Predicting pulmonary xenobiotic absorption in humans using combined in vitro tools and in silico kinetic models

Nos réf.: Ineris-[209001]-ID xxxxx

Date: 07/09/2022
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PRESENTATION OF THE INTERNSHIP

Within the Environmental characterization and impacts on human and biodiversity department, the experimental toxicology and modeling unit (TEAM) is exploring new approach methodologies to assess exposure to chemicals in humans. In the context of this internship, the candidate will focus on chemical exposure by inhalation. The toxic effects of an inhaled compound at topical and/or systemic levels depend on many factors, including the compound’s structure, and the size of the particles. Contrary to gastrointestinal tract absorption, absorption by inhalation is poorly accessible.

Some in vitro models are available such as the air-liquid interface models, lung organoids, etc. These models could provide information of interest such as the compound permeation and/or local toxicity in real life. In silico modeling could help evaluate the different in vitro models while providing accurate predictions of the compound kinetics.

In this context, the proposed internship will first focus on the acquisition of experimental data following the exposure of different cellular models to substances of interest. In a second step, data modeling will be performed. More precisely:

Experimental phase:
Two different pulmonary epithelial cell lines (Calu-3 and h-AELVi) will be exposed to permethrin or metolachlor (and possibly other substances to be determined), either in submerged mode or at the air-liquid interface, the latter allowing to better mimic the alveolar environment. For each compound, two doses will be chosen based on cytotoxicity and apparent permeability studies. The first dose will correspond to a LOAEL and the second will be 10 times lower. The compound in vitro kinetics will be explored by collecting three samples (apical and basolateral media, and the cellular compartment) at different times between 0 and 24h post-exposure. The measurement of the compartment concentrations will be outsourced.

Modeling phase:
In a second step, an existing in silico cellular model (VIVD model) will be adapted to the inhalation case to describe the kinetics of the compounds in the 3 compartments (apical and basolateral media, and cells). Experimental data will be compared to the predictions of the current in silico model for the different compounds, concentrations, and cellular models. In a second step, the model will be updated to improve its predictions.
This internship should contribute to:
- a better knowledge of the in vitro kinetics of the tested compounds in two cellular systems tested, and mode of exposure
- the improvement of a physiological-based kinetic model to estimate the behavior of inhaled environmental contaminants at the cellular level,
- the evaluation of the impact of the relevant in vitro ADME parameters on compound kinetics,

Ultimately, this work should lead to the establishment of a toolbox to link chemicals, cells, mode of exposure, and expected concentrations in intra and extra cellular compartments

PROFILE

**Background:** Master II student (Pharmacokinetics/bioinformatics or Toxicology)
**Hard skills:** Toxicology/Biomathematics, cell culture, R programming
**Soft skills:** be able to work in a multidisciplinary team, autonomous, rigorous, and organized.

MORE INFORMATION:

The French National Institute for the Industrial Environment and Risks (INERIS) carries out research and provides technical support to the Ministry in charge of the Environment and several public or private operators. In this context, INERIS contributes to the prevention of the risks that economic activities may cause to the health and safety of people, goods, and the environment.

Research activities span many fields in industrial and environmental risks including issues related to air, soil, and water pollution.

INERIS offers an outstanding international working environment along with training and development opportunities.

Ineris main research center is located at Verneuil-en-Halatte (60 km from Paris, 30 minutes from Paris by train + shuttle).

This internship is open to people with disabilities.