INCORPORATING CONFIDENCE INTERVALS IN PHYSIOLOGICALLY BASED TOXICOKINETIC (PBTK) MODELING

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ABSTRACT

It is well documented that metal implants experience wear and corrosion due to the biomechanochemical environment at the implantation site.[1-2] The local and systemic contamination caused by metal ions leaching from medical device materials poses a significant health problem. The International Organization of Standardization (ISO) has stressed the importance of a proper Toxicological Risk Assessment by implant manufacturers, which is now considered a prerequisite to biocompatibility testing.[3] General corrosion susceptibility and metal ion release are typically estimated through *in vitro* immersion tests as per the ISO and American Society of Testing and Materials (ASTM) standards; however, such tests have been noted to deviate from the actual release rates.[2,4] This has led both the Food and Drug Administration (FDA)[5] and the European Centre for Disease Prevention and Control (ECDC)[6] to suggest the use of modeling and simulation tools during the implant design stage. In this work, we generalize a recently proposed physiologically based toxicokinetic (PBTK) model proposed by Saylor et al. [7] to estimate nickel release from an implanted device, first by introducing time-dependent functions to describe all the biokinetic parameters, and second by considering kidneys as a separate model compartment. Furthermore, a probabilistic, Monte Carlo methodology is employed to calculate the proper confidence intervals for the model-derived predictions. A fully validated PBTK model will be instrumental early in the device design cycle, to enable manufacturers to optimally design and develop implantable devices of which the release of harmful substances is below permissible exposure limits. We expect that our work will be utilized for critical decision-making in clinical practice such as optimizing the implantation protocol or site of implantation to enable short- and long-term stability of implantable devices.

KEYWORDS: physiologically based toxicokinetic (PBTK) model, implantable devices, nickel leaching, Monte Carlo, Toxicological risk assessment

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