3186 Implications of Protein Binding for Predicting Pesticide Salivary Transport Using a Combination Experimental and Computational Approach

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Non-invasive biomonitoring with saliva has potential to significantly advance quantitative dosimetry as an integral component of epidemiology. However, quantitative predictions of chemical transport into saliva remain a challenge. In order to predict salivary clearance, a Transwell cellular transport system and accompanying computational model have been developed. By utilizing physiological protein levels representative of plasma and saliva, cellular systems are able to closely predict the *in vivo* saliva/blood concentration ratio (0.021 vs. 0.049) of 3,5,6-trichloro-2-pyridinol (TCPy), the major chemical-specific metabolite of chlorpyrifos. However, predicted cellular diffusion coefficients were slower than those observed *in vivo*. Here, we hypothesize that protein binding plays an important role in TCPy salivary transport. TCPy protein binding in cell culture medium and plasma were measured using ultracentrifugation and gas chromatography-mass spectrometry. Kinetic descriptions of protein binding were added to the cellular computational model and parameterized with data of TCPy protein binding in cell culture medium. Resulting model simulations predicted cellular transport data reasonable well. A physiologically based pharmacokinetic model (PBPK) for chlorpyrifos and TCPy was modified for congruent kinetic descriptions of protein binding and parameterized using TCPy plasma protein binding experimental data. Resulting PBPK model simulations accurately predicted *in vivo* concentrations of TCPy in rat saliva, suggesting that diffusion coefficients of unbound TCPy are consistent between cell culture systems and *in vivo*. Overall, these experiments demonstrate the importance of protein binding for salivary clearance of TCPy. This combination experimental and computational approach could serve as a platform to predict salivary transport of chemicals highly bound to proteins. *(Supported by CDC/NIOSH grant R01 OH008173 and R01 OH011023)*

3187 A Physiologically-Based Pharmacokinetic Modeling of 5 nm Cerium Oxide Nanoparticles in Intravenous-Infused Rats

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A clear understanding of cerium oxide nanoparticles (nanoceria) toxicokinetics is vital in determining the fate and target dose of nanoceria in tissues. The National Toxicology Program has recommended characterization of nanoceria toxicity and toxicokinetic studies due to inadequate data. To support health risk assessment and medical applications, Physiologically Based Pharmacokinetic (PBPK) models play important role by predicting internal dose and extrapolations. Our objective is therefore to develop a PBPK model for nanoceria administered intravenously into rats. The PBPK model structure and assumptions were based on Carlander et al (*International Journal of Nanomedicine* 2016, 11, 625-40). Berkeley Madonna and acslX-Libero were employed for parameter optimization and model simulation. Visual inspection and linear regression compared the results from calibration and validation studies. The PBPK model successfully describes and predicts the pharmacokinetics of 5 nm citrate-coated nanoceria following intravenous infusion in rats. Phagocytic capacity is found to be the most sensitive parameter.

3188 A Computational Approach for the Development of a New Benchmark Dose and Environmental Public Health Indicators for Chronic Exposure to Chlorpyrifos

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Organophosphorus (OP) compounds are the most widely used group of synthetic chemicals for the control of agricultural and domestic insect pests. Risk assessments for these chemicals have focused primarily on point-of-departure studies to determine benchmark doses (BMD) resulting in a given benchmark response. Based on their acute mode of action, the US EPA has established 10% acetylcholinesterase (AChE) inhibition in the brain as being the benchmark response that is "health protective in that no functional or behavioral effects have been noted below this level in adult of juvenile animals." However, many studies suggest a link between cognitive deficits and long-term OP exposure at doses below this BMD_{AChE10}. Thus, these measurable deficits could potentially serve as a more sensitive endpoint for point-of-departure studies compared to that based on AChE inhibition in the brain. To explore this possibility, a physiologically-based pharmacokinetic model and novel pharmacodynamic model were used to develop a point-of-departure BMD estimate to protect against cognitive deficits following low-dose, chronic exposure to chlorpyrifos (CPF). Previous chronic exposure studies in rats provided a BMD_{AChE10} of 0.67 mg/kg/day of CPF. In contrast, the methodology utilized in this study produced a BMD of 0.14 mg/kg/day for protecting against a 15% neurobehavioral deficit, specifically a decrease in spatial memory and learning. Furthermore, using these models, a method was developed for identifying environmental public health indicators to predict the level of cognitive deficit resulting from a given CPF dosing scenario. In summary, the results from this study not only demonstrate a potentially more protective point-of-departure BMD based on a deficit in cognition, but also illustrate a method for continuous monitoring of health-based outcomes of CPF exposure through quantitation of appropriate biomarkers.

