Physiologically Based Pharmacokinetic Pbpk Modeling And Simulations Principles Methods And Applications In The Pharmaceutical Industry

A variety of nanoparticles are under development for medicine, energy, food and cosmetics. Both organic and inorganic nanoparticles are playing an increased role in industrial and medical applications. However, little is known about their distribution and effects on the human body, and as a result concerns exist about potential health risks and safety problems. The long-term aim of this research is to quantify the distribution characteristics of nanoparticles and explore how the physicochemical properties of nanoparticles influence their distribution. A physiologically based pharmacokinetic (PBPK) model was successfully developed to describe the pharmacokinetics and biodistribution of nanoparticles in various tissues and blood of the body. A PBPK model based on permeability-limited distribution from the vasculature to tissue spaces was compared with the PBPK model based on flow-limited distribution using literature values for distribution of nanoparticles. In general, the blood-flow limited model is not accurate enough to explain the complete biodistribution of nanoparticles, whereas the permeability-flow limited model provides a more faithful simulation. We also applied a novel formulation of the PBPK model, in which

blood plasma kinetics are decoupled from tissue kinetics, and compared the description to those of traditional, coupled PBPK models. Our model parameterization suggested that the decoupled model method without elimination based on permeability-flow limited model accurately predicted the trends of nanoparticles concentration in both tissue and blood. This could indicate that partition coefficients of tissues combining with blood flow to tissue might have a great influence on the biodistribution of nanoparticles. This work provides a foundation for more accurate PBPK correlation of nanoparticle biodistribution that should be of utility both in the emerging area of nanotoxicology and in the preclinical drug development of nanomedicines.

This study refines risk analysis procedures for trichloroethylene (TCE) using a physiologically based pharmacokinetic (PBPK) model in conjunction with the Monte Carlo method. The Monte Carlo method is used to generate random sets of model parameters, based on the mean, variance, and distribution types. The procedure generates a range of exposure values for human excess lifetime cancer risk of lxl0 (exp-6), based on the upper and lower bounds and the mean of a 95% confidence interval. Risk ranges were produced for both ingestion and inhalation exposures. Results are presented in a graphical format to reduce reliance on qualitative discussions of uncertainty. A sensitivity analysis of the model was also performed. This method produced acceptable TCE exposures, for total amount TCE metabolized, greater than the Environmental Protection Agency's (EPA) by a factor of 23 for inhalation

and a factor of 1.6 for ingestion. Sensitive parameters identified were the elimination rate constant, alveolar ventilation rate, and cardiac output. This procedure quantifies the uncertainty related to natural variations in parameter values. Its incorporation into risk assessment could be used to promulgate, and better present, more realistic standards ... Risk analysis, Physiologically based pharmacokinetics, Pbpk, Trichloroethylene, Monte carlo method.

This report provides an analysis of perchlorate-mediated inhibition of the sodium-iodide symporter (NIS) in humans using published PBPK models, focusing on the degree of NIS inhibition as a function of lifestage. The models provide information that may be used to address differences in human responses to perchlorate across lifestages.

Abstract: Benzocaine, a local anesthetic for mammals, has potential for use as a general anesthetic in finfish. Its pharmacokinetics, metabolism, and residue profiles were characterized to support its approval in fish. To compare interspecies and temperature differences of these parameters channel catfish were studied at 16, 21, and 260C and yellow perch at 160C. The feasibility of "crop grouping" was investigated with a physiologically based pharmacokinetic (PBPK) model as a means to reduce the amount of testing required for aquaculture drug registration.

Physiologically-based pharmacokinetic (PBPK) modeling has become the tool of choice to develop estimates of target site dosimetries in animals and humans for risk assessment purposes. PBPK model compartments

correspond directly to the tissues and organs in the species. The drawbacks of PBPK modeling primarily relate to the time, effort and cost involved in appropriately developing, validating and applying a model. We outline some of the practical issues involved in the appropriate development of a PBPK model. Among the first models to be developed and used for risk assessment were those for volatile organics. These basic models are discussed in this report. For some chemicals, however, simpler models are not enough to adequately describe the data. We discuss some of the issues involved in the development of more complex PBPK models. Issues may include more detailed modeling of metabolic processes and specific organs; changes in physiology due to development, pregnancy or aging (life-stage modeling); and interactions between more than one chemical. It may also be necessary to interface the pharmacokinetic models with models of the interaction of the chemical with the target tissue (pharmacodynamic PD models) in order to provide a more complete description of the overall process. Certain experimental techniques are central to the successful development of PBPK models. These include methods to experimentally determine blood and tissue partition coefficients, metabolic parameters, and exposure kinetics.

