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

Targeting protein degradation using small molecules is one of the most exciting small-molecule therapeutic strategies in decades and a rapidly growing area of research. In particular, the development of proteolysis targeting chimera (PROTACs) as potential drugs capable of recruiting target proteins to the cellular quality control machinery for elimination has opened new avenues to address traditionally 'difficult to target' proteins. This book provides a comprehensive overview from the leading academic and industrial experts on recent developments, scope and limitations in this dynamically growing research area; an ideal reference work for researchers in drug discovery and chemical biology as well as advanced students.

Trichloroethylene is a chlorinated solvent widely used as a degreasing agent in industrial and manufacturing settings. It is also used as a chemical intermediate in making other chemicals and is a component of products such as typewriter correction fluid, paint removers, adhesives, and spot removers. In 2001, EPA issued a draft health risk assessment and proposed exposure standards for trichloroethylene. PA's Scientific Advisory Board (SAB) reviewed the draft and it was issued for public comment. A number of scientific issues were raised during the course of these reviews. Assessing the Human Health Risks of Trichloroethylene identifies and assesses the key scientific issues relevant to analyzing the human health risks of trichloroethylene, considering pertinent toxicologic, epidemiologic, population susceptibility, and other available information, including relevant published scientific literature, EPA's 2001 draft health risk assessment of trichloroethylene, scientific and technical comments received by EPA from public and private sources, and additional relevant information to be provided by the sponsoring agencies. This report highlights issues critical to the development of an objective, realistic, and scientifically balanced trichloroethylene health risk assessment. Guidance for hazard characterization of trichloroethylene is presented in Chapters 2 through 10. Chapter 2 provides guidance for evaluating large sets of epidemiologic data. In Chapter 3, the committee applies this guidance as an example in its evaluation of the epidemiologic data on trichloroethylene and kidney cancer, and this example should help guide evaluations of other cancer risks. Chapter 3 also assesses new information on the kidney toxicity of trichloroethylene and its metabolites and potential modes of action. Chapters 4, 5, 6, 7, and 8 evaluate the key issues regarding liver toxicity and cancer, reproductive and developmental toxicity, neurotoxicity, respiratory tract toxicity and cancer, and immunotoxicity, respectively. However, the committee's review focused on mode-of-action information to understand how trichloroethylene might affect certain processes differently in different species. Chapter 9 discusses susceptibility to trichloroethylene and its metabolites, and Chapter 10 describes important factors in considering trichloroethylene in mixtures. Physiologically based pharmacokinetic models are evaluated in Chapter 11, and guidance is provided on future directions for model development. Finally, Chapter 12 considers issues related to dose-response assessment and quantitative assessment of risk.

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.

Inhibition of the Sodium-iodide Symporter by Perchlorate

Human Biomonitoring for Environmental Chemicals

Key Issues and Case Studies (final Report).

Quantitative Modeling in Toxicology

Protein Degradation with New Chemical Modalities

Methods and Applications in Toxicology and Risk Assessment

Biomonitoring—a method for measuring amounts of toxic chemicals in human tissues—is a valuable tool for studying potentially harmful environmental chemicals. Biomonitoring data have been used to confirm exposures to chemicals and validate public health policies. For example, population biomonitoring data showing high blood lead concentrations resulted in the U.S. Environmental Protection Agency's (EPA's) regulatory reduction of lead in gasoline; biomonitoring data confirmed a resultant drop in blood lead concentrations. Despite recent advances, the science needed to understand the implications of the biomonitoring data for human health is still in its nascent stages. Use of the data also raises communication and ethical challenges. In response to a congressional request, EPA asked the National Research Council to address those challenges in an independent study. Human Biomonitoring for Environmental Chemicals provides a framework for improving the use of biomonitoring data including developing and using biomarkers (measures of exposure), research to improve the interpretation of data, ways to communicate findings to the public, and a review of ethical issues.

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.

