1373 MULTI-MODAL VALIDATION OF COMPUTATIONAL PULMONARY AIRFLOW SIMULATIONS IN THE RAT.

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Accurate computational particle deposition predictions are a necessary step toward linking cell response to site-specific dose and mass transfer in a multiscale model of the rat lung. A phase contrast 3He magnetic resonance (MR) measurement of lobar airflow was acquired in a single live rat. Separately, 1.0-μm fluorescent aerosols were administered to five anesthetized Sprague-Dawley rats. At necropsy, the lungs were air-dried and deposited fluorescent microspheres (FMS) were measured in each of the five rat lobes by fluorescence detection. Finally, computation fluid dynamics models of airflow were developed from three distinct Sprague-Dawley airway casts. Velocity at the trachea was based on ventilator measurements. For the first set of simulations, steady-state inhalation conditions were prescribed, assuming zero-pressure outlet boundary conditions for all airways Subsequently, a transient simulation was performed with the velocity waveform of the ventilator used in the FMS study. 1.0-μm particle deposition simulations were carried out based on both steady-state and transient airflows. The pattern of lobar ventilation distribution measured by FMS was quite reproducible and consistent with 3He MRI data whether or not the animal was on a respirator. Predictions for lobar ventilations based on steady-state assumptions, and with simplified outlet boundary conditions were in excellent agreement with both FMS and 3He MRI measurements, despite inter-animal variability in airway geometry. Transient predictions for lobar ventilations agreed well with FMS results, with minor differences during exhalation. These results represent a first order validation of 3D computational pulmonary airflow simulations in laboratory rodents. Future work includes more detailed time-dependent 3He flow measurements as well as quantitative measurement of localized particle deposition. Funded by NHLBI RO1 HL073598-01.

1374 COMPARING PHARMACOKINETIC MODELS FOR PERFLUOROOCTANOIC ACID IN MICE.

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Perfluorooctanoic acid (PFOA) is environmentally persistent and widely detected in humans and wildlife. Half-lives range from approximately 4 hrs in female rats, to 4 days in male rats, 20–30 days in monkeys, and 3–5 years in humans. Increasingly, reproductive and developmental toxicology studies of PFOA use mice. Hence, single and repeated exposures were used to evaluate PK models in this species. The PFOA single oral dose data included three tissues (blood sera, liver and kidney), two genders, and two doses (1 and 10 mg/kg) in two blocks, collected 4 hrs to 80 days post-dosing. Repeated dose sera data were from adult CD-1 male and female mice exposed to 20 mg/kg for 4 or 17 days. One and two compartment models with first order absorption and elimination rates were fitted using generalized nonlinear least squares analyses in the statistical software R. Model comparisons used a likelihood ratio test. A variant of the saturable reabsorption model of Andersen et al. (Toxicology 227:156-64, 2006) was compared to data using Matlab (Mathworks, Natick MA). The two compartment model converged for only 6 of 24 datasets, and results were not statistically significantly better than for the one compartment model. Model parameters - volume of distribution (Vd), absorption and excretion rates - were determined for the three tissues - serum half-life was 16 and 22 days and Vd 0.135 and 0.226 L/kg in females and males, respectively. Using these values, a one compartment model failed to predict the repeated dose data; a 1.2-day half-life is required for females. The saturable reabsorption model can simulate the single dose and repeated dose data attaining pseudo-steady state in 3–4 days consistent with measured serum levels. PFOA serum concentrations appear linear below 50–100 mg/L, but become increasingly nonlinear above that. This abstract does not necessarily reflect US EPA policy.

1375 PBPK MODELING OF THE MAJOR CHLORPYRIFOS METABOLITE TRICHLOROPYRIDINOL: A POTENTIAL BIOMONITORING STRATEGY.

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Chlorpyfios (CPF) is a commonly utilized organophosphorous insecticide and the major urinary metabolite, trichloropyridinol (TCPy), is used to biomonitor for exposure. Saliva has been proposed as a potential non-invasive biomonitoring matrix, but the utility of saliva TCPy to biomonitor for CPF exposures requires a methodology to correlate saliva TCPy with total CPF dose. In this regard, a TCPy PBPK model was developed to link with a validated CPF model to determine the relationship between blood and salivary TCPy in both rats and humans. The TCPy model includes fat, rapidly perfused, and slowly perfused compartments and compartments from which metabolism of CPF or CPF-oxon leads to TCPy production (brain, diaphragm, liver, and blood). Urinary clearance of TCPy was modeled as first-order elimination from the blood compartment and clearance into the saliva was perfusion-based. The pharmacokinetics of TCP in blood and urine were previously determined in rats following CPF oral doses of 1, 10 and 50 mg/kg, and the results used to calibrate the TCPy model. Based on maximum log likelihood function (MLLF) analysis, the model reasonable fit the TCPy blood and saliva concentrations (82 & 87% variation explained) at all doses with the TCPy concentration in blood exceeded saliva (~2-fold), although the kinetics were comparable. The model also reasonably predicted blood concentrations and urinary elimination of TCPy in humans exposed orally to 0.5 mg/kg CPF dose (MLLF >89% variation explained). These findings suggest that the TCPy PBPK model simulates blood and urinary TCPy concentrations following oral exposure to known doses of CPF in both rats and humans. Secondly based on the rat, the TCPy model simulates the kinetics of TCPy clearance from saliva; suggesting that the model can back estimate CPF dosimetry using saliva TCPy. PBPK modeling of TCPy in saliva may represent a viable quantitative biomonitoring approach with broad application for evaluating both occupational and environmental exposures to CPF. (Supported by CDC/NIOSH grant R01 OH008173-02)