Whole-body PBPK models were developed based on both the intestinal traditional model (TM) and segregated-flow model (SFM) to describe codeine sequential metabolism in man/rat. Model parameters were optimized with ScientistRTM and SimcypRTM simulator

to predict literature data after oral (p.o.) and intravenous (i.v.) codeine administration in man/rat. In vivo codeine PK studies on rats were performed to provide more data for simulation. The role of fm' (fractional formation clearance of morphine from codeine) in model discrimination between the TM and SFM was investigated. A greater difference between the [AUC M3G/AUCMorphine]p.o. and [AUCM3G/AUCMorphine]i.v. ratio existed for the SFM, especially when the fm' was low. It was found that our tailor-made PBPK models using ScientistRTM were superior to those from SimcypRTM in describing codeine sequential metabolism. Residual sum of squares and AUC's were calculated for each model, which demonstrated superiority of the SFM over TM in predicting codeine sequential metabolism in man/rat.

The only book dedicated to physiologically-based pharmacokineticmodeling in pharmaceutical science Physiologically-based pharmacokinetic (PBPK) modeling has becomeincreasingly widespread within the pharmaceutical industry over thelast decade, but without one dedicated book that provides theinformation researchers need to learn these new techniques, itsapplications are severely limited. Describing the principles,methods, and applications of PBPK modeling as used inpharmaceutics, Physiologically-Based Pharmacokinetic (PBPK)Modeling and Simulations fills this void. Connecting theory with practice, the book explores theincredible potential of PBPK modeling for improving drug discoveryand development. Comprised of two parts, the book first provides adetailed and systematic treatment of the principles behindphysiological modeling of pharmacokinetic processes,inter-individual variability, and drug interactions for

smallmolecule drugs and biologics. The second part looks in greaterdetail at the powerful applications of PBPK to drug research. Designed for a wide audience encompassing readers looking for abrief overview of the field as well as those who need more detail,the book includes a range of important learning aids. Featuringend-of-chapter keywords for easy reference—a valuable assetfor general or novice readers without a PBPK background—alongwith an extensive bibliography for those looking for furtherinformation, Physiologically- Based Pharmacokinetic (PBPK) Modelingand Simulations is the essential single-volume text on one of thehottest topics in the pharmaceutical sciences today.
Physiologically-Based Pharmacokinetic (PBPK) Modeling and SimulationsPrinciples, Methods, and Applications in the Pharmaceutical IndustryJohn Wiley & Sons
In this paper we present three physiologically based pharmacokinetic (PBPK) models for the systemic transport of trichloroethylene (TCE), with a focus on the adipose, or fat tissue. TCE is a widespread environmental contaminant, and has been shown to produce toxic effects in both animals and humans. A key characteristic of TCE is its tendency to accumulate in fat tissue, which has a major impact on the overall systemic disposition of TCE. Here we use PBPK models to predict the kinetics of TCE through the various tissues and organs, including the adipose tissue. The first model utilizes the standard "perfusion-limited" compartmental model for the fat tissue, while the second model uses a "diffusion-limited" model to describe the transport through the adipose tissue. Both of these ODE models are based on "well-mixed" and rapid equilibrium assumptions, and do not take into account the specific and largely heterogeneous physiology of adipose tissue. The third model we discuss is a PBPK hybrid model with an axial-dispersion type model for the adipose tissue. This PDE-based model is designed to

capture key physiological heterogeneities of fat tissue, including widely varying fat cell sizes, lipid distribution, and blood flow properties. Model simulations demonstrate that this model may be well-suited to predict the experimental behavior of TCE in adipose tissue using parameter estimation techniques.

Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulations The first book dedicated to the emerging field of physiologically based pharmacokinetic modeling (PBPK) Now in its second edition, Physiologically Based Pharmacokinetic (PBPK) Modelling and Simulations: Principles, Methods, and Applications in the Pharma Industry remains the premier reference book throughout the rapidly growing PBPK user community. Using clear and concise language, author Sheila Annie Peters connects theory with practice as she explores the vast potential of PBPK modeling for improving drug discovery and development. This fully updated new edition covers key developments in the field of PBPK modelling and simulations that have emerged in recent years. A brand-new section provides case studies in different application areas of PBPK modelling, including drug-drug interaction, genetic polymorphism, renal impairment, and pediatric extrapolation. Additional chapters address topics such as model-informed drug development (MIDD) and expose readers to a wide range of current applications in the field. Throughout the book, substantially revised chapters simplify complex topics and offer a balanced view of both the opportunities and challenges of PBPK modelling. Providing timely and comprehensive coverage of one of the most exciting new areas of pharmaceutical science, this book: Describes the principles behind physiological modeling of pharmacokinetic processes, inter-individual variability, and drug interactions for small molecule drugs and biologics Features a wealth of new figures and case studies of the applications of PBPK

modelling along the value chain in drug discovery and development Reflects the latest regulatory guidelines on the reporting of PBPK modelling analysis Includes access to a new companion website containing code, datasets, explanations of case examples in the text, and discussion of key developments in the field Contains a brief overview of the field, end-of-chapter keywords for easy reference, and an extensive bibliography Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulations: Principles, Methods, and Applications in the Pharmaceutical Industry, Second Edition is an indispensable single-volume resource for beginning and intermediate practitioners across the pharmaceutical sciences in both industry and academia. The physiologically based pharmacokinetic (PBPK) modelling has been accepted as one of the most effective mechanistic techniques to analyze pharmacokinetics (PK) of drugs in the drug development process. Its effectiveness in predicting the PK of drugs is important not only to the current drug development industry but also to potential growth of the pharmaceutical industry as it helps resolve ethical challenges. The PK of cisplatin as an anticancer drug, and its metabolic disposition are investigated by proposing a PBPK modelling framework. A plausible PBPK model is developed to test and validate its predictive utility for extrapolation to other species with the drug. Building and testing a PBPK modelling workflow for translating from rat to human PK scenarios for cisplatin is particularly emphasized. Moreover, this workflow may be helpful to studying and understanding the PK of cisplatin analogues in future studies. In this thesis, the PK of cisplatin is quantitatively studied by employing the PBPK modelling technique, and the modality of interspecies extrapolation from rat models to human models is then tested. As the metabolic mechanism of cisplatin is not evidently revealed, several assumptions have been made to

successfully construct the PBPK model which would closely reproduce observed PK data of cisplatin for rats as well as for humans. Based on these assumptions, several parameters which define cisplatin ADME in an organism are reasonably selected. These parameters are optimized based on observed rat PK data by using a numerical optimization process. The PBPK model constructed based on the rat PK data is then evaluated by means of validating the optimized values of the parameters through comparing the PK simulations with other observed PK data for rats. Lastly, the validity of the model for the predictive performance on humans is assessed by translating the model into a human model and evaluating it based on observed PK data for humans.

Dermal penetration of chemicals and drugs is important to both toxicologists and pharmacologists. Drug developers try to enhance and environmental professionals try to limit penetration of chemicals through the skin. Both can use predictive biologically-based mathematical models to assist in understanding the processes involved. When these models are based on physiological and biochemical parameters which can be measured in the laboratory, they can be extremely useful. Appropriately validated models based on first principles can be predictive of human exposures when the processes involved are adequately understood. In this thesis we develop four new physiologically-based pharmacokinetic (PBPK) models to predict blood concentrations of dibromomethane (DBM) in rats after neat liquid and vapor exposure. These four new models expand previously developed homogeneous models by adding skin subcompartments. These new models improve the prediction of the blood concentrations especially early in the exposure. Sensitivity analysis shows that one of the permeability constants followed by the blood air partition coefficient have

the most impact on blood concentration predictions. With proper validation the new models could be used to improve species, dose, and duration extrapolations of chemical or drug penetration. They could also be used to investigate and predict concentrations of drugs or chemicals in different parts of the skin.