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 Modeling

CYP450-mediated Drug-drug Interactions

Physiologically-Based Pharmacokinetic (PBPK) Models for the Description of Sequential Metabolism of Codeine to Morphine and Morphine 3-Glucuronide (M3G) in Man and Rat

Providing a Theoretical Basis for Nanotoxicity Risk Analysis Departing from Traditional Physiologically-based Pharmacokinetic (PBPK) Modeling

Assessing the Human Health Risks of Trichloroethylene

A General and Age-dependent Physiological Based Pharmacokinetic (PBPK) Model Development

Explore this comprehensive discussion of the application of physiologically- and physicochemical-based models to guide drug delivery edited by leading experts in the field Drug Delivery Approaches: Perspectives from Pharmacokinetics and Pharmacodynamics delivers a thorough discussion of drug delivery options to achieve target profiles and approaches as defined by physical and pharmacokinetic models. The book offers an overview of drug absorption and physiological models, chapters on oral delivery routes with a focus on both PBPK and multiple dosage form options. It also provides an explanation of the pharmacokinetics of the formulation of drugs delivered by systemic transdermal routes. The distinguished editors have included practical and accessible resources that address the biological and delivery approaches to pulmonary and mucosal delivery of drugs. Emergency care settings are also described, with explorations of the relationship between parenteral infusion profiles and PK/PD. The future of drug delivery is addressed via discussions of virtual experiments to elucidate mechanisms and approaches to drug delivery and personalized medicine. Readers will also benefit from the inclusion of: A thorough introduction to the utility of mathematical models in drug development and delivery An exploration of the techniques and applications of physiologically based models to drug delivery Discussions of oral delivery and pharmacokinetic models and oral site-directed delivery A review of integrated transdermal delivery and pharmacokinetics in development An examination of virtual experiment methods for integrating pharmacokinetic, pharmacodynamic, and drug delivery mechanisms Alternative endpoints to pharmacokinetics for topical delivery Perfect for researchers, industrial scientists, graduate students, and postdoctoral students in the area of pharmaceutical science and engineering, Drug Delivery Approaches: Perspectives from Pharmacokinetics and Pharmacodynamics will also earn a place in the libraries of formulators, pharmacokineticists, and clinical pharmacologists.

This book provides a comprehensive and up-to-date coverage of the relationship between drug metabolism enzymes and transporters on drug toxicity, along with methods to investigate their role on adverse drug reactions. Unites both the metabolism and transporter components of drug toxicity - two aspects not normally connected and the latter often neglected Familiarizes readers with the mechanism and species differences in drug metabolizing enzymes and transporters Discusses promising approaches to accurately predict human drug toxicity via the incorporation of human drug metabolism in toxicity evaluation

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 (PCO1/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.

Uncertainty and Variability in Physiologically-based Pharmacokinetic (PBPK) Models

Toxicokinetics and Risk Assessment

Physiologically Based Pharmacokinetic (PBPK) Model Development of Perfluorocarboxylic Acids for Rats and Humans

A Parameter Analysis of a Physiologically Based Pharmacokinetic (PBPK) Model Describing the Movements of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the Mouse

Consequences of a Lack of Adult Intravenous Data on the Prediction Accuracy of Pediatric Physiologically Based Pharmacokinetic (PBPK) Modeling

Biopharmaceutics

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.

Ecotoxicology Modeling is a comprehensive and well-documented text providing a collection of computational methods to the ecotoxicologists primarily interested in the study of the adverse effects of chemicals, their mechanisms of action and/or their environmental fate and behavior. Avoiding mathematical jargon, the book presents numerous case studies to enable the reader to understand the interest but also the limitations of linear and nonlinear models in ecotoxicology. Written by an international team of scientists, Ecotoxicology Modeling is of primary interest to those whose research or professional activity is directly concerned with the development and application of models in ecotoxicology. It is also intended to provide the graduate and post-graduate students with a clear and accessible text covering the main types of modeling approaches used in environmental sciences.

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.

Principles, Methods, and Applications in the Pharmaceutical Industry

Physiologically Based Pharmacokinetic Modeling of Nanoparticles in Rodents

Physiologically Based Pharmacokinetic (PBPK) Modelling of Cisplatin in Rats and Humans

Transporters and Drug-Metabolizing Enzymes in Drug Toxicity

Science and Applications

Ecotoxicology Modeling

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.

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.

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.

