# In Vitro Effect Extrapolation for Human Risk Assessment of Advanced materials

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## 1. Introduction

The widespread utilization of advanced materials (AdMas) across various sectors has ignited concerns about potential exposure and risk to human health and ecosystems. Risk Assessment (RA) (McIntosh & Pontius, 2017) is a scientific process to assess a specific stressor's nature and the magnitude of the risk to human health or ecological systems.

Hazard assessment for AdMas has largely shifted from animal testing (Council et al., 2007), which is resource-intensive and raises ethical concerns, to alternative methods such as in-vitro tests (Nel et al., 2013) and in silico (computer-based) (Raies & Bajic, 2016) approaches. In vitro datasets have gone through development to be able to predict more reliably the pulmonary effects observed in vivo. It has been realized that the available in-vitro data sets could be used as alternatives and another source for model evaluation and verification during model development.

To use in-vitro data in risk assessment, quantitative in-vitro to in-vivo extrapolations (QIVIVE) have been developed. QIVIVE approaches for risk assessment have been developed for more than 20 years: researchers simulated realistic physical conditions, using either Physiologically Based pharmacokinetic models (PBPK) ( (Lin & Lin, 2020),(Yoon et al., 2012)) or distribution equilibrium principles between cell and serum (Gülden & Seibert, 2003) to extrapolate the in-vivo substance distribution based on in vitro data. The PBPK model was able to describe the experimental data, but there are some limitations and uncertainty as some of the parameters are of high uncertainty (Dong et al., 2017; Wambaugh, 2018).

Besides, the estimations of points of departure (PODs), based on different in vitro studies, are needed to establish causality for the derivation of risk level. Given these differences in the estimation of health-protective exposure values between different studies, a key issue is how to create an integrated approach that can unify different toxicity endpoints from different types of critical studies to support the determination of health-protective exposure values.

To address the abovementioned knowledge gaps, this study developed a Bayesian model to analyse a comprehensive set of toxicity data to determine probabilistic PODs for AdMas. Furthermore, model applications were performed to predict internal

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dosimetry of relevance to risk assessment for reducing the uncertainty of extrapolation in the derivation of acceptable exposure levels.

## 2. Uncertainty space evaluation for toxicity extrapolation

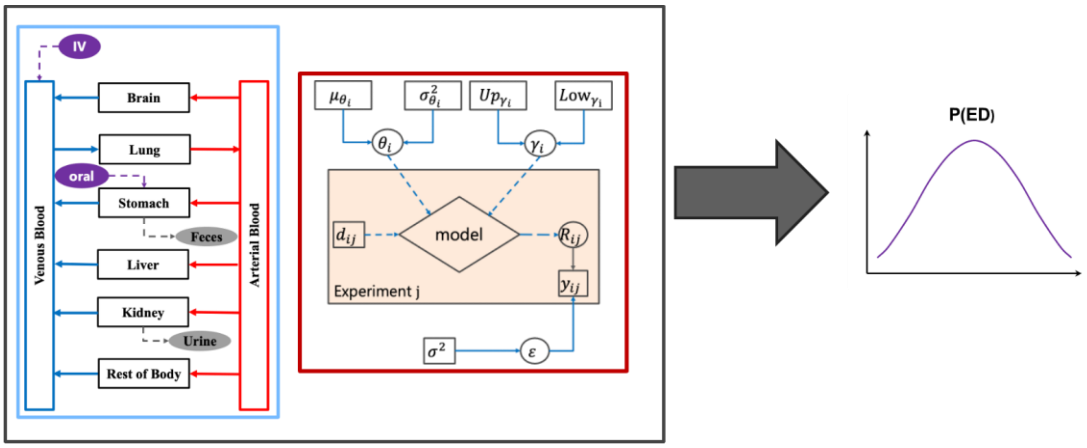


*Figure 1: Bayesian Structure to evaluate the parameter and dataset uncertainties.*

While some processes inside the PBPK models are well characterized, others are partly or poorly characterized. Information gaps or poor characterization of some physiological processes may cause the PBPK model to not fully capture the kinetics behaviour of particles inside the human body (Khalil & Läer, 2011). Therefore, it is essential to emphasize the uncertainty and variability concerning the PBPK model parameters. Rather than optimizing every possible model parameter, we intend to consider sensitive parameters in the model.

Bayesian analysis with Markov chain Monte Carlo simulation was performed to characterize the uncertainty of parameters and datasets and to further improve the model reliability. A sensitivity analysis of the optimized model parameters was conducted to assess the impact of uncertainty/variability in model parameter values on predictions of output.

Through this analytical approach, we gain insights into the influence of these uncertainties on the extrapolation of safe AdMas concentration levels, a pivotal aspect of risk assessment. It enables the estimation and evaluation of these uncertainties, allowing for a nuanced examination of their impact on the estimation of in vivo effective doses.

## 3. Conclusions

In conclusion, we are not yet there for a precise calculation of in vitro-based EFs. However, we showed promising methods to evaluate the uncertainties of results.

This collaborative approach allows for a comprehensive assessment of AdMas effects given in-vitro data, including the kinetics process inside the body and toxicological effects, thereby facilitating the development of robust risk assessment strategies.

## 4. Acknowledgements

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