OFFRE D'ALLOCATION DE THESE / PhD GRANT

ÉCOLE DOCTORALE SCIENCES EXACTES ET LEURS APPLICATIONS - ED 211 / NATURAL SCIENCES DOCTORAL SCHOOL

Avenue de l'université BP 1155 64 013 PAU Cedex – France

SUJET DE THESE / PhD SUBJECT

TITLE: Analytical developments and metallodrugs monitoring in Gave de Pau plain

Abstract : Pharmaceutical residues (or drugs) appear as emerging pollutants of resource water. Among them, metallodrugs used for medical diagnosis (iodine and gadolinium-based contrast media) and cancer treatment (platinum-based drugs) are poorly studied and their possible effects towards human and organisms of aquatic ecosystems remain little known. The main objective of this PhD project is to develop analytical methodologies to monitor metallodrugs (inorganic element based-drugs) in waste and resource water and to study the bioaccumulation of these compounds in exposed living organisms. This PhD project is part of a more global multidisciplinary project gathering chemists, geographers, economists and the local mixed association for water. Collaborative work with geographers and the local association will be established.

Mots clés (Keywords): metallodrugs, water, analytical chemistry, living organisms

CONDITIONS D'EXERCICE / WORKING CONDITIONS

Laboratoire : IPREM	**Site web :** https://iprem.univ-pau.fr
PhD Director: Florence PANNIER **PhD co-Director: Sandra MOUNICOU** **In Collaboration with – *if any* Maité BUENO**	
Place : Pau, France	
start: October 1st 2019	**duration:** 3 years
employer: Université de Pau et des Pays de l'Adour (UPPA)	
monthly salary before taxes: 1768 €	

SAVOIR-FAIRE DU LABORATOIRE / HOST LABORATORY PROFILE

The Institute of Analytical Sciences and Physico-Chemistry for Environment and Materials (IPREM) is a joint research unit CNRS / UPPA (UMR 5254). IPREM members are interested in the development of fundamental knowledge in physico-chemistry, analytical chemistry and microbiology, in relation to applications concerning the structure of the living, the management of the environment and the functional properties of different classes of materials.

Skills of IPREM members in physico-chemistry and analytical chemistry concern the development of methodologies for trace elements analysis and speciation (detection, identification and quantification of chemical forms of metals and metalloids) in environmental and biological samples. *In fine,* this research work benefits the understanding of essentiality or toxicity mechanisms of metals and metalloids thanks to interdisciplinary collaborative works. The developed methodologies include sample preparation and the coupling of separation techniques (chromatography, electrophoresis) with elemental and molecular mass spectrometry (ICP MS and ESI-FT-MS/MS).

MISSION - ACTIVITES PRINCIPALES / MISSION – PRINCIPAL ACTIVITIES

I. Le contexte scientifique / *Scientific Context*

Among emerging pollutants, inorganic-based pharmaceutical residues (metallodrugs and their derivatives), notably contrast media (used for medical diagnosis) and anti-cancer metallodrugs are found in wastewater but also in water intended for human consumption. Iodinated (I) contrast media are widely used in radiology while other metals (chromium, manganese, iron) or lanthanides (i.e gadolinium (Gd)) based contrast media are employed for magnetic resonance imaging (Lavigne *et al*, 2003).
Due to their high consumption at elevated doses, their low biodegradability and wastewater plant removal, iodinated contrast media are usually found in water at µg/L level (Fabbri *et al.,* 2016) and sometimes up to few hundred of µg/L like found in Spain (Mendoza et al., 2015). Gadolinium has been found at µg/L level in water (Rabiet et al., 2006). Platinum concentrations have been determined in the few to hundred µg/L range in hospital wastewater in Austria and England and correlated with the administration of Pt drugs (Lenz et al., 2005 ; Vyas et al., 2014). Considering their important half-life (more than 100 days in water column for Gd (Holzbecher et al., 2005), determining their concentration and fate in water appears crucial.
Consequently, because of the remanence of these compounds into aquatic ecosystems, living organisms are chronically exposed to these metallodrugs sometimes highly concentrated. If effects of these compounds towards humans are little known (allergies, nephrotoxicity, cardiovascular problems, …), they are even less known for aquatic organisms (Lavigne et al., 2003 ; Janus et al., 2018). For these reasons, it becomes important to investigate their presence into living organisms exposed to these pharmaceutical residues.

II. Les objectifs / *Objectives*

The global objective of the PhD thesis is to assess the occurrence in aquatic ecosystems of inorganic elements from pharmaceutical residues. For that purpose, the PhD work will be first to set up analytical methodologies to detect in waters, anomalies of inorganic elements (i.e, I, Gd, Pt, …) concentrations. Waters will be sampled following the survey of the PASSAGES laboratory (UPPA UMR 5319, SHS) to hospitals, radiology centers, and medical centers. Then, a second part of the thesis will aim at the study of the bioaccumulation and biodistribution of inorganic elements from pharmaceutical compounds in aquatic organisms (fish, crayfish, mussel, …) living in sites where the occurrence of these inorganic pollutants would have been demonstrated in the first part of the thesis.