JP-8 is a complex mixture of hundreds of components including straight and branched chain alkanes, cycloalkanes, diaromatics and naphthalenes. Inhalation and dermal are the most prevalent routes of exposure. Occupations of interest include aircraft fuel tank and exhaust workers. To assess potential health effects of such exposures, it is useful to predict target site dosimetry of JP-8 components. A first step in this process is to develop a physiologically based pharmacokinetic (PBPK) model for representative mixture components. Single-chemical models can then be "harmonized" (same physiological structure) and combined into a composite-mixture model. A harmonized model structure should be complex enough to take into account all important physiological processes undergone by any component in an integrated fashion; the same physiological structure must underlie each of the individual models. The initial framework for such a model is developed here on the basis of observed kinetic behavior of nonane, an aliphatic JP-8 component. Nonane is highly lipophilic and distributes preferentially in brain tissue. Three physiologically based pharmacokinetic

(PBPK) models for thesystemic transport of inhaled trichloroethylene (TCE) are presented. The major focus ofthese modeling efforts is the disposition of TCE in the adiposetissue, where TCE is known to accumulate. Adipose tissue is highly heterogeneous, with wide variations in fat cell size, lipid composition, blood flow rates and cellpermeability. Since TCE is highly lipophilic, the uneven distributionof lipids in the adipose tissue may lead to an uneven distribution of TCEwithin the fat. These physiological characteristics suggest that thedynamics of TCE in the adipose tissue may depend on spatial variations within the tissue itself. The first PBPK model for inhaled TCE presented here is a system ofordinary differential equations which includes the standardperfusion-limited compartmental model for each of the adipose, brain, kidney, liver, muscle and remaining tissue compartments. Model simulations predict relatively rapiddecreases in TCE fat concentrations following exposure, which may notreflect the accumulation and relative persistence of TCE inside the fattissue. The second PBPK model is identical to the first except forthe adipose tissue compartment, which is modeled as a diffusion-limited compartment. Although this model yields various concentration profiles for TCE inthe adipose tissue depending on the value of the permeabilitycoefficient, this model may not be physically appropriate for TCE, which is highly

lipophilic and has a low molecular weight. Moreover, neither of these two PBPK models is able to capture spatialvariation of TCE concentrations in adipose tissue as suggested bythe physiology. The third model we present is a hybrid PBPK model with adispersion-type model for the transport of TCE in the adipose tissue. Thedispersion model is designed to account for the heterogeneities within fattissue, as well as the corresponding spatial variation of TCE concentrationsthat may occur. This partial differential equation.

Intestinal permeability was predicted using a set of related compound data to correlate measured Caco-2 permeability with molecular descriptors by multivariate regression. Sensitivity analyses were conducted to evaluate the impact of PBPK model parameters on plasma level predictions. To evaluate patient population effects on exposure profiles, the PBPK model parameters were varied in meaningful ways using Monte Carlo methods. Based on population PBPK models, distributions of target tissue exposure in rats and humans were simulated and compared to derive human safe dose. As results, rat PBPK model-predicted aniline concentration time profiles were in reasonable agreement with published profiles. Distributions of target tissue exposure in rats and humans were generated and compared based on a criterion. A human reference dose was then selected at a value

of 1% criteria. This approach was compared to traditional risk assessment calculations. In conclusion, the PBPK modeling approach resulted in drug degradation product risk specifications that were less stringent than those estimated by conventional risk assessment approach. The PBPK modeling approach provides a rational basis for drug instability risk assessment by focusing on target tissue exposure and leveraging physiological, biochemical, biophysical knowledge of compounds and species.

The goal of this study was to develop a physiologically based pharmacokinetic (PBPK) model that predicts mammalian blood concentrations of dibromomethane following exposure by dermal absorption more accurately than a previously developed Homogeneous Dermal Model. The Homogeneous Dermal Model contains a dermal compartment with no dermal sub-compartments. The 1:1 Dermal Model developed in this research contains a dermal compartment with a stratum corneum and a composite dermal sub-compartment of equal volume. This model yields predictions which are 21.4 percent more accurate than the original homogeneous model. In order to represent skin anatomy more accurately, the 1:10 Dermal Model variation was developed. The 1:10 Dermal model contains a dermal compartment with a composite dermal sub-compartment ten times the volume of the

stratum corneum sub-compartment. The 1:10 Dermal Model yields predictions which are 17.7 percent more accurate than the original model. Finally, the 1:3:7 Dermal Model was developed which contains a viable epidermis sub-compartment three times the volume of the stratum corneum sub-compartment and a composite dermal sub-compartment which is seven times the volume of the stratum corneum sub-compartment. This model yields predictions 27.7 percent more accurate than the original model. Physiologically Based Pharmacokinetic model, Pharmacokinetic model, Mathematical model, Dermal Absorption.

