Pharmacology & Therapeutics 211 (2020) 107541

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Physiologically-based pharmacokinetic models for children: Starting to reach maturation?

Laurens F.M. Verscheijden [a], Jan B. Koenderink [a], Trevor N. Johnson [b], Saskia N. de Wildt [a,c], Frans G.M. Russel [a,*]

[a] Department of Pharmacology and Toxicology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[b] Certara UK Limited, Sheffield, UK
[c] Intensive Care and Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

ARTICLE INFO

Available online 1 April 2020

Keywords:
Pediatrics
Children
Ontogeny
PBPK
Physiologically-based pharmacokinetic modeling
Model-informed drug dosing

ABSTRACT

Developmental changes in children can affect the disposition and clinical effects of a drug, indicating that scaling an adult dose simply down per linear weight can potentially lead to overdosing, especially in very young children. Physiologically-based pharmacokinetic (PBPK) models are compartmental, mathematical models that can be used to predict plasma drug concentrations in pediatric populations and acquire insight into the influence of age-dependent physiological differences on drug disposition. Pediatric PBPK models have generated attention in the last decade, because physiological parameters for model building are increasingly available and regulatory guidelines demand pediatric studies during drug development. Due to efforts from academia, PBPK model developers, pharmaceutical companies and regulatory authorities, examples are now available where clinical studies in children have been replaced or informed by PBPK models. However, the number of pediatric PBPK models and their predictive performance still lags behind that of adult models. In this review we discuss the general pediatric PBPK model principles, indicate the challenges that can arise when developing models, and highlight new applications, to give an overview of the current status and future perspective of pediatric PBPK modeling.

Contents

1. Introduction

New drugs require pediatric studies as part of their market authorization, while marketed drugs often lack information on pediatric efficacy, safety and dosing (EMA, 2007; FDA, 2002/2003; Frattarelli, et al., 2014; Sachs, Avant, Lee, Rodriguez, & Murphy, 2012). To find out what doses are suitable for different age groups, it is important to realize that many developmental processes are not reflected by simple scalars

Abbreviations: CYP, cytochrome P450; DDI, drug-drug interaction; GFR, glomerular filtration rate; GST, glutathione s-transferase; kp, tissue-plasma partitioning coefficient; mAB, monoclonal antibody; OAT, organic anion transporter; OCT, organic cation transporter; PBPK, Physiologically-based pharmacokinetic; UGT, UDP-glucuronosyltransferase..

* Corresponding author at: P.O. Box 9101, Geert Grooteplein 21, Room k0.10 (route 128), 6500 HB Nijmegen, the Netherlands.
E-mail address: Frans.Russel@radboudumc.nl (F.G.M. Russel).

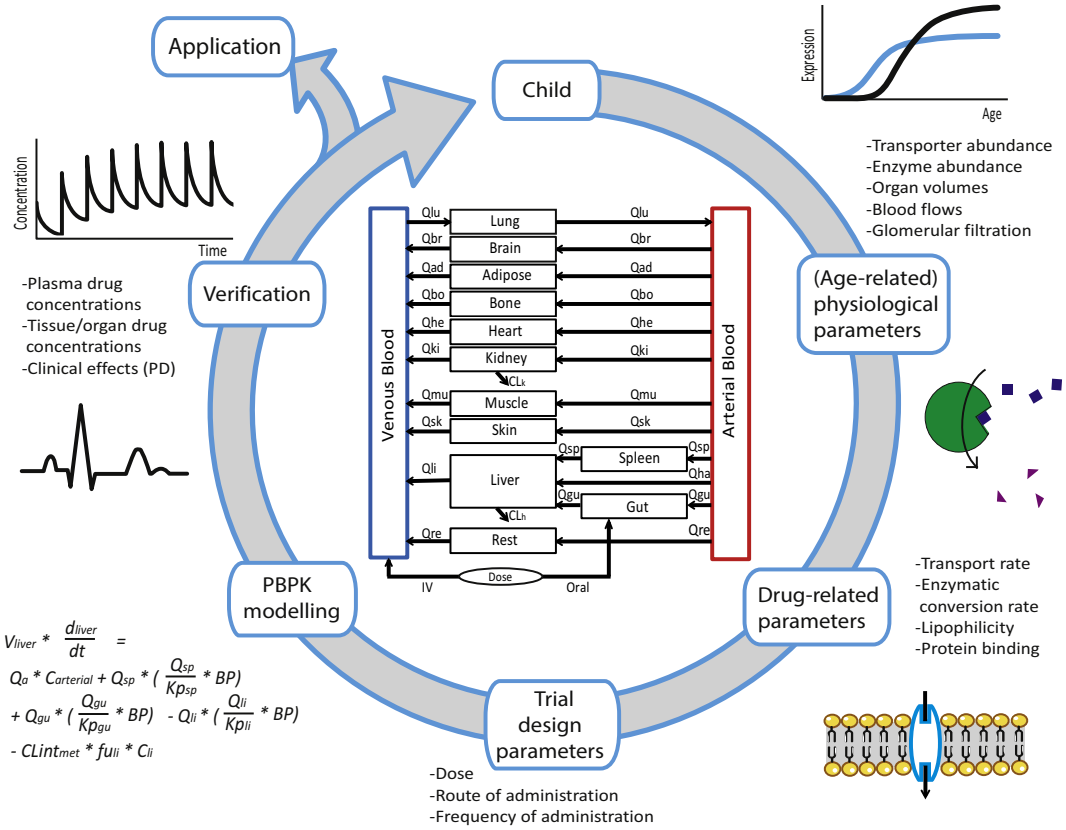
https://doi.org/10.1016/j.pharmthera.2020.107541

like body weight or body surface area (Cella, Knibbe, Danhof, & Della Pasqua, 2010). Drug metabolizing enzyme or transporter activity show protein-specific and organ-dependent developmental profiles (Daood, Tsai, Ahdab-Barmada, & Watchko, 2008; Lam et al., 2015; Mooij et al., 2014; Sadler et al., 2016; Upreti & Wahlstrom, 2016; van Groen et al., 2018). Moreover, other processes involved in the disposition of drugs also change in a nonlinear relationship with growth and development, as was reviewed recently (van den Anker, Reed, Allegaert, & Kearns, 2018).

Modeling and simulation has evolved as one of the cornerstones of pediatric drug development by making optimal use of available data (Manolis et al., 2011). In population PK (popPK) models, parameters are computationally scaled/fitted in order to best describe *in vivo* measured drug concentrations. In this approach patient-specific characteristics can be identified allowing for a more individualized therapy, although a robust estimation of population PK parameters requires relatively rich pharmacokinetic data, especially when multiple characteristics/co-variates are studied. Moreover, a PopPK parameter will reflect a combination of several physiological and drug-related processes, which is difficult to extrapolate to other populations or drugs (Brussee et al., 2018; Brussee et al., 2018). PBPK models provide mechanistic PK predictions and although the derivation of the required parameters could be challenging, theoretically they are more suitable for between-population or between-drug PK predictions (W. Zhou et al., 2018; W. Zhou et al., 2016). Integrating developmental changes in PBPK models has proven to be successful in predicting doses across the pediatric age span (Leong et al., 2012; Mansoor, Ahmad, Alam Khan, Sharib, & Mahmood, 2019). More specifically, regulatory authorities have also acknowledged the added value of these models and encourage their use in pediatric drug development (Leong et al., 2012). The development of PBPK and/or PopPK models is in accordance with FDA regulations (*e.g.* pediatric decision tree) as in any case pediatric drug pharmacokinetic (PK) and safety data need to be evaluated in order to bridge from the adult to the pediatric population.

1.1. PBPK modeling in adults and children

PBPK models represent the body as anatomically and physiologically recognizable compartments in which the processes of drug absorption, distribution, metabolism and excretion (ADME) are described with a set of differential equations. PBPK models provide a mechanistic framework that separately includes physiological parameters (often also referred to as system specific parameters), drug-related parameters, and parameters reflecting trial design, which aims to cover the complex processes governing drug disposition (Fig. 1). Models range from a simple minimal setup, consisting of only a few essential compartments, to full-body PBPK models in which all major organs in the body are represented by compartments connected through blood flow (Kuepfer et al., 2016; Upton, Foster, & Abuhelwa, 2016). Much progress has been made in accurately expressing the relevant physiological processes in terms of accurate parameters. While PBPK models usually consist of many parameters and developing a model may be labor intensive, previous models can be used to build upon as physiological parameters are not expected to change within a population of interest, which markedly reduces the effort that is needed for model building (Rostami-Hodjegan, 2012). Next to the physiological parameters, a variety of drug-related data affecting pharmacokinetics need to be obtained, which largely can be generated by *in vitro* experiments (Fig. 1).



$$V_{liver} * \frac{d_{liver}}{dt} = Q_a * C_{arterial} + Q_{sp} * \left(\frac{Q_{sp}}{Kp_{sp}} * BP\right) + Q_{gu} * \left(\frac{Q_{gu}}{Kp_{gu}} * BP\right) - Q_{li} * \left(\frac{Q_{li}}{Kp_{li}} * BP\right) - CLint_{met} * fu_{li} * C_{li}$$

Fig. 1. "Learn, confirm and apply" development cycle used to build and optimize pediatric PBPK models based on physiological, drug-related and trial design parameters. Qlu, Qbr, Qad, Qbo, Qhe, Qki, Qmu, Qsk, Qsp, Qgu, Qha, Qre, Qli denote blood flows towards, lung, brain, adipose tissue, bone, heart, kidney, muscle, skin, spleen, gut, liver (arterial flow), rest of tissues, and from liver, respectively (*e.g.* $Qlu = 300\ L * h^{-1}$ *in adults*). Physiological (system) parameters, drug-related parameters and trial-design parameters are separately included in PBPK models.