III. Plan de travail / *Work plan*

Workpackage 1 : In a first screening step, quantification of inorganic elements will be achieved by means of atomic mass spectrometry (ICP MS, quadrupole or Sector Field for improved sensitivity). Considering expected low levels (µg/L and lower) of these pharmaceutical compounds in waters, preconcentration protocols (through the use of resins or chromatographic columns) will have to be developed. In a second step, speciation methodologies (coupling HPLC, ICP MS and ESI-MS/MS) will be set up in order to describe the fate (chemical form and concentration) of this class of pharmaceutical compounds revealed during the first screening step.
Workpackage 2: Bioaccumulation and biodistribution of inorganic elements (I, Gd, Pt, and other metals) in organs and tissues of aquatic organisms will be studied with the development of mass spectrometry based methodologies, notably elemental imaging with Laser Ablation coupled to atomic mass spectrometry, LA-ICP MS).

IV. Références bibliographiques *(Literature References)*

LAVIGNE, T., IMHOFF O., ROEDLICH M.N., MEZIANI F., CASTELAIN V., SCHNEIDER F. Use of contrast media in emergency investigations: risks and guidelines for their prevention. Reanimation 12 (2003) 510-518
FABBRI D., CALZA P., DALMASSO D., CHIARELLI P., SANTORO V., MEDANA C., Iodinated X-ray contrast agents: Photoinduced transformation and monitoring in surface water. Sci Tot Environ, 572 (2016) 340-351
MENDOZA A., ACEÑA J., PÉREZ S., LÓPEZ DE ALDA M., BARCELÓ D., GIL A., VALCÁRCEL Y., Pharmaceuticals and iodinated contrast media in a hospital wastewater : a case study to analyse their presence and characterise their environmental risk and hazard. Environ Res 140 (2015) 225-241
RABIET M., TOGOLA A., BRISSAUD F., SEIDEL J.L., BUDZINSKI H. et ELBAZ–POULICHET F., Consequences of Treated Water Recycling as Regards Pharmaceuticals and Drugs in Surface and Ground Waters of a Medium-sized Mediterranean Catchment, Environ. Sci. Technol. 2006, 40, 5282-5288.
LENZ K., HANN S., KOELLENSPERGER G., STEFANKA Z., STINGEDER G., WEISSENBACHER N., MAHNIK S. N., FUERHACKER M., Presence of cancerostatic platinum compounds in hospital wastewater and possible elimination by adsorption to activated sludge, Science of the Total Environment 345 (2005) 141– 152.
VYAS N., TURNER A., SEWELL G., Platinum-based anticancer drugs in waste waters of a major UK hospital and predicted concentrations in recipient surface waters, Science of the Total Environment 493 (2014) 324–329.
HOLZBECHER, E., KNAPPE, A., PEKDEGER, A., 2005. Identification of degradation characteristics - exemplified by Gd-DTPA in a large experimental column. Environ.Model. Assess. 10, 1-8.
JANUS N., LAUNAY-VACHER V., DERAY G., Toxicité rénale des produits de contraste non iodés, Néphrologie & Thérapeutique 14 (2018) 484–490.

COMPÉTENCES REQUISES / REQUIRED COMPETENCES

The candidate must have a physic-chemistry and/or analytical chemistry education from a master in chemistry or engineer chemistry school. Theoretical or practical skills in mass spectrometry and chromatographic techniques will be strongly appreciated.
The candidate must demonstrate:
- a good organization and autonomy,
- a good capacity to synthetize and present its research work.

CRITÈRES D'ÉVALUATION DE LA CANDIDATURE / CRITERIA USED TO SELECT CANDIDATE

Selection process steps:
- Establishment of the selection committee
- evaluation of the applicants cv's
- Interview with the selected candidates and ranking

Criteria used in selection of the candidate:
- The candidate's motivation, scientific maturity and curiosity.
- Candidate's knowledge in organic and physical chemistry.
- Candidate's marks and rankings in M1 and M2.
- English proficiency

CONSTITUTION DU DOSSIER DE CANDIDATURE / REQUIRED DOSSIER,

Send an e-mail with your candidature containing:
- CV
- cover letter detailing candidate's motivations
- candidate's MSc marks and ranking
- any letters of recommendation
- contact details for 2 referees

DATE LIMITE DE DEPOT DU DOSSIER (limiting date):	**1st septembre 2019**

CONTACTS

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