Alejandra Pérez Vazquez (2024-2027)
Assessment and prediction of the toxicity of pharmaceuticals on surface water and sediment model organisms.
Co-supervisors: Stéphane Pesce (UR RiverLy EMA)/Floriane Larras (KREATiS)/ Christelle Margoum (UR RiverLy LAMA) **Secondments:** Dr. Benoît Ferrari (Oekotoxzentrum Centre Ecotox, Switzerland), Dr Adrian Love (AquaBiotech, Malta)
Doctoral School E2M2: Evolution Ecosystems Microbiology Modeling

Pharmaceuticals are widespread in aquatic ecosystems as they are constantly released to the environment mainly through WWTP effluents, as the removal rates of these compounds in the WWTP don't reach 100% (Royano et al., 2024). This load is known to potentially affect aquatic organisms (Hejna et al., 2022; Cannata et al., 2024), depending on their fate and behavior in the environmental matrices.

Their ecological hazard assessment is commonly performed in the laboratory, under controlled conditions and using model organisms, what is very time consuming and costly. As a result of this, regulators and Non-Governmental Organizations are increasingly calling for new alternative methodologies (NAMs) to reduce the number of organisms involved in toxicological testing (OECD, 2020) and to use more efficient methodologies. Therefore, it's considered that we are now in the era of the 3Rs (reduction, replacement, refinement of vertebrate animal testing). For example, the recent update of the European pharmaceutical regulation is encouraging the development of NAMs to possibly replace *in vivo* assays, as NAMs *in silico* methodologies showed to be a promising solution. *In silico* methodologies are based on the use of existing experimental data (e.g. from ECHA database) to predict biological properties (e.g., toxicity). However, the lack of pharmaceutical ecotoxicity data and the gap of knowledge prevent the development of these methodologies.

This PhD project aims to gain understanding of the fate and behavior of a set of pharmaceutical compounds in aquatic ecosystems as well as to characterize their toxicity to aquatic and sediment organisms, to ultimately develop quantitative predictive ecotoxicity models. Thus, the project lies at the interface of analytical and environmental chemistry, ecotoxicology and regulation.

To approach these aims first, a deep characterization of the pharmaceuticals compounds authorized in the European Economical Area (EEA) and their potential transformation products (TPs) will be performed. That step involves the location of physicochemical, ecotoxicological and mechanistic data, when available. A set of pharmaceutical model compounds will then be defined and investigated in the following step. Compounds of interest will be especially the ones representing potential danger for aquatic ecosystems and for which a gap of knowledge is identified.

Second, the fate and behavior of the selected pharmaceuticals and potential TPs in sediment and water compartments will be investigated following OECD guidelines. The pharmaceuticals will be characterized followed by the detection and identification of the potential TPs will be carried out by using LC-HRMS.

Third, acute and chronic ecotoxicity of the selected pharmaceuticals and potential TPs (depending on the commercial availability of standards) to sediment and surface water organisms will be performed following OECD guidelines.

Ultimately, the information retrieved in the previous steps will be used to gain and/or refine the *in silico* approaches developed by KREATiS what are highly correlated with the mechanistic understanding of the effect of the selected pharmaceuticals on the different tested organisms. Therefore, it is expected to ultimately develop models (e.g. (Quantitative) Structure-Activity Relationships and/or sophisticated machine learning approaches) to quantitatively predict the toxicity of certain pharmaceutical structures, including also their relevant TPs, on water and sediment organisms.

FUNDING

The PhD project is entirely supported by the Pharm-ERA Doctoral Network, which receives funding from the European Union's Horizon Europe Research and Innovation programme under the Marie Sklodowska-Curie Action No 101119261

Références

Cannata, C., Backhaus, T., Bramke, I., Caraman, M., Lombardo, A., Whomsley, R., Moermond, C.T.A., Ragas, A.M.J. (2024). Prioritisation of data-poor pharmaceuticals for empirical testing and environmental risk assessment. Environment International 183, 108379.

Hejna, M., Kapuscinska, D., Aksmann, A. (2022). Pharmaceuticals in the aquatic environment : A review on eco-toxicological and the remediation potential of algae. International Journal of Environmental Research and public health. 19, 7717.

OECD (2020), Overview of Concepts and Available Guidance related to Integrated Approaches to Testing and Assessment (IATA), OECD Series on Testing and Assessment, No. 329, Environment, Health and Safety, Environment Directorate, OECD.

Royano, S., Navarro, I., Torre, A. D. L., & Martínez, M. Á. (2024). Investigating the presence, distribution and risk of pharmaceutically active compounds (PhACs) in wastewater treatment plants, river sediments and fish. *Chemosphere*, *368*, 143759. https://doi.org/10.1016/j.chemosphere.2024.143759