Models can be adjusted to other populations by changing the population-dependent system parameters. They have successfully been translated from animals to humans (Ball, Bouzom, Scherrmann, Walther, & Decleves, 2012; Bi, Deng, Murry, & An, 2016; Lukacova et al., 2016; Parrott et al., 2011), from Caucasians to different ethnicities (Feng et al., 2016; Matsumoto et al., 2018), and from healthy to diseased populations (Radke et al., 2017; Rasool, Khalil, & Laer, 2015; Rhee, Chung, Yi, Yu, & Chung, 2017). Similarly, extrapolations from adults to children are based on adapting age-dependent adult physiological parameters to values appropriate for children. This approach is commonly applied in the development of pediatric models to evaluate key pharmacokinetic processes and confirm age-unrelated drug-dependent parameters in an adult population, before introducing age-related pediatric physiological parameters, for which data can be more sparse (Maharaj & Edginton, 2014).

Pediatric PBPK modeling has developed from 'proof of principle' to a valuable tool for the prediction of pharmacokinetics in children (Yellepeddi et al., 2018). Even more, PBPK-PD (PBPK-pharmacodynamic) modeling is increasingly used to predict drug effects. The increased interest is also reflected by an exponential rise in the number of publications on this topic during the last decade. On the other hand, the number of pediatric PBPK models and their predictive performance still lags behind adult models (Grimstein et al., 2019; Jamei, 2016; Sager, Yu, Ragueneau-Majlessi, & Isoherranen, 2015; Templeton, Jones, & Musib, 2018). The aim of this review is to (1) discuss the use of pediatric PBPK models for different purposes and identify challenges in model building, (2) provide key considerations to evaluate pediatric PBPK model quality, and (3) to give a future perspective on model development that will further increase their quality and acceptance, as well as their wider applicability into clinical care.

2. Pediatric PBPK model development

A tutorial for a general workflow to develop a pediatric PBPK model was described by Maharaj et al. and will not be further discussed here (Maharaj, Barrett, & Edginton, 2013; Maharaj & Edginton, 2014). Trends between adult and pediatric physiological parameters are summarized in Table 1.

In general, it is considered good practice to develop an adult model first before a pediatric model is built, to obtain insight into key pharmacokinetic processes and allow for the verification of age-independent drug-related parameters. Some of the physiological parameters that are subsequently included in the pediatric model are well established, such as organ volumes, however, information on others can be sparse or absent (*e.g.* transporter expression). This indicates that dependent on the route of administration (*e.g.* oral *versus* intravenous dosing) and the drug involved (*e.g.* CYP3A4 substrate *versus* UGT substrate) confidence in the model-predicted outcomes will be determined by the (un)certainty of the estimates for the included parameters. Although important information gaps may exist in ADME-related physiology for specific drug models, a pediatric PBPK model can be judged 'fit for purpose' if the relevant patterns related to age can be described and sufficiently verified with clinical data.

For pediatric model development, it is valuable to obtain PBPK drug-specific parameters from human *in vitro* studies that can be scaled to *in vivo* parameters (*in vitro-in vivo* extrapolations (IVIVE), or also called "bottom up approach"). For example, an *in vitro* clearance value can be calculated from recombinant drug metabolizing enzyme activity, which is subsequently scaled to whole liver clearance by taking into account age-appropriate liver weight and enzyme expression per gram. Such an approach can contribute to the development of first in child dosing regimens in case it is not possible to scale or fit parameters based on comparison of predicted model output with measured drug concentrations. In addition, it results in better mechanistic insight into the underlying ADME processes, for example the relative contribution of individual drug metabolizing enzymes in clearance (Jaroch, Jaroch, & Bojko, 2018; Johnson et al., 2018; Scotcher, Jones, Posada, Rostami-Hodjegan, & Galetin, 2016).

In practice, a combination of *in vitro* data and *in vivo*-derived drug concentrations are often used for model parametrization. If physiological or drug-related parameters for PBPK models are not available, they need to be scaled or fitted based on clinically measured drug concentration data. This "middle out approach" allows the quantification of processes affecting PK and to explore potential differences between adults and children (Emoto, Johnson, McPhail, Vinks, & Fukuda, 2018; Zane & Thakker, 2014). Similarly, pediatric models will also benefit from adult *in vivo* pharmacokinetic data. For instance, adult clearance values can be used to estimate pediatric clearances if differences in enzyme expression and activity of the elimination pathways involved are taken into consideration.

3. Use of models to mechanistically describe ADME processes

3.1. Absorption

Oral dosing is the preferred route of drug administration in children. Multi-compartment absorption models are used to predict drug absorption from different gut segments, in which the complex interplay between different physiological processes and their effect on absorption is incorporated. Age-related processes accounted for oral absorption in PBPK models are gastric emptying time, small and large intestinal transit time and intestinal surface area, which are only part of the physiological processes subject to developmental differences (Table 2). Recently, a gastro-intestinal model was built by Johnson et al. based on a review of the literature. They recognized knowledge gaps in the ontogeny of fluid volume dynamics in the GI tract, intestinal bile flows, and CYP enzyme and transporter expression. Nevertheless, disposition of the relatively high solubility and permeability drugs, paracetamol and theophylline, were predicted with good precision. In addition, accurate predictions were also made for the low solubility drug ketoconazole and carbamazepine. (Cristofoletti, Charoo, & Dressman, 2016; Johnson, Bonner, Tucker, Turner, & Jamei, 2018; Kohlmann, Stillhart, Kuentz, & Parrott, 2017) (Table 2).

Intestinal protein ontogeny data for CYP3A4 show a developmental increase in activity when children mature, whereas expression of the efflux transporter P-glycoprotein appears to be stable from fetal age until adulthood (Table 1, Fig. 2) (Johnson, Tanner, Taylor, & Tucker, 2001; Konieczna et al., 2011). Knowledge on intestinal abundance of other drug metabolizing enzymes and transporters is still limited. In that case PBPK models are useful in combination with measured clinical drug concentrations to explore developmental differences in enzyme and transporter expressions that have not yet been characterized at the protein level.

Models describing other routes of absorption such as dermal, pulmonary and ocular drug absorption were developed previously for adults, rodents and rabbits, however, for children they are scarce (Le Merdy et al., 2019; Poet et al., 2000; Salar-Behzadi et al., 2017; Valcke & Krishnan, 2010). One study described multi-route (oral, dermal, pulmonary) exposure to drinking water toxicants in neonates and children, providing proof of principle also for other xenobiotics including drugs (Valcke & Krishnan, 2010).

3.2. Distribution

Once in the systemic circulation, a drug will be distributed to organs and tissues, which is usually described in PBPK models by the (predicted) tissue-plasma partitioning coefficient (Kp) (Table 3)(Poulin & Theil, 2000; Rodgers, Leahy, & Rowland, 2005; Rodgers & Rowland, 2006). Age-appropriate calculations of the Kp value of a drug is dependent on the fractional volumes of tissue water and lipid, as well as fraction of the compound which is unbound in plasma. In general, neonates and young children will have a higher percentage of tissue water and

Table 1
Developmental trends in physiological parameters.

