CEFIC Long-range Research Initiative
Request for Proposals (RfP)

Title and Code Number:
In Vitro Data To Parameterise PBPK Models For Inhalation Exposure – **LRI-B21**

Background

In human health risk assessment we often face the situation that consumer and worker are exposed to chemicals via the inhalation route. The estimation of systemic available/internal doses after inhalation exposure is complex as chemicals may be inhaled as (nano)particles, aerosols or gases.
To date, in human health risk assessment, we assume a 100% absorption of the deposited fraction in the respiratory tract. This is a pragmatic, but rough worst case estimate and therefore there is a need for better methods, like PBPK models (reference 1, 2, 3). PBPK models combines the knowledge on the deposited fraction in the different lung compartments with the uptake and further distribution of the compounds in the human organism.

For chemicals only few experimental data in humans are available on the bioavailable concentration in plasma and tissues after inhalation exposure. Therefore, one challenge of the modelling is to surrogate in vivo data by relevant data from in vitro experiments.

This project aims to parameterize PBPK models with in vitro data that can be used to model the uptake and transport of substances through the different compartments of the respiratory tract. Furthermore, clearance processes (e.g. dissolution, mucociliary clearance and phagocytosis) will be analysed and integrated into the PBPK model. As gases, aerosols and (nano)particles differ with regard to the relevant uptake and clearance processes, exemplary model compounds will be tested from of these three classes.

The “Lung” PBPK Model” should provide information relevant to current regulatory needs and the improvement of internal dose assessment through new science-based approaches. It can build on or adapt existing kinetic models, e.g. PBPK models used in mammalian toxicology in the pharmaceutical, medical, and pesticide sciences. For a toxicokinetic human lung model to be credible and useful, it needs to be thoroughly tested and evaluated for uncertainties, sensitivities and domain of applicability. The PBPK model shall be made available to the public and the description of the model disseminated in the scientific literature.

Objectives

1. Evaluate the key steps of absorption and diffusion of gases, solid particles and aerosol by relevant in vitro methods.
2. Integrate clearance processes into the PBPK model
3. Integrate the in vitro measurements into a PBPK model, named IVIVE-PBPK model.

4. Analyse predictivity, uncertainty and sensitivity of the IVIVE-PBPK model by comparison with in vivo data.
5. Disseminate the PBPK model e.g. as user friendly web-application.
6. Disseminate results of the project at SOT/EUROTOX and in a peer-reviewed scientific publication.

Scope

The uptake of selected model compounds has to be tested by different in vitro methods using relevant routes of application e.g. air-liquid exposure. Three classes of compounds will be investigated namely gases, nanoparticles and aerosols. Suitable analytical methods will have to be developed and applied and particular efforts will have to be spend to measure the deposited fraction, as well as the kinetics /amount of the compounds in the lining fluid, the cells and the basolateral compartment. The development and improvement of the PBPK model with regard to the systemic circulation is not in the focus of this project.

As applicable, build from and/or utilize the open source models (for instance, but not limited to, PLETHEM http://www.scitovation.com/plethem.html) and to the extent of feasibility design the new modelling to integrate with, or to be interoperable with them. Proposals shall include a description of the open source models the new modelling will build from (or use) and indicate how the new modelling will integrate with, or to be interoperable with, these open source models.

Deliverables

The final report shall contain an executive summary (2 pages max), a main part (max. 50 pages) and a detailed bibliography.

It is expected that the findings will be developed into at least one peer reviewed publication, following postering(s) and presentation(s) at suitable scientific conference(s). At least one article related to the research project shall be published in the open access literature.

Cost and Timing

Start in Q1 2019
Duration: 2.5 years
Budget in the order of 300.000€

Partnering/Co-funding

Applicants should provide an indication of additional partners and funding opportunities that can be appropriately leveraged as part of their proposal. Partners can include, but are not limited to industry, government/regulatory organizations, research institutes, etc. Statements from potential partners should be included in the proposal package.

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Fit with LRI objectives/Possible regulatory and policy impact involvements/ Dissemination

Applicants should provide information on the fit of their proposal with LRI objectives and an indication on how and where they could play a role in the regulatory and policy areas. Dissemination plans should also be laid down.

References

Oberdörster, G. et al., J. Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles. Environ Health Persp 2005, 113 (7), 823–839.

J. L. J. Campbell, R. A. Clewell, P. R. Gentry, M. E. Andersen und H. J. 3. Clewell, Physiologically based pharmacokinetic/toxicokinetic modeling, Methods Mol Biol, Bd. 929, 439-499, 2012

Li, D.; Morishita, M.; Wagner, J. G.; Fatouraie, M.; Wooldridge, M.; Eagle, W. E.; Barres, J.; Carlander, U.; Emond, C.; Jolliet, O. In vivo biodistribution and physiologically based pharmacokinetic modeling of inhaled fresh and aged cerium oxide nanoparticles in rats. Part Fibre Toxicol 2016, 13 (1), 45. DOI: 10.1186/s12989-016-0156-2.

MPPD model: Schroeter, J.D., Asgharian, B., Price, O.T., Kimbell, J.S., Kromidas, L., Singal, M. 2016. Simulation of the phase change and deposition of inhaled semi-volatile liquid droplets in the nasal passages of rats and humans. Journal of Aerosol Science, DOI: 10.1016/j.jaerosci.2016.01.006

DEADLINE FOR SUBMISSIONS: 2 September 2018

Please see www.cefic-lri.org for general LRI objectives information, project proposal form and further guidance for grant applications.