COLLEGE SCIENCES DOCTORAL DE LA VIE BRETAGNE ET DE LA SANTE

Year 2022-2023

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☐ **Requested** ☒ **Acquired**	**Funding origin: Anses + PARC (Horizon Europe)**
Thesis title: **New Approaches and Methodologies for the Generation of a PBPK Model of Eniatin B1 Exposure and Characterization of its Hepatotoxicity**		3 keywords: NAMS mycotoxins TK/TD
Research Unit / team: **ANSES Fougères Laboratory (Teams EMAD/TC)**		
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Socio-economic and scientific context (approximately 10 lines):

Mycotoxins of the enniatin family are among the emerging natural contaminants of concern in the food chain and commonly found in cereals (EFSA 2014). They are metabolites produced by microfungi Fusarium, potentially toxic to humans and therefore represent a major public health issue. Due to climate change, human exposure to natural toxins is likely to increase, whereas enniatins are not currently among the mycotoxins regulated at European level, partly due to a lack of ADME (Absorption, Distribution, Metabolism, Excretion) data and HBGV (Health Based Guidance Value).

Among the enniatins, enniatin B1 is one of the emerging mycotoxins of interest to which humans are regularly exposed via their diet. Thus, a recent study showed that Enniatin B1 was found in 94% of urine samples in Italian volunteers. However, the available toxicity and ADME data are very scarce and show interspecies differences, which do not currently allow the determination of the risk for human. This lack of human data hinders the direct calculation of plasma concentrations of B1 enniatin and the estimation of oral exposure by biomonitoring coupled with reverse dosimetry.
Therefore, the objective of this PhD works will be to develop a physiologically based toxicokinetic model (PBTK) by extrapolating hepatic metabolism from in vitro to in vivo (IVIVE) and to study the molecular mechanisms of hepatotoxicity of enniatin B1.

Working hypothesis and aims (approximately 8 lines):
Toxicokinetic (TK) and toxicodynamic (TD) data are currently scarce. These PhD works therefore aims to combine New Approaches and Methodologies (NAMs) such as in vitro liver models, IVIVE-PBTK and metabolomics, to generate new data. The aim is to study the TK of enniatin B1 in vitro in rat and human liver cell models and in vivo in rats to build a PBTK model. In parallel, we will use a metabolomic approach to study the molecular mechanisms particularly involved in vitro during acute and chronic exposure to enniatin B1. These data will allow us to better characterise the risk associated with human exposure to enniatine B1, to better understand the mechanisms of toxicity and also to have a methodology based on NAMs for the new generation risk assessment (NGRA) that can be reused for other compounds.

Main milestones of the thesis (approximately 12 lines):

The objective of this project is to generate missing data in TK/TD based on NAMs and to contribute to the assessment of risks related to exposure to enniatin B1. The first task will be to :

-Determine the toxicokinetic parameters by extrapolation from in vitro to in vivo of enniatine B1, using in vitro models of primary rat hepatocytes, and the HepaRG cells as well as advanced liver models (3D co-cultures, human hLiMTs microtissues).

-Build PBTK rat and human models by IVIVE extrapolation using TK data generated in vitro and in silico.

-Conduct a kinetic study in rats to estimate the predictive ability of the rat model for extrapolation to humans.

-To determine the in vitro mechanisms of action of the acute and repeated toxicity of enniatin B1 by metabolomic approaches.
-Finally, to estimate the margin between the predicted internal concentrations and the concentrations activating molecular mechanisms.

Scientific and technical skills required by the candidate (2 lines): **Master 2 or Pharmacy diploma**
With skills in Pharmacacokinetics and/or Analytical Chemistry (Desired knowledge in Cellular Toxicology)

3 publications from the team related to the topic (last 5 years):

- **EFSA Pilot Project on New Approach Methodologies (NAMs) for Tebufenpyrad Risk Assessment. Part 1. Development of Physiologically-Based Kinetic (PBK) Model Coupled With Pulmonary and Dermal Exposure https://doi.org/10.2903/sp.efsa.2023.EN-7793**
- **A PBPK model to study the transfer of α-hexabromocyclododecane (α-HBCDD) to tissues of fast- and slow-growing broilers https://doi.org/10.1080/19440049.2019.1681596**
- **Three-dimensional HepaRG spheroids as a liver model to study human genotoxicity in vitro with the single cell gel electrophoresis assay https://doi.org/10.1038/s41598-019-47114-7**

National and international collaborations:

This topic will be carried out in the framework of the European PARC project. Exchanges will be particularly privileged with the Norwegian Veterinary Institute (NO) but also with the universities of Wageningen (NL) and Vienna (AT).