ADME process	Physiological parameter	Developmental pattern	Age range reported	Ref.
Absorption	Small intestinal length[a]	Increase	Fetuses-adult	(Gondolesi et al., 2012; Struijs, Diamond, de Silva, & Wales, 2009; Weaver, Austin, & Cole, 1991)
	Large intestinal length[a]	Increase	Neonates-adolescents	(Koppen et al., 2017; Mirjalili, Tarr, & Stringer, 2017)
	Gastric pH	Stable, subject to alkalinization by milk feeds	Neonates-adolescents	(Avery, Randolph, & Weaver, 1966; Schmidt et al., 2015; Whetstine, Hulsey, Annibale, & Pittard, 1995)
	Small intestinal pH	Stable	Neonates-children	(Barbero et al., 1952; Fallingborg et al., 1990)
	Gastric emptying	Stable	Neonates-adults	(Bonner et al., 2015)
	Gut transit time	Stable	Neonates- adults	(Maharaj & Edginton, 2016)
	Intestinal membrane transporters		Fetuses-adults	(Konieczna et al., 2011; Mizuno et al., 2014; Mooij et al., 2014)
	- Pgp[b,c]	Stable		
	- BCRP[c]	Stable		
	- MRP1[c]	Stable		
	- MRP2[b]	Stable		
	- OATP-2B1[b]	Decrease		
	Intestinal drug metabolizing enzyme		Fetuses-adults	(Fakhoury et al., 2005; Johnson et al., 2001)
	- CYP3A4[c]	Increase		
Distribution	Tissue composition		Fetuses-children 2 years of age	(Butte, Hopkinson, Wong, Smith, & Ellis, 2000; Carberry, Colditz, & Lingwood, 2010; Malina, 1969)
	- Protein[d]	Stable		
	- Water[d]	Decrease		
	- Fat[d]	Increase		
	Organ volumes[a]	Increase	Neonates-adults	(Ogiu, Nakamura, Ijiri, Hiraiwa, & Ogiu, 1997)
	Organ blood flow		Neonates-adults	(Chiron et al., 1992; Schoning & Hartig, 1996; Williams & Leggett, 1989)
	- Brain[a]	First increase, later decrease		
	- Other organs[a]	Increase		
	Carrier proteins		Neonates- children 3 years of age	(Johnson et al., 2006; Kanakoudi et al., 1995; Maharaj, Gonzalez, Cohen-Wolkowiez, Hornik, & Edginton, 2018; Sethi et al., 2016)
	- Albumin[e]	Increase		
	- A1AGP[e]	Increase		
	Hematocrit[f]	First decrease, later increase		(Fulgoni III et al., 2019; Jopling, Henry, Wiedmeier, & Christensen, 2009)
Metabolism	Liver enzyme expression		Fetuses- children 2 years of age	(Bhatt et al., 2019; Divakaran, Hines, & McCarver, 2014; Johnson et al., 2006; Salem et al., 2014; Song et al., 2017; Upreti & Wahlstrom, 2016; Zaya, Hines, & Stevens, 2006)
	CYP1A2[c]	Increase		
	CYP2B6[c]	Increase		
	CYP2C8[c]	Increase		
	CYP2C9[c]	Increase		
	CYP2C19[c]	Increase		
	CYP2D6[c]	Increase		
	CYP2E1[c]	Increase		
	CYP3A4[c]	Increase		
	UGT1A1[c]	Increase		
	UGT1A4[c]	Increase		
	UGT1A6[c]	Increase		
	UGT1A9[c]	Increase		
	UGT2B7[c]	Increase		
	UGT2B15[c]	Increase		
	Hepatic transporter expression		Fetuses-adults	(Mooij et al., 2016; Prasad et al., 2016; van Groen et al., 2018)
	- Pgp[c]	Increase		
	- BCRP[c]	Stable		
	- MRP1[c]	Increase		
	- MRP2[c]	Stable/increase		
	- MRP3[c]	Increase		
	- BSEP[c]	Stable/increase		
	- NTCP[c]	Increase		
	- OATP-1B1[c]	Stable		
	- OATP-1B3[c]	Stable/increase		
	- OATP-2B1[c]	Stable		
	- OCT1[c]	Increase		
	Microsomal protein[e]	Increase	Neonates-adults	(Barter et al., 2008)
Elimination	Glomerular filtration rate[a]	Increase	Fetuses-adults	(Hayton, 2000; Johnson et al., 2006; Piepsz, Tondeur, & Ham, 2006; Rhodin et al., 2009)
	Tubular transporter expression		Neonates-adults	(Cheung, van Groen, Spaans, et al., 2019)
	- Pgp[c]	Increase		

Table 1 (*continued*)

ADME process	Physiological parameter	Developmental pattern	Age range reported	Ref.
	- BCRP[c]	Stable		
	- MATE1[c]	Stable		
	- MATE2-k[c]	Stable		
	- URAT1[c]	Stable		
	- GLUT2[c]	Stable		
	- OAT1[c]	Increase		
	- OAT3[c]	Increase		
	- OCT2[c]	Increase		

Pgp, P-glycoprotein; BCRP, Breast cancer resistance protein; MRP, Multidrug resistance protein; OATP, Organic anion transporter protein; CYP, Cytochrome P450; A1AGP, Alpha-1-acid glycoprotein; UGT, Uridine diphosphate-glucuronyltransferase; BSEP, Bile salt export pump; NTCP, Sodium-taurocholate cotransporting polypeptide; OCT, Organic cation transporter; MATE, Multidrug and toxin extrusion; URAT, Urate transporter; GLUT, Glucose transporter; OAT, Organic anion transporter.

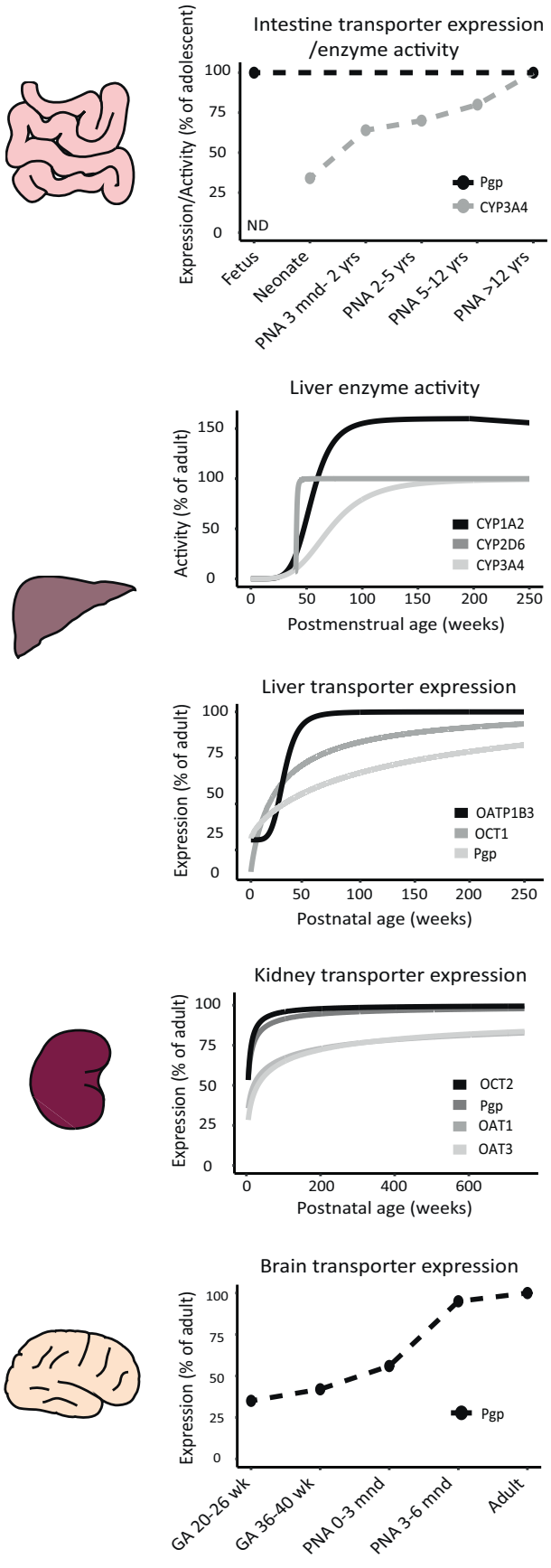
[a] Absolute length, volume, flow or rate.
[b] mRNA expression.
[c] Protein expression.
[d] Percentage of body weight.
[e] Concentration.
[f] Percentage of blood volume.

Table 2
PBPK models including prediction of oral absorption.

Study	Parameter fitting/optimization needed?	Pediatric systems parameters included	Software used	Age range	Drug	Ref.
Parrott et al.	No	Gut size, intestinal transit time	Gastroplus®	Neonate, infant	Oseltamivir	(Parrott et al., 2011)
Johnson et al.	Yes	GI tract size, CYP3A4 ontogeny	Simcyp®		Quetiapine	(Johnson et al., 2014)
Khalil et al.	Yes	Radius and length of intestinal segments, effective surface area intestinal sections, intestinal enzyme ontogeny	Simcyp® and PK-Sim®	11d–17.7y	Sotalol	(Khalil & Laer, 2014)
Willman et al.	Yes	Gastric emptying time, small and large intestinal transit time, effective surface area intestinal sections	PK-Sim®	0.5–18y	Rivaroxaban	(Willmann et al., 2014; Willmann et al., 2018)
Rasool et al.	Yes	Not stated	Simcyp®	0.12–19.3y	Carvedilol	(Rasool et al., 2015)
Cristofoletti et al.	Yes	Intestinal volumes, bile salt concentration, Gastric pH	Simcyp®		Fluconazole, Ketoconazole	(Cristofoletti et al., 2016)
Villiger et al.	Yes	Intestinal length, intestinal surface area, small intestinal transit time, fluid secretion volume	Gastroplus®	Newborns, infants, children	Sotalol, Paracetamol	(Villiger, Stillhart, Parrott, & Kuentz, 2016)
Moj et al.	Yes	Not stated	PK-Sim®	0–17y	Vorinostat	(Moj et al., 2017)
Kohlman et al.	No	Gut size and GI transit times	Gastroplus®	Newborns-adolescents	Carbamazepine	(Kohlmann et al., 2017)
Samant et al.	No	Not stated	Gastroplus®	0–22y	Desipramine	(Samant et al., 2017)
Johnson et al.	No	Gastric emptying, gastric and intestinal pH, intestinal length and diameter, intestinal transit time, salivary flow rates, gastric and intestinal volumes, intestinal bile salt concentration	Simcyp®	0–25y	Theophylline, Paracetamol, Ketoconazole	(Johnson, Bonner, et al., 2018)
Balbas-Martinez et al.	Yes	Not stated	PK-Sim®	3 m-12y	Ciprofloxacin	(Balbas-Martinez et al., 2019)

lower plasma albumin and alpha 1-acid glycoprotein concentrations compared to adults (Table 1), which is reflected in altered Kp values. These age-related changes may consequently result for a specific drug in a different predicted volume of distribution per kg body weight (Samant, Lukacova, & Schmidt, 2017).