1376 UNCERTAINTY ANALYSIS OF HUMAN EXTRAPOLATIONS BY USE OF A PBPK MODEL FOR 1, 2-DICHLOROETHANE (DCE).

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The U.S. EPA is revising its IRIS assessment for DCE, a high production volume chemical used in production of vinyl chloride and other chlorinated chemicals, as a lead scavenger, fumigant and solvent. DCE exposure causes tumors in multiple tissues of rats and mice. A previous PBPK model for DCE dosimetry in rats (D'Souza et al., 1988) was updated and extrapolated to mice, but no data exist to validate a human version. The model describes oxidation and glutathione (GSH) conjugation of DCE and the oxidative metabolite in liver and lung, along with depletion and replenishment of GSH, and the regulation of GSH synthetase. Thus there are multiple key parameters for which human data are unavailable, resulting in high qualitative uncertainty in the extrapolation. Further, there are 8 dose metrics one can consider. We identified a small number of candidate values for each parameter, covering their likely ranges, yielding 30 possible combinations of these parameter candidates. We then automated the computation of human equivalent exposures (HEEs) for each parameter combination and dose metric, and calculated simple summary statistics for the HEEs for each metric, route of exposure, for both mouse- and rat-based points of departure (PODs). The resulting HEEs varied more than 2 orders of magnitude (across all metrics) and were highly uncertain for a number of specific metrics. But for some metrics the HEEs were quite robust (insensitive) with respect to the parameter options; e.g., DCE AUC varied by a factor of only 1.35 between highest and lowest when extrapolated from the rat inhalation POD. The choice of metric/HEE should also reflect mechanistic considerations (e.g., tissue-specific metabolism is most relevant to toxicity in a tissue) and a desire to be health-protective in the face of remaining uncertainty, but the presentation of results across metrics greatly facilitates selection of the most appropriate.
The analysis, results, and opinions presented are those of the authors and do not necessarily represent EPA policy or decisions.

1377 A PBPK MODELING APPROACH FOR *IN VITRO-IN VIVO* EXTRAPOLATION OF DRUG-DRUG METABOLIC INTERACTIONS.

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In vitro screening assays for drug-drug interactions (DDI) are becoming routine procedures in preclinical research for the selection of drug candidates. However, the interpretation of the generated data for the in vivo situation still represents a challenge. In this study, a mechanistically based modeling approach for extrapolating in vitro metabolic DDI data to the in vivo situation is proposed and applied for binary mixtures of debrisoquine (DBQ), bunitrolol (BUN) and R-bufuralol (BUF) in isolated perfused rat liver (IPRL). The model framework is represented by mathematical descriptions that (i) take into account the physiology of the liver and (ii) enable

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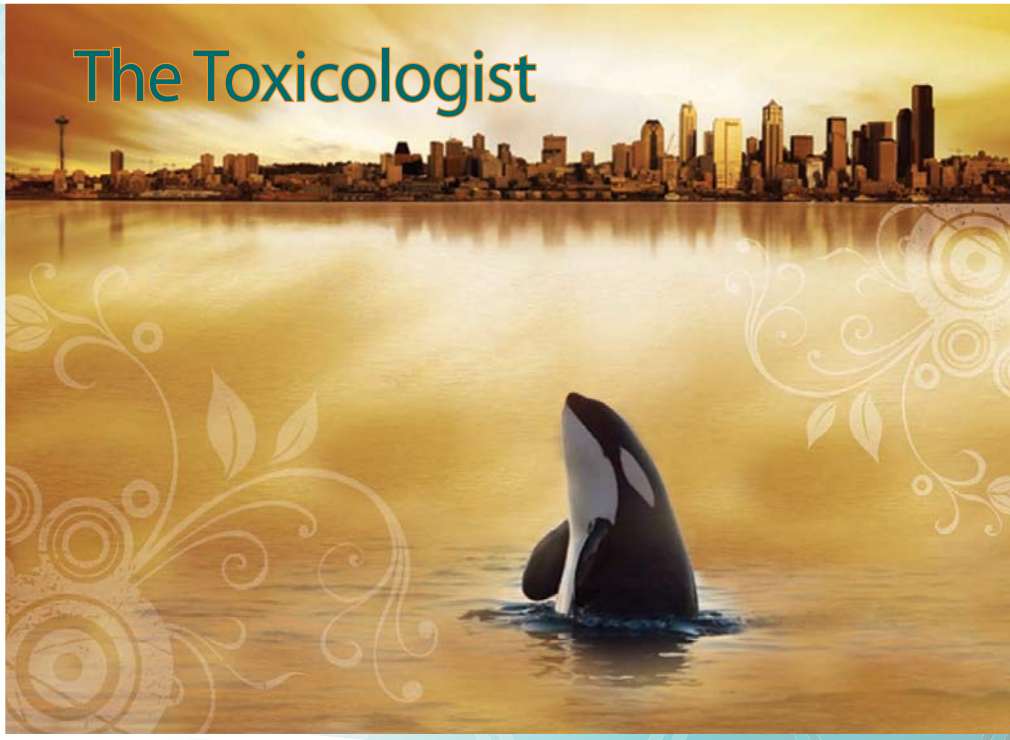

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