Classical approaches to pharmacokinetics, such as compartmental and non-compartmental analysis, provide the basis for most dosing regimens and meat and milk withholding intervals. These models are limited by their descriptive nature to dose, route of administration, and species. In addition, current pharmacokinetic modeling approaches are unable to predict possible adverse drug reactions due to drug interactions. As combination drug therapy is rapidly increasing, so too does the chance for an adverse drug reaction due to drug interactions. There is a need within veterinary medicine for more predictive and flexible pharmacokinetic modeling approaches that can also be used to explore the possibilities and consequences of adverse drug reactions. Physiologically based pharmacokinetic (PBPK)

models predict drug disposition based on mass balance. This mechanistic approach is predictive and flexible in terms of dose, route of administration, and species. Current uses of PBPK models include human health risk assessment, design of rational dosing regimens, and mechanistic studies of drug interactions. In veterinary medicine, there are only a few validated models. Protection of the safety of the food supply is an important application of pharmacokinetics. By federal law, no animal products are allowed into the food chain until drug residue levels are below set tolerance limits. Sulfamethazine is a sulfonamide antibiotic that is commonly found above tolerance limits in swine. Sulfonamide drugs are associated with hypersensitivity reactions in humans and are carcinogenic in certain strains of rats. Thus violative residues could contribute to a significant public health hazard. To address this concern, a PBPK model was designed and validated for intravenous use of sulfamethazine in swine. This model had tissue blocks for all edible tissues. Correlation coefficients for each tissue ranged from 0.86 to 0.99. The model accurately predicted withdrawal intervals after intravenous ext.

A physiologically based pharmacokinetic (PBPK) model was developed which provides a comprehensive description of the kinetics of trichioroethylene (TCE) and its metabolites,

trichloroethanol (TCOH), and trichloroacetic acid (TCA), in the mouse, rat, and human, for both oral and inhalation exposure. The model includes descriptions of the three principal target tissues for cancer identified in animal bloassays: liver, lung, and kidney. Dose metrics that can be calculated with the model for cancer risk assessment include the area under the concentration curve (AUC) for TCA in the plasma or liver, the peak concentration and AUC for chloral (CHL) in the tracheo-bronchial region of the lung, and the production of a thioacetylating intermediate from dichlorovinylcysteine (DCVC) in the kidney. Additional dose metrics that can be calculated for noncancer risk assessment include the peak concentrations and AUCs for TCE and TCOH in the blood, as well as the total metabolism of TCE divided by the body weight. There is currently no adequate data available with which to confidently parameterize a description for another metabolite of interest, dichloroacetic acid (DCA). Model predictions of TCE. TCA, and TCOH concentrations in rodents and humans are consistent with a variety of experimental data, suggesting that the model should provide a useful basis for evaluating cross-species differences in pharmacokinetics for these chemicals. In the case of the lung and kidney target tissues, however, only limited data are available for establishing cross-species pharmacokinetics. As a result, PBPK model calculations for these dose

metrics are highly uncertain.

Human health risk assessment is “the process to estimate the nature and probability of adverse health effects in humans who may be exposed to chemicals in contaminated environmental media, now or in the future.” Currently, most data required for human risk assessment are derived from toxicological studies conducted in laboratory animals. The “Toxicology in the 21st Century” initiative expands the toxicity testing tools to include the development of alternative toxicity testing methods that examine pathways of toxicity (on a large scale) and the employment of dose-response and extrapolation modeling tools. While the latter methodology is in its infancy, several methodologies for dose-response and extrapolation modeling are more mature. Over the last decade, physiologically based pharmacokinetic (PBPK) modeling has gained acceptance as a computational tool for use in public health assessments. In this chapter, we present examples of quantitative structure-activity relationship (QSAR) models, physiologically based pharmacokinetic (PBPK) models, and biologically based dose response (BBDR) models that have been developed for use in public health assessments and advancing knowledge gained through in silico examinations of biological systems. Physiologically-based pharmacokinetic (PBPK) models integrate system specific anatomy and physiology information with drug specific physicochemical and pharmacokinetic properties to predict drug disposition. Such integration permits items, events, processes, and pathways to communicate and influence each other interactively. By taking advantage of such mechanistic nature of PBPK modeling, drug dispositions under untested scenarios could be predicted by extrapolation from observed data in known conditions. Renal clearance is one of the major pathways