Drug disposition into organs can also be described by diffusion-limited compartments. This mainly will be useful in cases where delayed drug penetration into organs is expected and/or transporter-mediated transfer of compounds across cell membranes needs to be accounted for. Data on maturation of drug transporters in the different organs are, however, limited and lagging behind the knowledge on the expression profiles of drug metabolizing enzymes (Table 1). Proof of principle for this approach was given in a study where OCT1-mediated liver uptake of morphine was included in a pediatric PBPK model, which could be verified by comparison of predicted and measured clearance values (Emoto et al., 2018). Because morphine is a high extraction drug, clearance is mainly dependent on morphine delivery to the hepatocytes, which is influenced by hepatic blood flow and OCT1-mediated liver uptake, and to a lesser extent by UGT2B7 activity (Emoto, Johnson, Neuhoff, et al., 2018). First, OCT1 genotype was investigated as a source of variation in morphine liver uptake in adults and children older than 6 years of age (Emoto et al., 2017). Subsequently, ontogeny of OCT1 and an optimized relation between cardiac output and age, which influences hepatic blood flow, were included into the pediatric PBPK model to describe the clearance in neonates and young infants (Emoto et al., 2017; Emoto, Johnson, Neuhoff, et al., 2018). In a follow-up study, the ontogeny of UGT2B7 expression was also included in the modeling (Bhatt et al., 2019).



3.3. Metabolism

Most efforts have been directed at incorporating age-dependent changes in metabolic clearance into pediatric PBPK models (Fig. 2, Table 4). Data from *in vitro* assays (*i.e.* recombinant enzymes, human liver S9 fractions, human liver microsomes, or human hepatocytes) have been used to estimate hepatic clearance in adult models, which can also be applied to pediatric models by taking into account reported differences in enzyme expression/activity. Investigations on the expression ontogeny of hepatic CYP enzymes have resulted in accurate predictions for children down to an age of 1 month for drug metabolism covered by the enzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (Table 4) (W. Zhou et al., 2018). An *in vitro* study on the ontogeny profiles of different CYP enzyme activities, showed that for drugs handled by CYP1A2 and CYP3A4 these values resulted in an underestimation of the *in vivo* clearance in the pediatric age range (Johnson, Rostami-Hodjegan, & Tucker, 2006; Salem, Johnson, Abduljalil, Tucker, & Rostami-Hodjegan, 2014; Upreti & Wahlstrom, 2016). By using clinically determined clearance values of midazolam and sufentanil (both CYP3A4), theophylline and caffeine (both CYP1A2), the ontogeny for these enzymes was further refined (Salem et al., 2014). Subsequently, this was verified with clearance values for alfentanil (CYP3A4) and ropivacaine (CYP1A2) (Salem et al., 2014). A major drawback is that *in vivo* clearance data were obtained in ill children, which potentially has affected enzyme activity, but a good correlation between predicted and measured clearance values was found (Salem et al., 2014; Upreti & Wahlstrom, 2016). Although CYP enzyme developmental patterns are relatively well described, in several situations prediction of clearance was complicated by the absence of maturation profiles of metabolizing enzymes. Studies have been published describing models incorporating GST- and UGT-mediated clearance, in which only theoretical functions (*i.e.* not based on observed data) were used to describe enzyme ontogeny, for instance based on other isoenzymes or fitting to measured drug concentrations. While this indicates that prediction for these enzymes is more difficult, these efforts aid in further establishing their ontogeny profiles. (Diestelhorst et al., 2014; Jiang, Zhao, Barrett, Lesko, & Schmidt, 2013).

In neonatal and preterm models, measured drug concentration are less well predicted by PBPK models compared to older children and adults (Khalil & Laer, 2014; Templeton et al., 2018; T'Jollyn, Vermeulen, & Van Bocxlaer, 2018). Recently, developmental physiological parameters in the preterm/neonatal population were re-evaluated to provide a better mechanistic basis for this age group and drug plasma concentrations for six drugs were accurately described (Abduljalil, Pan, Pansari, Jamei, & Johnson, 2019a, 2019b). Another aspect considered specifically in neonates is that system-specific parameters can change rapidly over a relatively short period of time. In PBPK models parameters usually are fixed for a "virtual individual" during the time course of the simulation. However, to account for time varying physiology in neonates, in other words, to include growth and/or maturation in virtual individuals, a model has been developed in which the values for physiological parameters are re-defined during the time course of the (prolonged) simulation (Abduljalil, Jamei, Rostami-Hodjegan, &

Fig. 2. Developmental patterns in enzyme and transporter expression or activity in intestine, liver, kidney and brain. Solid lines indicate ontogeny profiles for which age-related equations are described. Dotted lines with point estimates indicate expression/activity levels at specific age groups. Refs: Intestine (Johnson et al., 2001; Konieczna et al., 2011), liver (enzymes) (Salem et al., 2014; Upreti & Wahlstrom, 2016), liver (transporters) (Prasad et al., 2016), kidney (Cheung, van Groen, Spaans, et al., 2019), brain (Lam et al., 2015). Pgp, P-glycoprotein; CYP, Cytochrome P450; OCT, Organic cation transporter; OAT, Organic anion transporter.

Table 3
PBPK models including prediction of drug distribution.

Study	Permeability-limited compartments included	Estimation method tissue-plasma partitioning coefficients (perfusion-limited compartments)	Software used	Age range	Drug	Ref.
Samant et al.	No	Lucacova	Gastroplus®	0–15 years	Desipramine	(Samant et al., 2017)
Emoto et al.	Liver	Rodgers and Rowland	Simcyp®	0–3 years	Morphine	(Emoto, Johnson, Neuhoff, et al., 2018)
Verscheijden et al.	Brain	Rodgers and Rowland	Rstudio®	0.25–15 years and adults	Paracetamol, naproxen, flurbiprofen, ibuprofen, meropenem	(Verscheijden et al., 2019)
Maharaj et al.	Brain	Rodgers and Rowland	PK-Sim®	0 years - adult	Lorazepam	(Maharaj et al., 2013)
Lukacova et al.	All tissues	Not applicable	Gastroplus®	11 days - 17 years and adults	Ganciclovir, valganciclovir	(Lukacova et al., 2016)

Table 4
PBPK models including prediction of metabolic elimination.

Study	Enzyme ontogeny	Software used	Age range	Drug	Ref.
Yun et al.	CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYPD6, CYP2E1, CYP3A4	PK-Sim®	1 week - adult	Alfentanil, diclofenac, esomeprazole, itraconazole, lansoprazole, midazolam, ondansetron, sufentanil, theophylline, tramadol	(Yun & Edginton, 2019)
Zhou et al.	CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4	Simcyp®	1 month - adult	Theophylline, desloratidine, montelukast, diclofenac, esomeprazole, lansoprazole, tramadol, itraconazole, ondansetron, sufentanil	(W. Zhou et al., 2018)
Salem et al.	CYP1A2, CYP3A4	Simcyp®	1 day - adult	Caffeine, theophylline, midazolam, ropivacaine, alfentanil	(Salem et al., 2014)
Upreti and Wahlstrom	CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A	Simcyp®	1 day - adult	Caffeine, cotinine, nicotine, cyclophosphamide, methadone, phenytoin, tolbutamide, omeprazole, pantoprazole, propafenone, sevofluorane, sufentanil, midazolam, sildenafil, theophylline, S-warfarin, alfentanil, montelukast, efavirenz, lansoprazole, metronidazole, nevirapine, pantoprazole, ropivocaine	(Upreti & Wahlstrom, 2016)
Johnson et al.	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18/19, CYP2D6, CYP2E1, CYP3A4/5,	Simcyp®	1 day - adult	Midazolam, caffeine, diclofenac, omeprazole, cisapride, carbamazepine, theophylline, phenytoin, S-warfarin	(Johnson et al., 2006)
Edginton et al.	CYP1A2, CYP2E1, CYP3A, SULT, UGT1A1, UGT1A1, UGT1A6, UGT1A9, UGT2B7	PK-Sim®	1 day - adult	Paracetamol, alfentanil, morphine, theophylline, levofloxacin	(Edginton, Schmitt, & Willmann, 2006)
Bhatt et al.	UGT2B7	Simcyp®	1 day - adult	Morphine, zidovudine	(Bhatt et al., 2019)
Jiang et al.	CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, SULT, UGT1A1, UGT1A9, UGT2B15	Simcyp®	1 day - adult	Paracetamol	(Jiang et al., 2013)

Johnson, 2014). In this model, parameters involved in metabolic clearance *e.g.* CYP3A4 and CYP2C9 expression and liver weight were included, which resulted in better correlations between predicted and measured data for sildenafil (Abduljalil et al., 2014).

Finally, in case the relevant ontogeny profiles in children are robustly described in PBPK models, more complex age-related variation in drug metabolism may be detected. For example, a change in relative enzyme contribution during growth, as has been described for paracetamol and sirolimus, or a change in relative contribution of eliminating organs, as described for caffeine (Filler, 2007; Mooij et al., 2017; Pons et al., 1988).

