconcentration and toxicity potential of both the parent drug and its metabolites is crucial, as these derivatives significantly influence the overall safety profile of pharmaceutical compounds. Pharmaceuticals and their metabolic byproducts are increasingly found in aquatic environments, with extensive data documenting their presence over the past decade. After administration, drugs are excreted either unchanged or as byproducts, known as metabolites, resulting from biochemical reactions in the body. This excretion typically involves a single major metabolite or, more commonly, a mix of multiple metabolites. Most studies to date have focused on the removal efficiency of pharmaceuticals during water treatment by measuring the disappearance of the parent compound, rather than the generation of byproducts. In addition, the European Medicines Agency (EMA) now requires reporting the total concentrations of drugs, including both the parent compound and its metabolites.

Cloudpharm's platform is a novel computational tool, which can predict the potential metabolites of a given compound, offering a comprehensive approach to evaluating the ecotoxicity of pharmaceuticals by assessing both the parent compound and its metabolites according to green chemistry principles. This user-friendly platform will be accessible to medicinal and computational chemists, as well as other scientists in drug discovery. Users can input their chemical designs and receive green toxicology metrics as output. The ultimate goal is to integrate this innovative screening method into the drug discovery process, serving as a regulatory checkpoint in the pharmaceutical industry.

Environmental monitoring campaigns in Greece and Italy

Environmental monitoring campaigns in Greece and Italy, being conducted in the ENVIROMED project by the Athens Water Utility Company (EYDAP), the Mitera Hospital, and the Consiglio Nazionale delle Ricerche (CNR), are focused on assessing environmental pollution caused by pharmaceutical residues in water systems. These activities address the growing concern of pharmaceutical contaminants entering ecosystems and posing risks to both environmental and human health.

Exploring the depths: scuba diver collecting seawater samples in Psytallia

EYDAP, specifically, oversees the monitoring of the Psytallia Wastewater Treatment Plant (WWTP), focusing on detecting pharmaceutical compounds such as diclofenac, carbamazepine, metoprolol, and hydrochlorothiazide in the plant's influent and effluent. This process involves sampling at both the entrance and exit points of the WWTP and conducting detailed chemical analyses to accurately determine the concentration of these substances.

The Mitera Hospital, one of Athens' largest hospitals, plays a key role by collecting wastewater samples from hospital sources. This monitoring activity aims to help better understand how pharmaceutical use within large healthcare facilities contributes to environmental pollution. Detailed chemical analyses of the obtained samples are performed also in this case. The outcomes of the analyses in both case studies not only will support the definition of mitigation measures but will also enable the evaluation of the novel Wastewater Spectroscopic Analyser that is being developed in ENVIROMED by the Ulm University in collaboration with the Cyprus Research & Innovation Centre (CYRIC).

In parallel with the above activities, a marine monitoring campaign is also conducted, aiming to help to better understand the pharmaceuticals' effects in a marine aquatic environment. To this end, samples are collected by EYDAP at multiple locations and depths near the WWTP and the sampling procedures are conducted seasonally to capture variations over time. Besides water samples, marine invertebrate organisms are also collected, and the samples are then shipped to CNR in Naples for in-vivo assessment of the effects of long-term pharmaceuticals' accumulation.

The first seasonal campaign, launched on October 21, 2024, involved synchronised sampling at the Mitera Hospital, the Psytallia WWTP, and the surrounding marine environment. Marine organisms were collected by scuba divers at depths up to 30 meters, where hard substrate fauna is found, and both water and animal samples were transported to CNR for the assessment.

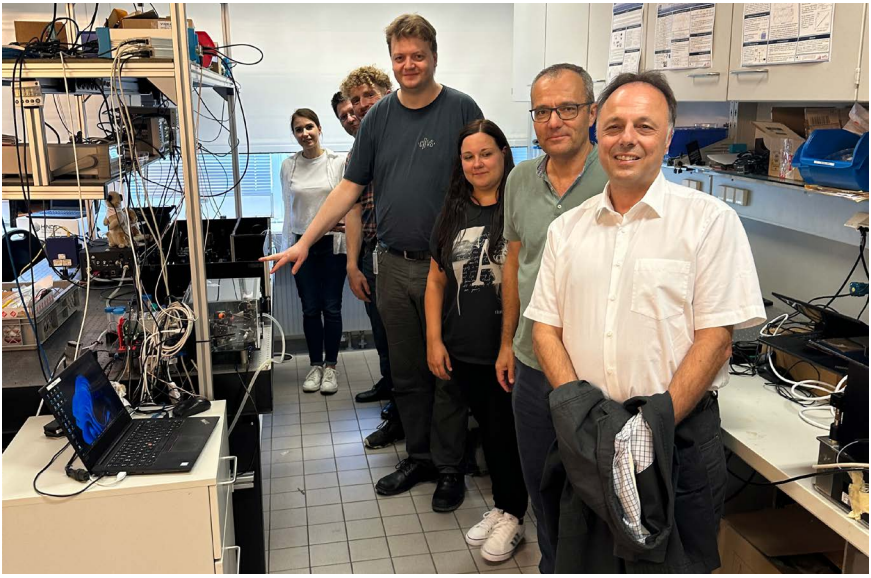
Environmental monitoring campaign in Psytallia: sampling procedures

The ENVIROMED monitoring campaigns are a part of broader efforts to evaluate pharmaceutical pollution's impact on ecosystems and to develop more effective water treatment and monitoring technologies. Through these campaigns, researchers aim to gather crucial data to guide future environmental policies, improve wastewater treatment processes, and protect marine life and human health.

