

## Proposition de Thèse 2016/2019

### Metabolic profiling to evidence exposure and effects markers of pharmaceuticals in the Mediterranean mussel

**Key words:** Emerging contaminants, markers of exposure, markers of effect, mixture, metabolic profiling, *Mytilus Galloprovincialis*

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**Deadline for applications:** 30/09/16

**PhD starting date:** end of 2016 – beginning of 2017

**Candidate profile:** Skills in environmental chemistry or ecotoxicology and/or with a first experience in mass spectrometry

**Context:** The presence of pharmaceuticals and personal care products (PPCPs) in the environment is known since the 70s. However, over the past decade, advances in analytical techniques have allowed a more precise quantification of these substances in water, soil and biota. Despite the low levels observed, these molecules are considered pseudo-persistent due to their continuous release after human and veterinary therapeutic use and the diffuse nature of their discharge. Depending on the molecules and the countries considered, concentrations ranging from ng/L to hundreds of ng/L in surface water and groundwater have been observed (Pal *et al.*, 2010). In most cases, pharmaceuticals are characterized by highly specific modes of action (MoA), high potency and prolonged activity in order to minimize dosing requirements and potential toxicity in patients. It is possible to hypothesize that these compounds may then be pharmacologically active in organisms in which the drug targets are expressed and functional; therefore, concerns regarding the risk of ecotoxicological effects of such contamination have been raised (Fent *et al.*, 2006).

The study of the combined effects of multiple stressors is currently a challenge in both ecotoxicology and toxicology. The development of new approaches is then requested in order to generate data on the behavior of contaminants in organisms and on their effects, with the view to elucidate mechanisms of action and understand cumulative effects (mixtures). Taking into account the challenges expressed metabolic profiling is worth exploring. The principle of the approach is based on the generation of metabolic profiles on different sub- groups of samples by a suitable analytical technique. The comparison of these metabolic profiles can reveal any similarities and / or differences between the sub- groups of samples investigated and highlight any changes in the metabolism between a 'control' population and a 'test' population. This approach has made significant inroads into the environmental research community (Viant, 2007) and has considerable potential for characterizing the responses of aquatic organisms to natural and anthropogenic stressors, and to finally assess environmental quality. Metabolomics is believed to assist in identifying drug MoA and highlight biomarkers of toxicity.

**Objectives:** During this PhD project, we plan to assess the potential of metabolic profiling to get a characterization of the exposure to pharmaceuticals and the effects induced on aquatic organisms, using

as a model *Mytilus Galloprovincialis*, the Mediterranean mussel. The candidate will investigate whether metabolic profiling has the potential to study the response of aquatic organisms exposed to human pharmaceuticals, either i) as single toxicant or ii) as mixtures for the evaluation of the contribution of the approach in the issue of multiple exposures. This thesis work will as well challenge the ability of metabolic profiling to deliver biomarkers of exposure and effects.

**Method:** To achieve the thesis objectives, exposure experiments carried out in the laboratory may allow working on effects provided under the most frequent conditions in the environment: low dose exposure and mixtures exposure. The Mediterranean mussel *M. galloprovincialis* will be exposed firstly to three pharmaceuticals as single toxicant with the view to identify the strengths and weaknesses of the metabolomics approach and elucidate MoA's pharmaceuticals and secondly, it will be exposed to the mixture to give original information on cumulative effects. After laboratory studies on single substances, multiple exposure will be tested. Finally, the combination of the results will give the opportunity of further comparison of the data obtained to meet the objectives of mechanistic understanding of pharmaceuticals effects in aquatic organisms and identification of exposure and effects markers with the view to protect human and ecosystem health.

**Expected results:** This project intends to give answers in key aspects related to the presence of emerging contaminants in environment by implementing a multidisciplinary approach. The main expected results lie in both ecotoxicology and toxicology with 1/ elucidation of MoA and toxicity of pharmaceuticals in the selected non-target specie, 2/ a better understanding of the effect of mixtures and 3/ the development and assessment of metabolomics approach to deliver markers of exposure and effects which may be used later to monitor environmental quality.

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