3.4. Excretion

Renal excretion of drugs depends on (1) freely filtered drug that is determined by glomerular filtration rate and protein binding, (2) tubular secretion, and (3) tubular reabsorption. Equations describing ontogeny profiles for glomerular filtration rate (GFR) have been reported in multiple studies and used to estimate the amount of drug that is freely filtered (Duan et al., 2017; Johnson et al., 2006; Rhodin et al., 2009; Schwartz et al., 1976). In recently described models, GFR is predicted based on ontogeny functions derived from inulin and ^{51}CR-EDTA measurements, which gives more accurate results than using the creatinine clearance (Johnson et al., 2006; Rhodin et al., 2009). Inclusion of tubular secretion and absorption *via* transporter-mediated processes has lagged behind in pediatric applications, as data on human membrane transporter ontogeny were, until recently, very scarce (Table 5, Fig. 2) (Cheung et al., 2019). By measuring the *in vivo* renal clearance of the P-glycoprotein substrate digoxin over a broad age range, the contribution of tubular secretion in children was used as a surrogate marker for the transporter's ontogeny profile (Willmann et al., 2014). This was done by subtracting the age-related GFR-mediated clearance from total digoxin clearance, which enabled simulation of rivaroxaban plasma concentrations (another P-glycoprotein substrate) over the pediatric age range. In this case the authors assumed that P-glycoprotein transport is the rate-limiting factor in tubular substrate secretion.

In case the transporter involved is unknown, or no transporter-specific substrate data is available to estimate transporter-mediated absorption or secretion, the ratio of $GFR_{pediatric}/GFR_{adult}$ has been used as a surrogate for pediatric renal clearance. However, this assumes that maturational processes in transporters are paralleling the development of GFR, which is often not the case (Cheung, van Groen, Spaans, et al., 2019; Duan et al., 2017; Johnson et al., 2006; Rhodin et al., 2009). The limitation of this assumption is also exemplified by a PBPK study in which this method was used to scale pediatric clearance for nine renally cleared drugs. Although for most children acceptable predictions were obtained, a trend towards an overestimation of renal clearance was found for children <2 years of age, indicating that physiological processes that affect renal clearance differ quantitatively between adults

and young children (W. Zhou et al., 2016). This might be explained by lower renal proximal tubular transporter expression of P-glycoprotein (apical), organic anion transporter (OAT)1, OAT3 and organic cation transporter (OCT)2 (basolateral) in neonates and young children (Cheung, van Groen, Spaans, et al., 2019). The largest overprediction of renal clearance was observed for vancomycin, which is transported by OCT2 (Sokol, 1991; W. Zhou et al., 2016). If urinary excretion of a drug is of minor influence on its total body clearance, ontogeny of renal clearance is often ignored in modeling (Walsh et al., 2016). Modeling the clearance of renally excreted drugs hence awaits inclusion of kidney transporter ontogeny and a means to scale *in vitro* to *in vivo* transport rates. A recent study indicates that this indeed leads to better predictions (Cheung et al., 2019). To our knowledge pediatric models including age-appropriate elimination *via* other routes such as bile, exhalation and sweat glands are not yet reported.

4. 4 Exploratory pediatric PBPK models

4.1. Predictions of (target) tissue concentrations

Most PBPK models are used to describe plasma concentration-time profiles, but due to their compartmental structure, tissue concentrations can be predicted as well, which likely correlate better with the pharmacological/toxicological effects (Gerard et al., 2010; Hornik et al., 2017). Especially concentrations in brain are of interest, as this organ is protected by the blood-brain barrier equipped with multiple drug uptake and efflux transporters. For lipophilic drugs, relatively simple blood flow-limited models might be sufficient due to the rapid transfer of the drug into the brain and predictions can be done by calculating brain-plasma partitioning coefficients (Alqahtani & Kaddoumi, 2016; Donovan, Abduljalil, Cryan, Boylan, & Griffin, 2018). These models are not suitable for more polar drugs, where low BBB permeability restricts brain access resulting in low exposure levels and a lag-time between plasma and brain concentrations. One group started with a permeability-limited rat model that was adjusted for adult humans. This model was further refined to allow predictions on brain morphine extracellular fluid concentrations in children between 3 and 13 years of age (Ketharanathan et al., 2018; Yamamoto et al., 2017; Yamamoto et al., 2018). In another study, an adult PBPK-CSF model was extrapolated to children between 3 months and 15 years of age and verified with multiple drug CSF concentrations (Verscheijden, Koenderink, de Wildt, & Russel, 2019). Both groups did not specifically consider the influence of age on brain transporter expression, which is of main interest for further studies, as accumulating evidence indicates that at least P-glycoprotein activity appears age-related in the pediatric population (Nicolas & de Lange, 2019). Tissue concentrations in other organs have been described using simple Kp-based predictions, for example in skin, bone and lung (Hornik et al., 2017; Ogungbenro, Aarons, Cresim, & Epi, 2015; Thompson et al., 2019).

To date, models for the estimation of tissue concentrations have been more exploratory in nature as compared to models for predicting the course of the plasma drug concentration. This is due to limited access to tissue drug concentrations for verification, knowledge about disposition between different parts of an organ, and on organ transporter ontogeny. For a better applicability of these models, more studies are required to obtain mechanistic information on the processes that govern tissue exposure.

4.2. Prediction of fetal tissue concentrations

By linking fetal compartments to a maternal PBPK model, combined maternal and fetal ADME processes can be described. Maternal pregnancy-induced changes have been reported for volume of distribution, enzyme activity, blood flows, and plasma albumin and alpha-acid glycoprotein concentrations (Abduljalil, Furness, Johnson, Rostami-Hodjegan, & Soltani, 2012). For the fetal model, physiological parameters and their developmental pattern are needed to predict drug exposure (Abduljalil, Jamei, & Johnson, 2019; Ke, Greupink, & Abduljalil, 2018). Recently, more data has become available for ontogeny of physiological parameters in the fetus, for instance concerning developmental patterns in organ volumes (Abduljalil, Jamei, et al., 2019; Abduljalil, Johnson, & Rostami-Hodjegan, 2018; Zhang et al., 2017).

Quantitative information on drug transfer from the maternal side to the fetal compartments can be obtained from clearance studies in the isolated perfused human placental cotyledon, or by measuring drug transfer over a cell line monolayer (De Sousa Mendes et al., 2017; Schalkwijk et al., 2018; Zhang et al., 2017; Zhang & Unadkat, 2017). Placental perfusion experiments are usually performed with normal term placentas, which means that transporter and enzyme expression are likely to be different at a lower gestational age, making extrapolation to earlier stages of pregnancy difficult. Experiments with cell line monolayers suffer from similar problems, as quantification of transporter expression is needed for the complete gestational age range to correct for the differences in abundance between fetal placenta and the cell system used for predictions (Ke et al., 2018). In addition, parameter optimization and model verification are challenging as for obvious reasons fetal drug exposure data at an early gestational age may be hard to acquire. Model verification of fetal compartments with cord blood is an important source of data, although samples are only available at birth and differences in timing between the last dose and sampling introduces variability in the concentrations measured. Also single measurements do not give information on the underlying fetal concentration-time profiles (Schalkwijk et al., 2018).

4.3. Predictions for monoclonal antibodies

Therapeutic use of monoclonal antibodies (mAbs) and large protein molecules has grown rapidly over the years. Although their body disposition is rather different from that of small molecule drugs, PBPK models can also be valuable in predicting the pharmacokinetics of biologicals (Gill, Gardner, Li, & Jamei, 2016). Models for mAbs require incorporation of different physiological processes, compared to small molecules, such as lysosomal degradation, lymph flows, endogenous antibody concentrations, and FcRn receptor-mediated recycling, which also show age-related variation (Edlund, Melin, Parra-Guillen, & Kloft, 2015; Jones, Mayawala, & Poulin, 2013; Malik & Edginton, 2018). Data is not yet available for all processes affecting pharmacokinetics of mAbs, which underscores the need for studies unraveling these developmental physiological parameters. Nevertheless, an attempt was made to scale an adult PBPK model to a pediatric variant for the therapeutic monoclonal IgG antibodies bevacizumab and palivizumab and although many parameters were uncertain, this approach can be used as a framework for building a generic pediatric PBPK model that captures all complexities (Hardiansyah & Ng, 2018).

4.4. Determine effects of non-maturational factors

In addition to age-related variation in ADME processes, PBPK models are very well suited to explore and/or incorporate the effect of non-maturational factors, such as disease, genetics and drug-drug interactions (DDIs) on pharmacokinetics (Zakaria & Badhan, 2018). For example, depending on the maturation profiles of the proteins involved in a DDI, the magnitude of interaction may be different in various age groups, which indicates that information on enzyme/transporter protein ontogeny, and their effects on the interaction needs to be described (Salem, Johnson, Barter, Leeder, & Rostami-Hodjegan, 2013). Simulations of DDIs are not yet common practice in pediatric populations, although some papers have been published, mainly on CYP3A4 (A. Li, Yeo, Welty, & Rong, 2018; Ogungbenro, Aarons, & Cresim, & Epi, C. P. G., 2015; Olafuyi, Coleman, & Badhan, 2017). In these studies, no verification was performed in children < 2y of age, in which developmental differences in CYP3A4 expression are expected to have the largest

Table 5
PBPK models including prediction of renal elimination.