3189 Developing a Pharmacokinetic-Pharmacodynamic (PKPD) Model for On-Target Electrophysiological R-Wave Amplitude Reduction

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Target-related toxicity is often a concern with oncology agents that may have effects on both healthy as well as tumor cells. Understanding the exposure-response relationships for efficacy and toxicity can enable us to identify dosing schedules that mitigate toxicity while still maintaining efficacy. Here, we applied pharmacokinetic-pharmacodynamic (PKPD) modeling to identify optimal schedules for a small molecule oncology therapeutic with cardiovascular toxicity. Preclinical telemetry studies of a targeted oncology therapeutic revealed target-related electrophysiological changes in the form of dose-dependent reductions in the amplitude of the R-wave portion of the EKG trace. This is a highly unusual phenomenon, with little mention in the literature as to mechanism or mitigation, but one which was vital to understand in order to help progress the project. The raw telemetry data showed a delayed onset of the dynamic R-wave response to the systemic exposure (typically first observed ~0.5-1.0 hour after start of infusion) with a non-linear relationship between dose and magnitude of the R-wave deflection, making it difficult to determine if the toxicity was driven by maximal concentration (Cmax) or area under the (concentration) curve (AUC). In order to characterize this relationship quantitatively, we developed a multi-compartment PKPD model for the R-wave deflection and recovery to doses administered over varying infusion lengths. The model used was an integrated PKPD model in which drug kinetics were described with a two-compartment PK model, and pharmacodynamics by an effect compartment coupled to an indirect-response EMax model. This model enabled a quantitative description of the R-wave response to a tenfold range of dose amounts administered over infusion lengths from 0.5 to 3.0 hours. Drug teams often describe effects as being driven by Cmax or AUC; this model allowed us to show that the adverse cardiac symptoms could be driven by both Cmax and AUC for a particular dose. We performed integrated simulations of our PKPD model for toxicity with a tumor-growth model for efficacy in order to create an integrated view of therapeutic index model. We then explored how the therapeutic index (extent of separation between safety and efficacy) changed as a function of infusion duration. Optimization of the integrated TI model showed a 'sweet-spot' for the infusion length - where longer infusions could potentially mitigate R-wave changes yet remain efficacious.

3190 HIF-1α Pathway and Hypoxia: A Mathematical Model

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Episodes of hypoxia were suspected in F-22 Air Force (AF) pilots after training missions in which questions about pilot performance and mission accomplishment were raised. These episodes identified data gaps in the understanding of how hypoxia relates to potential alterations in brain function of pilots in high performance aircraft. Responses to hypoxia take place at multiple levels. The initial response is through carotid body altering physiology (breathing, blood flow). Tissue level responses involve regulating demand for oxygen through altered function. Key to understanding these responses both at the physiological and tissue (brain) level are oxygen sensing pathways, particularly those involving HIF1α. These linked pathways need to be understood mechanistically and quantitatively. *In vitro* studies include HIF1α activation


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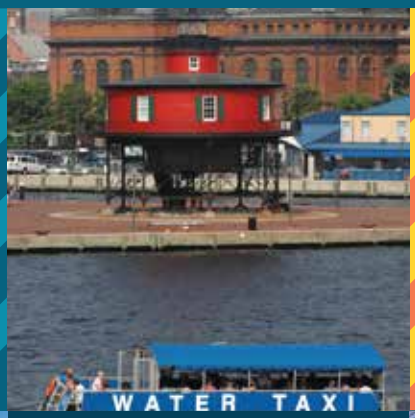

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