Collaborative Site Visits: Advancing Liquid and Surface Analysis Technologies

Work Package 4 (WP4) of the ENVIROMED project focuses on the creation of customised lasers (by Alpes Lasers) and the design and implementation of three innovative monitoring devices including a Surface Inspection Analyser – SIA (by RECENDT), a Liquid Monitoring Analyser – LMA (by TU Wien - TUW), and a Wastewater Spectroscopic Analyser – WSA (by the Ulm University in collaboration with CYRIC). The new analysers will be validated in laboratory environments (TRL4) by HORIBA and Fraunhofer based on specifications before being deployed in real-world environments at our pilots' sites; specifically, the SIA and LMA will be tested by our pharmaceutical partners Pfizer and Novo Nordisk in WP5, while the WSA will be tested in clinical facilities (Mitera Hospital) and for WWTP monitoring (by EYDAP) in WP7.

In this context, our partners HORIBA, Fraunhofer, Alpes Lasers and Novo Nordisk visited in August 2024 the laboratories of TUW and RECENDT, to gain more insight into the development and status of the monitoring analysers currently being implemented by the latter.



Lab tour at TUW. In the picture (from left to right): Alicja Dabrowska (TUW), Sascha Just (HORIBA), Jack Thomas (Fraunhofer), Leopold Lindenbauer (TUW), Julia Großeheilmann (HORIBA), Bernhard Lendl (TUW), Marcus Rieker (HORIBA).

The first visit took place in the research group of Prof. Bernhard Lendl at TUW. Within the ENVIROMED project, TUW is developing a Liquid Analyser based on photothermal spectroscopy that should allow to measure concentration of pollutants in organic and aqueous solutions down to ppm range. This approach aims to significantly reduce the consumption of rinsing solutions in industrial cleaning processes. Following a research topics introduction of Bernhard Lendl's team an impressive lab tour took place to demonstrate the developed experimental setup for photothermal lens spectroscopy of liquids and interesting discussions were held. Some insights into the photothermal spectroscopy (PTS) were given. PTS's sensor response scales directly in proportion to laser power, making it a very appealing sensing scheme for trace analysis. The various system setups, modes of operation and example measurements were shown and the further procedure for validating the system was discussed.

On the next day, another visit was arranged to RECENDT, which is developing the Surface Inspection Analyser based on stationary polarisation state infrared absorption spectroscopy, as part of the ENVIROMED project. This technology is planned to be used in vessels and pipes using specially designed heads and

Visit at RECENDT. In the picture (from left to right): Markus Brandstetter (RECENDT), Raux Mathieu (Alpes Lasers), Marcus Rieker (HORIBA), David Nielsen (Novo Nordisk), Sascha Just (HORIBA), Julia Großeheilmann (HORIBA), Ivan Zorin (RECENDT), Jack Thomas (Fraunhofer CAP).

should make it possible to detect dried residues especially on metal surfaces. The objective of the meeting at RECENDT was to ensure that all involved partners are aligned and to discuss the status of the sensor for different use cases (e.g. measurements in vessels and pipes) as well as the challenges and future plans (e.g. validation). During the meeting, operation of a laboratory unit was presented for detection of low concentration of Active Pharmaceutical Ingredients (APIs) on stainless steel where all the partners had the chance to test on their own the developed Surface Inspection Analyzer on various samples.

The two meetings facilitated information exchange and partners' alignment and set the ground for defining validation and deployment strategies, ensuring also successful technology transfer between WP4 and WP5. The involved partners are also planning in the next period a visit to the Ulm University that is implementing the Wastewater Spectroscopic Analyser to be deployed in the pilots under WP7.

Annual Meeting on Green Pharmaceuticals: Driving Sustainable Innovation

On **December 10, 2024, ENVIROMED delegates** including the Coordinator RISA Sicherheitsanalysen GmbH and the consortium partners TU Wien, IRES, and Metis Baltic, will participate in the **Annual meeting of the Group of EU Funded Projects on Green Pharmaceuticals**, in Brussels. This event will focus on advancing sustainable practices within the pharmaceutical industry, showcasing five innovative projects funded by **Horizon Europe.**

The meeting will highlight cutting-edge approaches to **green pharmaceutical manufacturing,** with a focus on reducing environmental impacts and promoting eco-friendly methods. Attendees will have the opportunity to engage with **key stakeholders** from both the public and private sectors, fostering collaboration on the future of environmentally sustainable pharmaceuticals.

This event is an excellent opportunity for **industry professionals, researchers, and policy makers** to exchange ideas and explore the latest developments in green drug manufacturing.

Research article published

Recently, a research article detailing the work conducted in ENVIROMED was released!

The following article has been co-authored by our partner, TU Wien (TUW):

Guido Schlögel, Rüdiger Lück, Stefan Kittler, Julian Kopp, Jürgen Zanghellini, Mathias Gotsmy (2024-10-11). Optimizing bioprocessing efficiency with OptFed: Dynamic nonlinear modeling improves product-to-biomass yield. Computational and structural biotechnology journal, 23 (2024) 3651–3661.

https://doi.org/10.1016/j.csbj.2024.09.024

The research article emphasises the beneficial role of mechanistic process modelling for enhancing product-to-biomass yield in fed-batch processing. Traditional process designs typically use simple feed profiles and basic statistical methods for data analysis. In contrast, OptFed framework adjusts temperature and feed rate profiles to achieve a 19% increase in recombinant protein L yield. Hence, this study demonstrates a modern approach to leveraging old experimental data for further process optimisation.

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