Study	GFR ontogeny	Tubular secretion/absorption ontogeny	Software used	Age range	Drug	Ref.
Balbas-Martinez	Rhodin ontogeny	p-Aminohippuric acid ontogeny	PK-Sim®	3 m-12y	Ciprofloxacin	(Balbas-Martinez et al., 2019)
Lukacova et al.	PEAR module ontogeny	Optimized to measured data Adult transporter expression levels	Gastroplus®	11 days – 17 years and adults	Ganciclovir, valganciclovir	(Lukacova et al., 2016)
Zhou et al.	Johnson ontogeny	Same as GFR ontogeny	Simcyp®	Neonates- adults	Nine renally cleared drugs	(W. Zhou et al., 2016)
Walsh et al.	NA	NA	Simcyp®	0–12 months and adults	Actinomycin D	(Walsh et al., 2016)
Parrott et al.	1/10th of adult	1/10th of adult	Gastroplus®	Neonates, young infants, adults	Oseltamivir	(Parrott et al., 2011)
Duan et al.	Johnson ontogeny	Same as GFR ontogeny	Simcyp®	1 day – 17 years	Linezolid, emtricitabine	(Duan et al., 2017)
Willmann et al.	Rhodin ontogeny	Digoxin tubular secretion (P-glycoprotein) ontogeny	PK-Sim®	Neonates-adolescents	Rivaroxaban	(Willmann et al., 2014)
Cheung et al.	Not stated	Kidney developmental drug transporter expression data	Not stated	0–7 years and adults	Tazobactam	(Cheung, van Groen, Burckart, et al., 2019)

impact on the difference in DDI magnitude compared to adults. Disease effects have been incorporated in adult models for patients with impaired kidney (Yee et al., 2017; L. Zhou et al., 2019) and liver function (Rhee et al., 2017), but inclusion in pediatric models is hampered by the lack of quantitative data on the pathophysiological processes (G. F. Li, Gu, Yu, Zhao, & Zheng, 2016; Rasool et al., 2015; Watt et al., 2018). This is also seen in studies where the effects of a reduction in blood flow were investigated, which at this stage could not be mechanistically included, because of pathophysiological differences in organ blood flow in children compared to adults (Emoto, Johnson, McPhail, et al., 2018; Rasool, Khalil, & Laer, 2016). Effects of genetic polymorphisms have been studied in pediatric PBPK models, often associated with changes in metabolizing enzyme activity (Ogungbenro & Aarons, 2015; Zakaria & Badhan, 2018). Similarly, genetic variation in transporters and target receptors can be incorporated (Hahn et al., 2018). If more physiological data about specific patient groups becomes available, better individualized PBPK model predictions can be made allowing subclassification within age groups, thereby reducing unexplained inter-individual variability and paving the way for more individualized modeling.

4.5. PBPK-PD models

Determination of PD differences between adults and children is of major importance to allow pediatric bridging studies for drugs in development. Introducing the relevant pharmacodynamic processes into pediatric PBPK models will be the next step to determine fully age-appropriated drug doses. The structure of many different PBPK models developed so far is relatively uniform, however, pharmacodynamic modules have their unique structure that is dependent on available knowledge and the process that is being described. Most straightforward is to compare drug concentrations with target thresholds in case of antibiotics, although in a more complex model bacterial count over time could be described (Mohamed, Nielsen, Cars, & Friberg, 2012; Thompson et al., 2019). There are relatively few examples of models that have incorporated a more complex pharmacodynamic component for adults and children (Kechagia, Kalantzi, & Dokoumetzidis, 2015; Kuepfer et al., 2016; Moj et al., 2017; Smith, Hinderliter, Timchalk, Bartels, & Poet, 2014). An important aspect for future model development will be the inclusion of age-related drug effects instead of connecting an adult pharmacodynamic model to a pediatric pharmacokinetic component, for which more developmental *ex vivo* and clinical research is clearly needed (Marshall & Kearns, 1999).

5. Physiologically-based toxicokinetic models

The same principles for building a PBPK model are also applied when assessing the kinetics of a toxic compound, referred to as physiologically-based toxicokinetic (PBTK) models. In fact, the physiologically-based kinetic modeling approach has been around in toxicology longer than in the field of pharmacology (Pelekis, Gephart, & Lerman, 2001). These type of models are usually developed for different animal species and subsequently translated to humans to predict internal exposure as part of the risk assessment of a wider range of chemicals, like pollutants (Emond, Ruiz, & Mumtaz, 2017; Tohon, Valcke, & Haddad, 2019), metals (Fierens et al., 2016; Kirman, Suh, Proctor, & Hays, 2017), pesticides (Lu, Holbrook, & Andres, 2010; Oerlemans et al., 2019) and industrial products (Edginton & Ritter, 2009). Children have also been considered as a vulnerable group at risk, as they may experience relatively higher exposures to chemicals and/or be more sensitive to harmful effects. For example, a higher exposure to bisphenol A was predicted in children, because of their lower elimination capacity compared to adults and the potentially higher weight-normalized intake (Edginton & Ritter, 2009). A difficulty encountered while predicting developmental toxicity is that compared to PBPK models, human and particularly pediatric PBTK models often will carry more uncertainty about the dose internalized, and hence higher variability in predictions (Lu et al., 2010).

6. Quality control

The widespread adoption of PBPK modeling in pediatric drug development and personalized dosing, largely depends on the quality of the models and their validity to accurately predict exposure. The variety in claims made by authors on reliability of the model predictions can be explained by differences in quality and certainty of model parameter estimates. Confidence in modeling results could be increased by performing simulation with similar drugs/formulations (Johnson, Zhou, & Bui, 2014), or the ability to predict drug-drug interactions (Ogungbenro et al., 2015).

Assessing the quality of PBPK models is a complicated task due to the wide variety of different purposes for model use, difference in (mechanistic) complexity, the number of data that is available for building and verification, and heterogeneity in quality measures (Sager et al., 2015). For pediatric PBPK models this might be even more difficult as also developmental processes need to be incorporated and validated. Depending on the purpose of the PBPK model, its quality needs to be evaluated accordingly. In case a model is designed to replace clinical studies in children, confidence in model performance ideally should be high and

parameter uncertainty low, whereas for exploring mechanistic hypotheses (*e.g.* age-related differences in ontogeny), a lower level of confidence in less essential parameters could be acceptable (EMA, 2016). To have more insight into model quality, the following key aspects need to be considered while evaluating PBPK models.

6.1. Mechanistic uncertainty

Uncertainty in the mechanistic bases of the model increases the prediction error, while translating processes affecting absorption, distribution and elimination from adults to children. For example, the contribution of different enzymes involved in drug metabolism can be unknown, or disease-mediated changes on physiological processes are not quantitatively described (Johnson, Cleary, et al., 2018). This means that assumptions are required, of which the impact on model outcomes needs to be evaluated by sensitivity analysis.

6.2. Scaling/fitting parameters

If (multiple) parameters are scaled, uncertainties in other parameters could be masked or compensated in case they are not uniquely identifiable. Apparently acceptable concentration-time profiles produced by a model for one drug or (pediatric) population, will in this case not be reproducible for another drug or in another population (Calvier et al., 2018). Ideally, external datasets are needed to confirm the validity of the scaled parameter in a learning-confirming cycle. As a minimum requirement, biological plausibility of the scaled parameter could be evaluated.

6.3. Quality and quantity of in vivo data for verification

The number and quality of data for verification is variable, ranging from sparse or opportunistic data to dense clinical trial data. Models are generally accepted when they correlate to observed data even if they are sparse, although the latter requires extra caution if for example a measured concentration-time profile is not available for comparison with simulated data (Sager et al., 2015).

6.4. Software package

Multiple software programs are used for modeling and some can be considered better validated, as they have been tested and employed by a large number of users. Currently available commercial software programs for pediatric PBPK modeling include Gastroplus, Simcyp and PK-Sim. Gastroplus has historically focused on prediction of drug absorption, and Simcyp is often used for prediction of DDI's, although areas of application have been extended. The open access software platform PK-Sim is another option for which no coding skills are required. Manually coded models are more prone to errors even after review, but may be more flexible in order to answer specific research questions.

6.5. Transparency

To gain insight into parameter certainty, ideally an overview of the model parameters (drug-related as well as physiological parameters) is described along with the references from which they originated.

7. Regulatory applications

Because physiological and drug-specific parameters are included separately, PBPK models are suited to predict drug concentrations in a population, or for applications where extensive clinical pharmacokinetic information is not yet available. Currently, of all PBPK models used in drug approval applications submitted to the FDA about 15% serve a pediatric purpose, which is more than seen for other "special populations" like elderly, or patients with impaired renal or hepatic function (Grimstein et al., 2019; Jamei, 2016). PBPK modeling in general, and pediatric PBPK modeling in particular, is a relatively new discipline, but its application is increasing rapidly in the majority of pharmaceutical companies. Examples are now available where clinical studies have been replaced or informed by pediatric PBPK simulation efforts (Shebley et al., 2018; Wagner et al., 2015). For example, models have been used to (1) set a starting dose in a clinical trial with eribulin in children and adolescents 6–18 years of age, (2) bridge from immediate release to extended release quetiapine formulations in children and adolescents 10–17 years of age, and (3) inform deflazacort dose adjustments needed when given together with drugs that may cause interactions in children and adolescents 4–16 years of age (FDA, 2016; Johnson et al., 2014; Shebley et al., 2018). Regulatory authorities have recognized the potential of PBPK modeling and guidelines were issued mainly focused on what information should be incorporated in the PBPK model documentation by pharmaceutical industry, which might further standardize the process of model development in regulatory applications (EMA, 2016; FDA, 2018).

