Development of a physiologically based pharmacokinetic model to address the diffusion of toxic substances in humans

Local and systemic contamination caused by metal ions leaching from medical device materials is a significant and continuing health problem. The increasing need for verification and validation, and the imposition of stringent government regulations to ensure that the products comply with the quality, safety, and performance standards, have led regulatory bodies worldwide, such as U.S. Food and Drug Administration (FDA), to strongly recommend the use of modeling and simulation tools to support medical device submissions. We have first expanded a previously published PBTK model [and have provided an analytical solution to it (Ref. 41)] that predicts Nickel leaching from cardiovascular stents, by considering an additional separate tissue compartment to better resemble normal physiology and by the introduction of time-dependent functions to describe all biokinetic parameters (Ref. 37). The new model is exercised in conjunction with state-of-the-art probabilistic, Monte Carlo methodology to calculate the predictions' confidence intervals and incorporate variability associated with toxicological biodistribution studies, which was proposed for the first time in the literature. The quantitative consistency of the model-derived predictions is validated against reported data following the implantation of nickel-containing cardiovascular devices in humans and minipigs. This is particularly important as the acquisition of many in vivo samples is prohibitively costly and time-consuming; thus, the confidence intervals should be estimated as accurately as possible to avoid adverse local and systemic health problems. We have further proposed a new methodology for compartmental toxicological risk assessment that can be used for forward or reverse dosimetry (Ref. 37). In a more recent publication, (Ref. 39) the PBTK model has been extended to include the most important tissues/organs and excreta. It also reports on the necessary *in vivo* data to parameterize it; to the best of our knowledge, this is the very first study that provides *in vivo* data for so many tissues/organs. Furthermore, a computer-implemented machine learning method is presented to perform a toxicological risk assessment of cardiovascular stents early in their device design cycle.

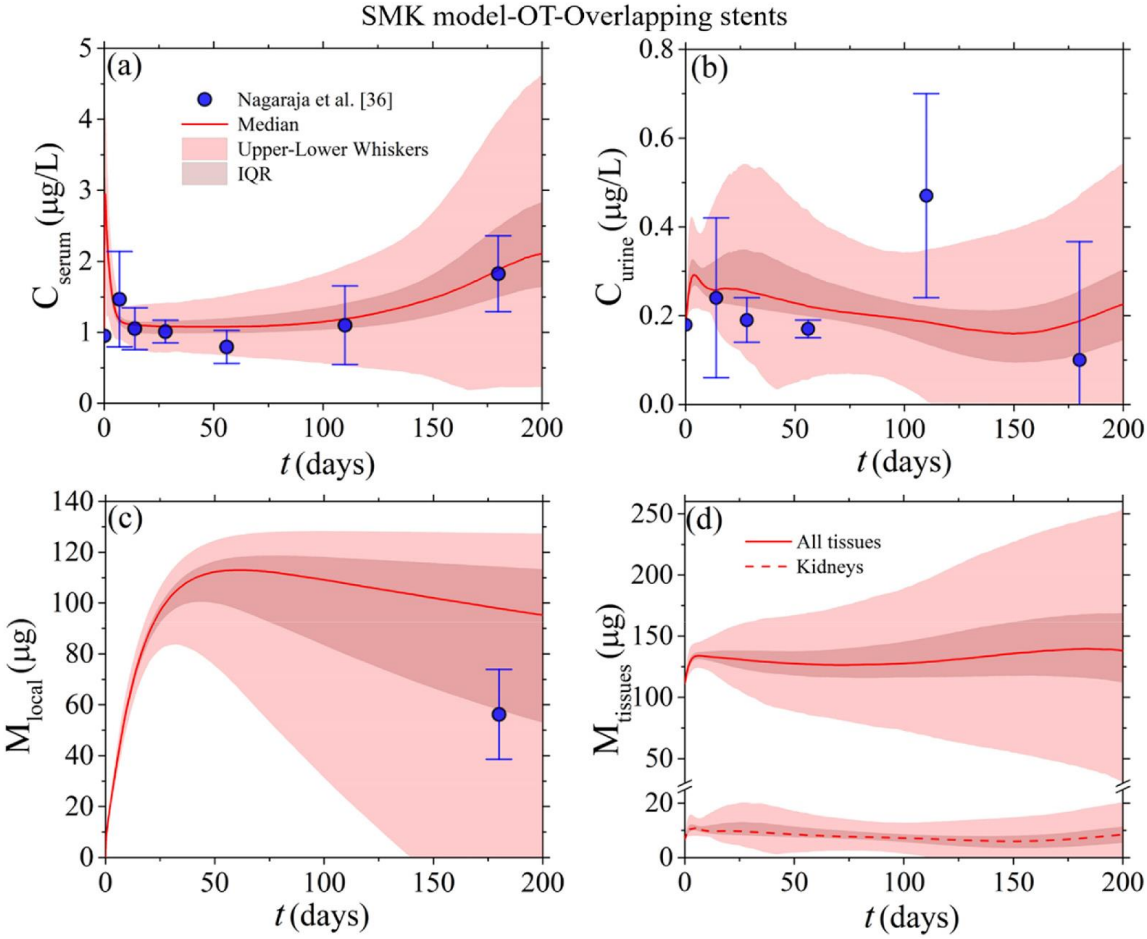

Figure: New model derived-predictions of the nickel concentration-time profiles, released from overlapping OT stents, in the various tissue and body fluid compartments.

References

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