Translational Physiologically-based Pharmacokinetic (PBPK) Modeling and Simulation to Support Drug Development and Pharmacotherapy

From Fundamentals to Industrial Practice

Use of Physiologically Based Pharmacokinetic Models to Quantify the Impact of Human Age and Interindividual Differences in Physiology and Biochemistry Pertinent to Risk

Perspectives from Pharmacokinetics and Pharmacodynamics

In Vitro-In Vivo Correlations

Pharmacokinetic-Pharmacodynamic Modeling and Simulation

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.

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

Governments around the world are passing laws requiring industry to assess the toxicity of the chemicals and products they produce, but to do so while reducing, refining, or even replacing testing on animals. To meet these requirements, experimental toxicologists and risk assessors are adopting quantitative approaches and computer simulations to study the biological fate and effects of chemicals and drugs. In Quantitative Modeling in Toxicology leading experts outline the current state of knowledge on the modeling of dose, tissue interactions and tissue responses. Each chapter describes the mathematical foundation, parameter estimation, challenges and perspectives for development, along with the presentation of a modeling template. Additionally, tools and approaches for conducting uncertainty, sensitivity and variability analyses in these models are described. Topics covered include: the quantitative models of pharmacokinetics of individual chemicals and mixtures models for toxicant-target tissue interaction. models for cellular, organ, and organism responses. approaches, tools and challenges for model application and evaluation A website containing computer codes accompanies the book to help the reader reconstruct the models described and discussed in the various chapters. Quantitative Modeling in Toxicology serves as an essential reference source and tool box for risk assessors and researchers and students in toxicology, public health, pharmacology, and human toxicology interested in developing quantitative models for a better understanding of dose-response relationships.

Applications of Physiologically Based Pharmacokinetic Models in Veterinary Medicine

Physiologically-based Pharmacokinetic (PBPK) Modeling of PC01/FS and PFASS in Humans

Computational Toxicology

Prediction and Assessment, Second Edition

Physiologically Based Pharmacokinetic (PBPK) Modeling

Key Concepts for the FRCA

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.

Explore the latest research in biopharmaceutics from leading contributors in the field In Biopharmaceutics - From Fundamentals to Industrial Practice, distinguished Scientists from the UK's Academy of Pharmaceutical Sciences Biopharmaceutica Focus Group deliver a comprehensive examination of the tools used within the field of biopharmaceutics and their applications to drug development. This edited volume is an indispensable tool for anyone seeking to better understand the field of biopharmaceutics as it rapidly develops and evolves. Beginning with an expansive introduction to the basics of biopharmaceutics and the context that underpins the field, the included resources go on to discuss how biopharmaceutics are integrated into product development within the pharmaceutical industry. Explorations of how the regulatory aspects of biopharmaceutics function, as well as the impact of physiology and anatomy on the rate and extent of drug absorption, follow. Readers will find insightful discussions of physiologically based modeling as a valuable asset in the biopharmaceutics toolkit and how to apply the principles of the field to special populations. The book goes on to discuss: Thorough introductions to biopharmaceutics, basic pharmacokinetics, and biopharmaceutics measures Comprehensive explorations of solubility, permeability, and dissolution Practical discussions of the use of biopharmaceutics to inform candidate drug selection and optimization, as well as biopharmaceutics tools for rational formulation design In-depth examinations of biopharmaceutics classification systems and regulatory biopharmaceutics, as well as regulatory biopharmaceutics and the impact of anatomy and physiology Perfect for professionals working in the pharmaceutical and biopharmaceutical industries, Biopharmaceutics - From Fundamentals to Industrial Practice is an incisive and up-to-date resource on the practical, pharmaceutical applications of the field.

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.

Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment

Drug Delivery Approaches

An Evaluation of Life Stage Sensitivity Using Physiologically Based Pharmacokinetic (PBPK) Modeling

Fundamentals of Pediatric Drug Dosing

Key Scientific Issues

Physiologically-Based Pharmacokinetic/Toxicokinetic Modeling in Risk Assessment

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.

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.