governing drug dispositions, which has three main mechanisms: unbound filtration, passive reabsorption, and active secretion. In comparison to intestinal absorption and hepatic metabolism, renal clearance has been relatively underappreciated. Controlled clinical experiments that test renal clearance changes under altered conditions and mechanisms have been primarily focusing on drug-drug interaction on active secretion. However, huge gaps in understanding renal clearance still exist in other areas such as altered urine pH and impaired renal function. Further, passive reabsorption has not been paid significant attention by the pharmaceutical field. Therefore, the overarching goal of this thesis is to leverage mechanistic PBPK modeling technique to understand and predict renal clearance of drugs and metabolites under altered urine pH and impaired renal function, with a special focus on compounds undergoing significant renal passive reabsorption. In Chapter 2, to predict the spatiodynamic process of renal passive reabsorption in human, we developed a dynamic physiologically-based mechanistic kidney model based on human data that can integrate drug permeability, tubular surface area, ionization status, and drug concentration gradient between lumen and system to estimate renal passive reabsorption and predict renal clearance of drugs. Using 46 test compounds with a variety of physicochemical properties, the model successfully predicted the renal clearances of 87% compounds within 2-fold and 98% compounds within 3-fold. Further, by incorporating active secretion, the model also successfully predicted the renal clearances of para-aminohippuric acid (PAH), cimetidine, salicylic acid, and memantine. In Chapter 3, to ensure the simulation output from PBPK models can be meaningfully compared to the arm vein plasma drug concentrations collected in clinical studies, we developed a forearm model that captures the tissue distribution at the

peripheral sampling site using human arm physiology data, allowing for a better prediction of plasma drug concentrations that are comparable to observed data. The model was successfully verified using arterial and venous concentrations of nicotine, ketamine, lidocaine, and fentanyl simultaneously. Further, I demonstrated that use of a discrepant sampling site in PBPK modeling than observed clinical studies may lead to biased model evaluation, erroneous model parameterization, and misleading prediction in unstudied clinical scenarios. In Chapter 4, to predict the altered renal excretion and systemic AUC of drug and metabolite when urine pH is changed, the mechanistic kidney model developed and verified from Chapter 2 was integrated with the peripheral arm sampling and full body PBPK model developed from Chapter 3. The model was successfully verified with methamphetamine and amphetamine under varying urine pH statuses, and showed feasibility to predict quantitatively and clinically significant changes in drug and metabolite disposition under comedications and diseases that can alter urine pH. In Chapter 5, to predict renal clearance in patients with impaired renal function such as chronic kidney diseases, physiological changes in tubular flow and urine flow observed in chronic kidney disease patients were incorporated into the mechanistic kidney model developed and verified from Chapter 2. The model accounts for the adaptive renal tubular filtrate flows that decrease disproportionately with glomerular filtration rate, and was successfully verified using three parent-metabolite pairs, six non-permeable drugs, six permeable drugs, and two secreted drugs. In conclusion, in this thesis, I developed and verified a physiologically-based mechanistic kidney model to translate drug properties such as plasma protein binding, transcellular permeability, and active transport into renal clearance of drugs and metabolites. This mechanistic kidney model allows prediction of alterations in

renal clearance of drugs and metabolites upon changes in urine pH and renal functions, and can be incorporated into a full-body PBPK model to predict alterations in systemic disposition of drugs and metabolites.

A definitive, single source of information on PBPK modeling Physiologically-based pharmacokinetic (PBPK) modeling is becomingincreasingly important in human health risk assessments and insupporting pharmacodynamic modeling for toxic responses. Organizedby classes of compounds and modeling purposes so users can quicklyaccess information, this is the first comprehensive reference ofits kind. This book presents an overview of the underlying principles of PBPKmodel development. Then it provides a compendium of PBPK modelinginformation, including historical development, specific modelingchallenges, and current practices for: * Halogenated Alkanes * Halogenated Alkenes * Alkene and Aromatic Compounds * Reactive Vapors in the Nasal Cavity * Alkanes, Oxyhydrocarbons, and Related Compounds * Pesticides and Persistent Organic Pollutants * Dioxin and Related Compounds * Metals and Inorganic Compounds * Drugs * Antineoplastic Agents * Perinatal Transfer * Mixtures * Dermal Exposure Models In addition to pinpointing specific information, readers canexplore diverse modeling techniques and applications. Anauthoritative reference for toxicologists, ecotoxicologists, riskassessors, regulators, pharmacologists, pharmacists, and graduatestudents in pharmacokinetics and toxicology, Physiologically-BasedPharmacokinetic Modeling compiles information from leaders in thefield and discusses future directions for PBPK modeling.