8. Future perspectives

PBPK modeling in children aids in predicting the pediatric pharmacokinetics of drugs for which no or sparse data is available. Whereas model performance is currently more challenging for neonatal populations, drugs metabolized by non-CYP enzymes, drug transporter substrates, and drugs which are orally absorbed, PBPK models are continuously improved and refined in a learn-and-confirm cycle by the inclusion of more accurate model parameters.

One aspect that could further improve pediatric PBPK model development is to fill the gap in availability and quality of systems data. For this purpose, quantitative proteomics is an attractive technique to assess ontogeny patterns for absolute expression of drug metabolizing enzymes and transporters in different organs and the interplay with other co-variates. This approach is especially suitable for pediatric populations where a low number or size of samples is usually available. As multiple proteins can be quantified at the same time, correlation between protein expression can also be considered (Achour, Barber, & Rostami-Hodjegan, 2014; Heikkinen, Lignet, Cutler, & Parrott, 2015). The number of studies in children is limited, pediatric PBPK modeling therefore will require pooling of data, resources and knowledge. This also includes combining tissue material, plasma and body fluid samples from different institutions and biobanks to cover the full age range of pediatric development.

In addition to obtaining better defined physiological parameters, there is a need for verification of models. Opportunistic sampling of plasma and other body fluids or tissues would be a way to obtain measurements for drugs already on the market, which were not thoroughly investigated previously (Hahn et al., 2019; Salerno, Burckart, Huang, & Gonzalez, 2019). Open access publishing and publication of raw data will aid in making optimal use of already available clinical data. If it is still not possible to obtain enough data, micro-dosing studies could provide a good alternative, as long as saturation of enzymes and transporters is not expected at therapeutic doses. By administering a small amount of a labeled drug (often 1/100 of usual dose) its pharmacokinetics can be determined, without the risks associated with potential toxic effects (Mooij et al., 2017; Roth-Cline & Nelson, 2015). From a modeling perspective, good quality clinical data is extremely valuable for studying the ontogeny of system parameters in case biological samples are hard to obtain (*e.g.* blood brain barrier transporter expression).

Whereas in the coming years pediatric PBPK model improvement will be focused on prediction in specific age groups and for children having co-morbidities by better capturing the underlying (patho)physiological parameters, an area of potential future benefit is the use of PBPK modeling in personalized medicine. This will require even more detailed information on demographic, genotypic, and phenotypic characteristics. Development of a "virtual twin" in which patient-specific

features like, age, weight, height, gender, ethnicity, and genetics of drug metabolizing enzymes/transporters are taken into account in PBPK models, will contribute to better personalized dosing and predictions within specific age groups. This will allow pediatric PBPK models to find their way into clinical practice (Tucker, 2017).

9. Conclusion

The application of pediatric PBPK models have gained momentum over the last years, partly because their development has been stimulated by the increased interest of regulatory authorities in this "special population" and the obligation of investigating pharmacological differences between children and adults. Different pediatric PBPK models have been developed for a wide variety of purposes, including substitution of clinical studies. While uncertainty in some physiological parameters is higher and less data might be available for model verification in children, pediatric PBPK models have become more robust and start to approach the mechanistic basis seen in their adult counterparts. In the coming years model quality and mechanistic basis will further improve by inclusion of more (reliable) physiological data, which will provide a sound basis for pediatric model acceptance (Burckart & van den Anker, 2019). In this way, with concerted efforts of academia, PBPK model developers, industry and regulators, the use of this approach will further expand and be applied to optimize drug development in the pediatric population. The role of modeling and simulation in drug development will undoubtedly increase and particular effort should be invested in the development of these models for children, to exploit the enormous potential of this evolution also for the pediatric population.

Declaration of Competing Interest

TNJ is an employee of Certara UK Limited and involved in the development of the commercial Simcyp PBPK model. LFMV, JBK, SNW and FGMR declare that there are no conflicts of interest.

References

Abduljalil, K., Furness, P., Johnson, T. N., Rostami-Hodjegan, A., & Soltani, H. (2012). Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: A database for parameters required in physiologically based pharmacokinetic modelling. *Clinical Pharmacokinetics 51*, 365–396.

Abduljalil, K., Jamei, M., & Johnson, T. N. (2019). Fetal physiologically based pharmacokinetic models: Systems information on the growth and composition of fetal organs. *Clinical Pharmacokinetics 58*, 235–262.

Abduljalil, K., Jamei, M., Rostami-Hodjegan, A., & Johnson, T. N. (2014). Changes in individual drug-independent system parameters during virtual paediatric pharmacokinetic trials: Introducing time-varying physiology into a paediatric PBPK model. *The AAPS Journal 16*, 568–576.

Abduljalil, K., Johnson, T. N., & Rostami-Hodjegan, A. (2018). Fetal physiologically-based pharmacokinetic models: Systems information on fetal biometry and gross composition. *Clinical Pharmacokinetics 57*, 1149–1171.

Abduljalil, K., Pan, X., Pansari, A., Jamei, M., & Johnson, T. N. (2019a). A preterm physiologically based pharmacokinetic model. Part I: Physiological parameters and model building. *Clinical Pharmacokinetics 59*, 485–500.

Abduljalil, K., Pan, X., Pansari, A., Jamei, M., & Johnson, T. N. (2019b). Preterm physiologically based pharmacokinetic model. Part II: Applications of the model to predict drug pharmacokinetics in the preterm population. *Clinical Pharmacokinetics 59*, 501–518.

Achour, B., Barber, J., & Rostami-Hodjegan, A. (2014). Expression of hepatic drug-metabolizing cytochrome p450 enzymes and their intercorrelations: A meta-analysis. *Drug Metabolism and Disposition 42*, 1349–1356.

Alqahtani, S., & Kaddoumi, A. (2016). Development of a physiologically based pharmacokinetic/Pharmacodynamic model to predict the impact of genetic polymorphisms on the pharmacokinetics and pharmacodynamics represented by receptor/transporter occupancy of central nervous system drugs. *Clinical Pharmacokinetics 55*, 957–969.

van den Anker, J., Reed, M. D., Allegaert, K., & Kearns, G. L. (2018). Developmental changes in pharmacokinetics and pharmacodynamics. *Journal of Clinical Pharmacology 58* (Suppl. 10), S10–S25.

Avery, G. B., Randolph, J. G., & Weaver, T. (1966). Gastric acidity in the first day of life. *Pediatrics 37*, 1005–1007.

Balbas-Martinez, V., Michelet, R., Edginton, A. N., Meesters, K., Troconiz, I. F., & Vermeulen, A. (2019). Physiologically-based pharmacokinetic model for ciprofloxacin in children with complicated urinary tract infection. *European Journal of Pharmaceutical Sciences 128*, 171–179.

Ball, K., Bouzom, F., Scherrmann, J. M., Walther, B., & Decleves, X. (2012). Development of a physiologically based pharmacokinetic model for the rat central nervous system and determination of an in vitro-in vivo scaling methodology for the blood-brain barrier permeability of two transporter substrates, morphine and oxycodone. *Journal of Pharmaceutical Sciences 101*, 4277–4292.

Barbero, G. J., Runge, G., Fischer, D., Crawford, M. N., Torres, F. E., & Gyorgy, P. (1952). Investigations on the bacterial flora, pH, and sugar content in the intestinal tract of infants. *The Journal of Pediatrics 40*, 152–163.

Barter, Z. E., Chowdry, J. E., Harlow, J. R., Snawder, J. E., Lipscomb, J. C., & Rostami-Hodjegan, A. (2008). Covariation of human microsomal protein per gram of liver with age: Absence of influence of operator and sample storage may justify interlaboratory data pooling. *Drug Metabolism and Disposition 36*, 2405–2409.

Bhatt, D. K., Mehrotra, A., Gaedigk, A., Chapa, R., Basit, A., Zhang, H., ... Prasad, B. (2019). Age- and genotype-dependent variability in the protein abundance and activity of six major uridine diphosphate-glucuronosyltransferases in human liver. *Clinical Pharmacology and Therapeutics 105*, 131–141.

Bi, Y., Deng, J., Murry, D. J., & An, G. (2016). A whole-body physiologically based pharmacokinetic model of Gefitinib in mice and scale-up to humans. *The AAPS Journal 18*, 228–238.

Bonner, J. J., Vajjah, P., Abduljalil, K., Jamei, M., Rostami-Hodjegan, A., Tucker, G. T., & Johnson, T. N. (2015). Does age affect gastric emptying time? A model-based meta-analysis of data from premature neonates through to adults. *Biopharmaceutics & Drug Disposition 36*, 245–257.

Brussee, J. M., Yu, H., Krekels, E. H. J., de Roos, B., Brill, M. J. E., van den Anker, J. N., ... Knibbe, C. A. J. (2018). First-pass CYP3A-mediated metabolism of midazolam in the Gut Wall and liver in preterm neonates. *CPT: Pharmacometrics & Systems Pharmacology 7*, 374–383.

Brussee, J. M., Yu, H., Krekels, E. H. J., Palic, S., Brill, M. J. E., Barrett, J. S., ... Knibbe, C. A. J. (2018). Characterization of intestinal and hepatic CYP3A-mediated metabolism of midazolam in children using a physiological population pharmacokinetic modelling approach. *Pharmaceutical Research 35*, 182.