Oral Drug Absorption, Second Edition thoroughly examines the special equipment and methods used to test whether drugs are released adequately when administered orally. The contributors discuss methods for accurately establishing and validating in vitro/in vivo correlations for both MR and IR formulations, as well as alternative approaches for MR an

Physics, Pharmacology and Physiology for Anaesthetists

Physiologically Based Pharmacokinetic Models for the Systemic Transport of Trichloroethylene

Towards Prediction and Informed Dose Recommendation Using Physiologically-based Pharmacokinetic (PBPK) Modeling

A Comparison of Physiologically-Based Pharmacokinetic (PBPK) Models of Methyl-Tertiary Butyl Ether (MTBE)

Oral Drug Absorption

Mechanistic Physiologically Based Pharmacokinetic (PBPK) Modeling of Renal and Systemic Disposition of Drugs and Metabolites

This is a second edition to the original published by Springer in 2006. The comprehensive volume takes a textbook approach systematically developing the field by starting from linear models and then moving up to generalized linear and non-linear mixed effects models. Since the first edition was published the field has grown considerably in terms of maturity and technicality. The second edition of the book therefore considerably expands with the addition of three new chapters relating to Bayesian models, Generalized linear and nonlinear mixed effects models, and Principles of simulation. In addition, many of the other chapters have been expanded and updated.

A quick reference to basic science for anaesthetists, containing all the key information needed for FRCA exams.

This book represents the invited presentations and some of the posters presented at the conference entitled "In Vitro-In Vivo Relationship (IVIVR) Workshop" held in Sep tember, 1996. The workshop was organized by the IVIVR Cooperative Working Group which has drawn together scientists from a number of organizations and institutions, both academic and industrial. In addition to Elan Corporation, which is a drug delivery com pany specializing in the development of ER (Extended Release) dosage forms, the IVIVR Cooperative Working Group consists of collaborators from the University of Maryland at Baltimore, University College Dublin, Trinity College Dublin, and the University of Not tingham in the UK. The principal collaborators are: Dr. Jackie Butler, Elan Corporation Prof. Owen Corrigan, Trinity College Dublin Dr. Iain Cumming, Elan Corporation Dr. John Devane, Elan Corporation Dr. Adrian Dunne, University College Dublin Dr. Stuart Madden, Elan Corporation Dr. Colin Melia, University of Nottingham Mr. Tom O'Hara, Elan Corporation Dr. Deborah Piscitelli, University of Maryland at Baltimore Dr. Araz Raoof, Elan Corporation Mr. Paul Stark, Elan Corporation Dr. David Young, University of Maryland at Baltimore The purpose of the workshop was to discuss new concepts and methods in the devel opment of in vitro-in vivo relationships for ER products. The original idea went back ap proximately 15 months prior to the workshop itself. For some time, the principal collaborators had been working together on various aspects of dosage form development.

Physiologically-Based Pharmacokinetic (PBPK) Modeling and Simulations

Development and Evaluation of a Physiologically Based Pharmacokinetic (PBPK) Population Model for Elderly Individuals

Chapter 2. Quantitative Structure-Activity Relationship (QSAR) Models, Physiologically Based Pharmacokinetic (PBPK) Models, Biologically Based Dose Response (BBDR) and Toxicity Pathways: Computational Tools for Public Health

Successful Strategies in Drug Discovery and Chemical Biology

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

Focused on pediatric physiology, pharmacology, pharmacokinetics and pharmacodynamics, this book illustrates the differences between the pediatric population and adults; knowledge of extreme importance not only during pediatric drug development but also in the clinical practice. Physicians, nurses, clinical pharmacologists, researchers and healthcare professionals will find this an invaluable resource. With the advent of pediatric exclusivity, and requirements to conduct clinical studies in children, an emphasis has been placed on finding a safe and efficacious dose of a drug in children. Children are not ‘ small adults ’, and drug dosing in this population requires special consideration. There are subtle physiological and biochemical differences among neonates, infants, children, adolescents and adults and dosing in pediatrics requires proper understanding of these factors. Furthermore, dosing in children, as in adults, should be based on pharmacokinetic and pharmacodynamic data. This is an evolving area, as pediatric pharmacokinetic studies are becoming mandatory for getting approval of new drugs in this population.