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Ability of 3 extraction methods (BCR, Tessier and Protease K) to estimate the bioavailable metals in sediments from Huelva Estuary, southwestern Spain

Daniel Rosado
Universidad de Sevilla, Spain

We estimated the bioavailable fraction of metals (Zn, Cu, Cd, Mn, Pb, Ni, Fe, and Cr) in sediments of the Huelva estuary and its littoral of influence by carrying out the most popular methods of sequential extraction (BCR and Tessier) and a biomimetic approach (extraction with protease K). We compared the results obtained with enrichment factors found in *Arenicola marina*. The linear correlation coefficients (R2) obtained between the fraction mobilized by the first step of the BCR sequential extraction; by the sum of the first and second steps of the Tessier sequential extraction; and by protease K. The enrichment factors in *Arenicola marina* are at their highest for protease K extraction (0.709), followed by BCR first step (0.507) and the sum of the first and second steps of Tessier (0.465). This observation suggests that protease K represents the bioavailable fraction more reliably than traditional methods (BCR and Tessier), which have a similar ability.

danrosalc@alum.us.e

P-gp mediated DDI prediction by Simcyp modeling: Systematic literature review and a case study

Di Bei[1], **Jin Zhang**[2], **Haiying Sun**[2] and **Xuemin Jiang**[2]
[1]University of Florida, USA
[2]Novartis Institutes for BioMedical Research, USA

P-gp mediated drug-drug interaction (DDI) has been a challenge for accurate prediction in clinical. Complex *in-vitro* to *in-vivo* extrapolation (IVIVE) occurs when the perpetrator concurrently inhibits on both metabolizing enzyme and transporter. Therefore, physiologically-based pharmacokinetic (PBPK) model is useful in this case to integrate drug's absorption, distribution, metabolism and excretion (ADME) together with human's intrinsic and extrinsic factors. In our study, Simcyp (version 13) with the advanced dissolution, absorption and metabolism (ADAM) module and the full PBPK module was utilized to describe clinical PK and further evaluate p-gp mediated DDI between drug A and drug B. Drug A was a substrate of both CYP3A4 and P-gp while drug B was a TDI of CYP3A4 and a potent inhibitor of p-gp. *In vitro* measured drug properties, preclinical DDI data and the clinical DDI were incorporated into the model. The rationale of our simulations and optimizations was based on FDA guidance and systemic literature review. 4 models were compared considering the predictability and physiological feasibility. The final model with the optimized p-gp kinetics described the clinical observations reasonably, with the modeled drug A's C_{max} and AUC ratios at 3.3 and 3.1-fold increase, respectively versus observed C_{max} and AUC ratios at 3.3 and 3.1-fold increase in the clinical study. Thus, it was concluded that p-gp kinetics needs to be well characterized in order to improve the predictability of the model. And Clinical DDI data are valuable for PBPK model modification. The bottom-up approach combined with top-down approach can provide helpful insight.

db4dc@ufl.e