Development of nanospecific physiologically based pharmacokinetic (PBPK) models Deliverable 4.17

Introduction

Physiologically based pharmacokinetic (PBPK) models have the potential to describe and predict the biokinetics of nanomaterials (NMs) in organisms on the basis of physicochemical or other characteristics of a NM, and may strongly contribute to the efficiency of risk assessment and the implementation of Safe by Design. Such models are well suited to describe, understand and predict how nanoparticles are taken up, distributed, degraded and excreted from the body, to extrapolate for species (e.g. from *in vitro* and animals to humans), to extrapolate between routes (e.g. between intravenous, oral, dermal and inhalation) and to predict the biokinetics and target doses for new exposure scenarios

Modelling reduces the need for in vivo experiments and do not require additional in vivo tests to make new predictions when exposure conditions and species are changed. Consequently, time and resources can be saved.

Different from medicine, such models are not yet operational for nanomaterials. Deliverable 4.17 reports the result of the development of such a model.

Description of Work

A conceptual nanospecific physiologically-based pharmacokinetic (PBPK) model for intravenous administration to rats was developed and applied on different types of inert nanoparticles using experimental data from recently published scientific publications. The development of the model followed the principles of conventional PBPK models and can be subdivided into the following parts:

1. Literature review and evaluation,
2. Identification of critical processes and rate limiting factors in absorption, distribution and clearance of nanoparticles,
3. Develop a generic physiological model describing mammal in this case rats,
4. Mathematical description of the model as mass-balance equations,
5. Identification of parameter values for the model values taken from the literature and/or by fitting the model to experimental data
6. Comparison between experimental data and in vivo data and
7. Evaluation with independent data.

As nano-EHS data generated in the NANoREG project only became available in a late stage of the project, the development and calibration of the model is based on datasets from other projects and with other materials than NANoREG core materials.

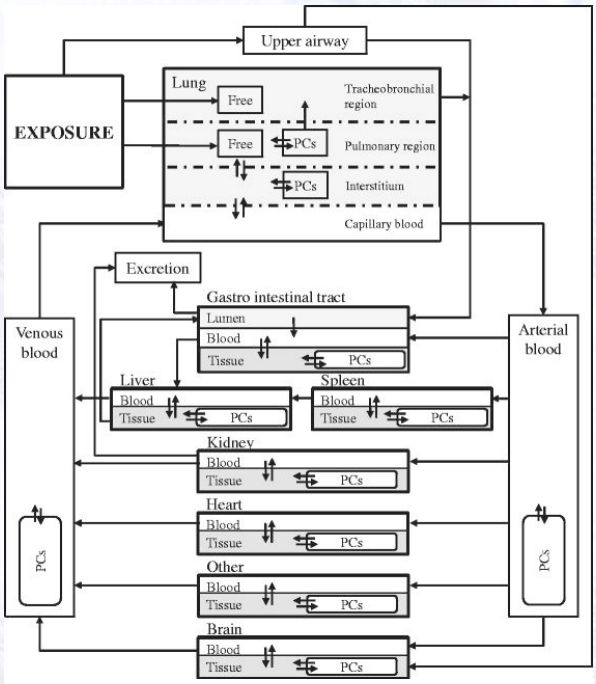
Main results and evaluation

A conceptual model was constructed based on findings from literature review and organs analysed in study on PAA-PEG injected intravenously into rats. Next, the model was refined and optimized to data sets on PAA, gold and titanium dioxide. The model consists of 10 compartments; arterial blood, venous blood, liver, spleen, lung, kidney, heart, brain, bone marrow and carcass. Each compartment is divided into three sub compartments: capillary blood, tissue and phagocytic cells.

The exchange of nanoparticles between blood and tissue in each organ is described by flow- and diffusion-limited processes. Diffusion between blood and tissue is controlled by a permeability coefficient, which limits the effective blood flow. The uptake by phagocytic cells is designed to be saturable.

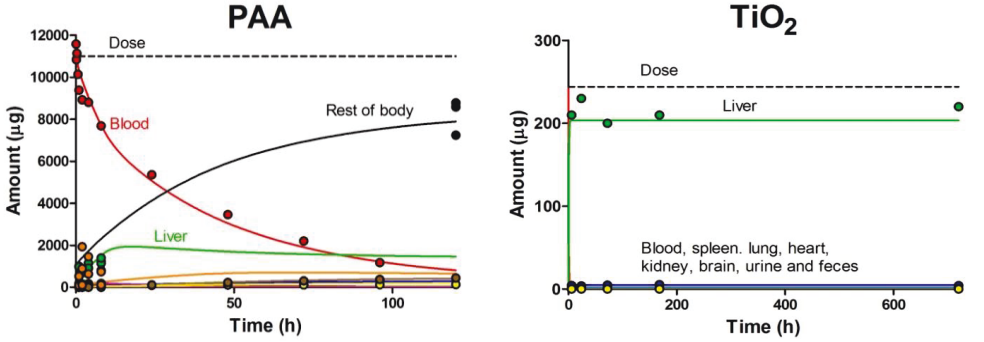
The model was expanded to include inhalation exposure by including deposition in the respiratory system and transfer to the gastrointestinal tract (see figure).

The model includes physiologically based as well as nanoparticle dependent parameters. Physiological parameters such as organ weights weight and blood flows were generally taken from the literature but replaced by individual experimental data when possible. Nanoparticle dependent parameters in the models include; uptake and release rate to phagocytic cells, uptake capacity of phagocytic cells in tissues, partitioning between blood and tissue and permeability. These parameters were obtained by best fit to the experimental biokinetic data.



Schematic illustration of physiologically-based pharmacokinetic model for inhalation exposure.

To evaluate if the PAA-PEG model can be used as a general model the model was tested on three additional types of nanoparticles; PAA, Gold and Titanium Dioxide. The model adequately describes the biokinetic behaviour of all four NP types only by adjusting nanoparticle related parameters (R^2 on the log scale ranging from 0.88 to 0.96). The fitted parameters that varied most were the clearance to urine and faeces, the blood-tissue permeability coefficients and the uptake rate and capacity of phagocytic cells.



Simulated and experimentally observed amounts of polyacrylamide (PAA) and titanium dioxide (TiO2) nanoparticles in different tissues and organs of the rat after various time-points. Simulated (solid lines) and observed (symbols) time-courses

Additional data on NP properties such as corona formation and physiological parameters, such as number of phagocytic cells in different tissues and their capacity and turnover, are required to further improve the model.

The PBPK model expanded with inhalation, describes the biodistribution of inhaled nanoceria well and is able to reproduce the different experimentally observed trends (R^2 on the log scale ranging from 0.68 to 0.95).

The conceptual model developed described in Deliverable 4.17 is the first one to include a separate compartment for saturable phagocytic cells. This structure has subsequently been adapted and modified in other published models, which supports its importance in nanospecific PBPK models.

In agreement with the results from experimental biodistribution studies, the modelling exercises demonstrate that kinetics depends on both nanoparticles properties and exposure conditions.

Despite some major achievements, these nano-PBPK models are still in their infancy and cannot yet be readily used in the regulatory arena. On the other hand, PBPK modeling provides valuable information about uptake and distribution but need to be further refined before they can be successfully used as regulatory tools. The deliverable gives recommendations for further improving the nano-PBPK models.

For more details about NANoREG please visit the official website www.nanoreg.eu.

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