Toxicokinetics in Risk Assessment discusses the noncancer risk assessment process and its reliance on uncertainty factors in order to facilitate the continued study and refinement of the scientific basis for health risk assessment. This text clearly demonstrates the application of

physiologically-based pharmacokinetic (PBPK) modeling in human healt

Physiologically Based Pharmacokinetic (PBPK) Modeling: Methods and Applications in Toxicology and Risk Assessment presents foundational principles, advanced techniques and applications of PBPK modeling. Contributions from experts in PBPK modeling cover topics such as pharmacokinetic principles, classical physiological models, the application of physiological models for dose-response and risk assessment, the use of in vitro information, and in silico methods. With end-of-chapter exercises that allow readers to practice and learn the skills associated with PBPK modeling, dose-response, and its applications to safety and risk assessments, this book is a foundational resource that provides practical coverage of PBPK modeling for graduate students, academics, researchers, and more. Provides end-of-chapter exercises to teach hands-on computational tools used in toxicology Supplies computer code and explanations and includes examples of applied models used in regulatory toxicology and research Authored by expert editors and contributors who are among the best PBPK modelers in the world

The value of any Physiologically Based Pharmacokinetic (PBPK) model depends largely on the quality of the parameter estimates entered into the model. One of the critically important parameters requiring estimation is the partition coefficient. Commonly in the field of pharmacokinetics, partition coefficients are determined by the modified version of the vial equilibration technique. This method is an in vitro method in which an animal must be sacnficed, and the tissue and blood harvested to complete the procedure. In the vial equilibration technique, certain physiological aspects must be compromised as the tissues are isolated from a living system. However, a method to

determine various partition coefficients in vivo would reduce or eliminate the compromises inherent in the in vitro approach. This technical report describes a method that was developed to determine in vivo partition coefficients by using microdialysis probes. If the microdialysis probe method of determining partition coefficients in vivo is shown to be valid, then it could be used in collaboration with the vial equilibration method to provide partition coefficients of better quality than is currently available. Therefore, the data produced by the pharmacokinetic models in which partition coefficients are used would be greatly enhanced.

Genistein is an endocrine-active compound found naturally in soy products. It has been linked to various health effects, both beneficial and adverse. The liver is a major site of genistein transformation. Experimental data suggest genistein is metabolized in the liver into its glucuronide form, and taken back into the gut lumen via biliary excretion. The data show a nontrivial, dose dependent delay in biliary excretion of genistein. Traditional physiologically-based pharmacokinetic (PBPK) modeling methods fail to accurately describe the observed data. We have developed several models that incorporate techniques not typically found in PBPK models to simulate the observed dynamics. The first of these models developed is based on delay differential equations (DDE), where the observed lag in biliary excretion is mathematically described by a time delay. Existence and uniqueness of a solution to the system of equations was obtained and the unknown parameters were obtained via an inverse problem formulation. The nonlinear system of state-dependent delay equations was approximated by a three-stage, implicit, Runge-

Kutta method. Using a statistical hypothesis test, we showed that the delay model with the optimal set of parameters obtained is a statistically significant improvement over the PBPK model in simulating the experimental data. Our second modeling approach was taken by considering a dispersion modeling technique. We seeked to develop a fully functioning model for the liver that simulates the distribution, metabolism and excretion of chemicals, and is able to accommodate spatial variations in biologically- and physiologically-based parameters. Our modeling strategy considers the liver as a series of cylindrical tubes, one representing the blood vessel space and one representing the bile duct space, with hepatocytes in between. Dispersion coefficients were adjusted to create a biologically relevant distribution of the concentration of genistein and its metabolites. W.

Els models farmacocinètics (PBPK) són representacions matemàtiques del cos humà, que tenen com a objectiu calcular la concentració de compostos químics en els teixits humans. Els models PBPK poden millorar el càlcul del risc per a la salut humana, però de moment no han estat escassament utilitzats. Entre els compostos ambientals més perillosos per a la salut humana destaquen les dibenzo-p-dioxines policlorades i dibenzofurans policlorats (PC01/Fs) i els compostos perfluorats (PFASs). L'objectiu de la present tesis es el desenvolupament de un model PBPK per calcular la concentració de PC01/Fs i PFASs en teixits humans. Prèviament al desenvolupament del model PBPK, es va desenvolupar un índex de risc utilitzant mapes auto-

organitzats (SOM), per calcular els compostos ambientals més perillosos per a la salut humana. Entre els compostos més perillosos es van trobar els PFASs. Després es va desenvolupar el model PBPK per predir les concentracions de PC01/Fs en sang i en teixit adipós. Els resultats finals van ser altament coincidents amb els resultats experimentals trobats a l'àrea de Tarragona (NE d'Espanya), y per això es va considerar el model com a validat. A continuació el model es va adaptar per calcular les concentracions de PFASs. Per això, primer es va adaptar el model per PFOS i PFOA, que són els compostos perfluorats més estudiats en la literatura, i després es va estendre el model a 9 PFASs més. Finalment, es va fer un anàlisis de la incertesa del model PBPK, i la incertesa paramètrica es va estudiar visual i estadísticament.

Lack of pediatric clinical data has led to a large gap in knowledge concerning drug efficacy, safety and dosing guidelines within the pediatric population. Many pediatric off-label doses are based largely on adult studies with little or no pediatric experience; this has the potential to lead to treatment failures, toxicities, and various other drug-related adverse events. Given that recruitment to pediatric trials is difficult, researchers have recently used physiologically-based pharmacokinetic (PBPK) models as a means to efficiently plan pediatric clinical studies. PBPK models are mechanistic in nature and mathematically describe the disposition of drugs in an organism. This in silico technique predicts pharmacokinetic (PK) profiles based on compound physicochemical properties and multiple physiological

input parameters of the individual, such as organ volumes, tissue composition, blood flow, and clearance (CL). Pediatric PK parameters are typically predicted using a pediatric PBPK model that has been developed using an adult PBPK model and clinical PK data. Within this workflow for pediatric PBPK model development, adult intravenous (IV) data is typically used; however, there are many instances where there may not be an IV formulation available for certain compounds. As a result, the question remains if the workflow for pediatric PBPK modeling produces accurate pediatric PK predictions in the absence of adult IV data. In this case, IV data from pre-clinical species (i.e. rat) may be an alternative to human IV data. The objective of this study was to assess the ability of pediatric PBPK models to predict observed pediatric PK parameters using a model development workflow that uses rat IV PK data, as opposed to adult human IV PK data. The implications of both workflows were assessed by comparing the precision and bias of the predicted vs. observed PK exposure metrics in children. This study demonstrated that rat IV data is a viable alternative to using adult IV PK data within the pediatric PBPK model development workflow and the majority of exposure metrics were within 2 fold from the observed pediatric data, regardless of workflow or Biopharmaceutics Classification System (BCS) class of the compound. Ultimately, the model was not hindered in its prediction accuracy, despite a lack of distribution and clearance data that would otherwise have been derived from human IV data. Overall, the application of rat IV data as a substitute for human IV data in PBPK modeling

is a novel approach that has significant potential for future application.

This book describes the application of physiologically based pharmacokinetic (PBPK) modeling to characterize the disposition of therapeutic monoclonal antibodies (MAbs). These macromolecules exhibit distinctly different pharmacokinetic features compared with conventional small-molecule drugs. A PBPK model was developed to characterize the biodistribution of the pancarcinoma MAb CC49 in normal and neoplastic tissues of nude mice. The model included all the major processes involved in determining the disposition characteristics of MAbs. The applicability of the model was tested by predicting the disposition of di- and tetravalent scFv constructs of CC49 in mice. Further, the model was applied to study the differences in disposition between Mabs labeled with 125I and 177Lu. Finally, the clinical utility of the model was tested by attempting to predict the disposition and tumor uptake of CC49 in patients. This model may be used to study the biodistribution and tumor localization of different combinations of radionuclides and engineered antibody fragments in an effort to establish the most effective approach to achieve the optimal therapeutic ratio for tumor therapy.