Burckart, G. J., & van den Anker, J. N. (2019). Pediatric ontogeny: Moving from translational science to drug development. *Journal of Clinical Pharmacology 59*(Suppl. 1), S7–s8.

Butte, N. F., Hopkinson, J. M., Wong, W. W., Smith, E. O., & Ellis, K. J. (2000). Body composition during the first 2 years of life: An updated reference. *Pediatric Research 47*, 578–585.

Calvier, E. A. M., Nguyen, T. T., Johnson, T. N., Rostami-Hodjegan, A., Tibboel, D., Krekels, E. H. J., & Knibbe, C. A. J. (2018). Can population modelling principles be used to identify key PBPK parameters for Paediatric clearance predictions? An innovative application of optimal design theory. *Pharmaceutical Research 35*, 209.

Carberry, A. E., Colditz, P. B., & Lingwood, B. E. (2010). Body composition from birth to 4.5 months in infants born to non-obese women. *Pediatric Research 68*, 84–88.

Cella, M., Knibbe, C., Danhof, M., & Della Pasqua, O. (2010). What is the right dose for children? *British Journal of Clinical Pharmacology 70*, 597–603.

Cheung, K. W. K., van Groen, B. D., Burckart, G. J., Zhang, L., de Wildt, S. N., & Huang, S. M. (2019). Incorporating ontogeny in physiologically based pharmacokinetic modeling to improve pediatric drug development: What we know about developmental changes in membrane transporters. *Journal of Clinical Pharmacology 59*(Suppl. 1), S56–s69.

Cheung, K. W. K., van Groen, B. D., Spaans, E., van Borselen, M. D., de Bruijn, A., Simons-Oosterhuis, Y., ... de Wildt, S. N. (2019). A comprehensive analysis of ontogeny of renal drug transporters: mRNA analyses, quantitative proteomics, and localization. *Clinical Pharmacology and Therapeutics 106*, 1083–1092.

Chiron, C., Raynaud, C., Maziere, B., Zilbovicius, M., Laflamme, L., Masure, M. C., ... Syrota, A. (1992). Changes in regional cerebral blood flow during brain maturation in children and adolescents. *Journal of Nuclear Medicine 33*, 696–703.

Cristofoletti, R., Charoo, N. A., & Dressman, J. B. (2016). Exploratory investigation of the limiting steps of Oral absorption of fluconazole and ketoconazole in children using an in silico pediatric absorption model. *Journal of Pharmaceutical Sciences 105*, 2794–2803.

Daood, M., Tsai, C., Ahdab-Barmada, M., & Watchko, J. F. (2008). ABC transporter (P-gp/ABCB1, MRP1/ABCC1, BCRP/ABCG2) expression in the developing human CNS. *Neuropediatrics 39*, 211–218.

De Sousa Mendes, M., Lui, G., Zheng, Y., Pressiat, C., Hirt, D., Valade, E., ... Benaboud, S. (2017). A physiologically-based pharmacokinetic model to predict human fetal exposure for a drug metabolized by several CYP450 pathways. *Clinical Pharmacokinetics 56*, 537–550.

Diestelhorst, C., Boos, J., McCune, J. S., Russell, J., Kangarloo, S. B., & Hempel, G. (2014). Predictive performance of a physiologically based pharmacokinetic model of busulfan in children. *Pediatric Hematology and Oncology 31*, 731–742.

Divakaran, K., Hines, R. N., & McCarver, D. G. (2014). Human hepatic UGT2B15 developmental expression. *Toxicological Sciences 141*, 292–299.

Donovan, M. D., Abduljalil, K., Cryan, J. F., Boylan, G. B., & Griffin, B. T. (2018). Application of a physiologically-based pharmacokinetic model for the prediction of bumetanide plasma and brain concentrations in the neonate. *Biopharmaceutics & Drug Disposition 39*, 125–134.

Duan, P., Fisher, J. W., Yoshida, K., Zhang, L., Burckart, G. J., & Wang, J. (2017). Physiologically based pharmacokinetic prediction of linezolid and Emtricitabine in neonates and infants. *Clinical Pharmacokinetics 56*, 383–394.

Edginton, A. N., & Ritter, L. (2009). Predicting plasma concentrations of bisphenol a in children younger than 2 years of age after typical feeding schedules, using a physiologically based toxicokinetic model. *Environmental Health Perspectives 117*, 645–652.

Edginton, A. N., Schmitt, W., & Willmann, S. (2006). Development and evaluation of a generic physiologically based pharmacokinetic model for children. *Clinical Pharmacokinetics 45*, 1013–1034.

Edlund, H., Melin, J., Parra-Guillen, Z. P., & Kloft, C. (2015). Pharmacokinetics and pharmacokinetic-pharmacodynamic relationships of monoclonal antibodies in children. *Clinical Pharmacokinetics 54*, 35–80.

EMA (2007). *Pediatric regulation*. In: European Medicines Agency.

EMA (2016). *Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation*. In: European Medicines Agency.

Emond, C., Ruiz, P., & Mumtaz, M. (2017). Physiologically based pharmacokinetic toolkit to evaluate environmental exposures: Applications of the dioxin model to study real life exposures. *Toxicology and Applied Pharmacology 315*, 70–79.

Emoto, C., Fukuda, T., Johnson, T. N., Neuhoff, S., Sadhasivam, S., & Vinks, A. A. (2017). Characterization of contributing factors to variability in morphine clearance through PBPK modeling implemented with OCT1 transporter. *CPT: Pharmacometrics & Systems Pharmacology 6*, 110–119.

Emoto, C., Johnson, T. N., McPhail, B. T., Vinks, A. A., & Fukuda, T. (2018). Using a vancomycin PBPK model in special populations to elucidate case-based clinical PK observations. *CPT: Pharmacometrics & Systems Pharmacology 7*, 237–250.

Emoto, C., Johnson, T. N., Neuhoff, S., Hahn, D., Vinks, A. A., & Fukuda, T. (2018). PBPK model of morphine incorporating developmental changes in hepatic OCT1 and UGT2B7 proteins to explain the variability in clearances in neonates and small infants. *CPT: Pharmacometrics & Systems Pharmacology 7*, 464–473.

Fakhoury, M., Litalien, C., Medard, Y., Cave, H., Ezzahir, N., Peuchmaur, M., & Jacqz-Aigrain, E. (2005). Localization and mRNA expression of CYP3A and P-glycoprotein in human duodenum as a function of age. *Drug Metabolism and Disposition 33*, 1603–1607.

Fallingborg, J., Christensen, L. A., Ingeman-Nielsen, M., Jacobsen, B. A., Abildgaard, K., Rasmussen, H. H., & Rasmussen, S. N. (1990). Measurement of gastrointestinal pH and regional transit times in normal children. *Journal of Pediatric Gastroenterology and Nutrition 11*, 211–214.

FDA (2002/2003). *Best pharmaceuticals for children act and pediatric research equity act*. In: Food & Drug Administration.

FDA (2016). Deflazacort clinical pharmacology review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208684,208685Orig1s000ClinPharmR.pdf.

FDA (2018). *Physiologically based pharmacokinetic analyses — Format and content guidance for industry*. In: Food & Drug Administration.

Feng, S., Shi, J., Parrott, N., Hu, P., Weber, C., Martin-Facklam, M., ... Peck, R. (2016). Combining "Bottom-Up" and "Top-Down" methods to assess ethnic difference in clearance: Bitopertin as an example. *Clinical Pharmacokinetics 55*, 823–832.

Fierens, T., Van Holderbeke, M., Standaert, A., Cornelis, C., Brochot, C., Ciffroy, P., ... Bierkens, J. (2016). Multimedia & PBPK modelling with MERLIN-expo versus biomonitoring for assessing Pb exposure of pre-school children in a residential setting. *Science of the Total Environment 568*, 785–793.

Filler, G. (2007). Optimization of immunosuppressive drug monitoring in children. *Transplantation Proceedings 39*, 1241–1243.

Frattarelli, D. A., Galinkin, J. L., Green, T. P., Johnson, T. D., Neville, K. A., Paul, I. M., ... American Academy of Pediatrics Committee on, D (2014). Off-label use of drugs in children. *Pediatrics 133*, 563–567.

Fulgoni, V. L., III, Agarwal, S., Kellogg, M. D., & Lieberman, H. R. (2019). Establishing pediatric and adult RBC reference intervals with NHANES data using piecewise regression. *American Journal of Clinical Pathology 151*, 128–142.

Gerard, C., Bleyzac, N., Girard, P., Freyer, G., Bertrand, Y., & Tod, M. (2010). Influence of dosing schedule on organ exposure to cyclosporin in pediatric hematopoietic stem cell transplantation: Analysis with a PBPK model. *Pharmaceutical Research 27*, 2602–2613.

Gill, K. L., Gardner, I., Li, L., & Jamei, M. (2016). A bottom-up whole-body physiologically based pharmacokinetic model to mechanistically predict tissue distribution and the rate of subcutaneous absorption of therapeutic proteins. *The AAPS Journal 18*, 156–170.

Gondolesi, G., Ramisch, D., Padin, J., Almau, H., Sandi, M., Schelotto, P. B., ... Solar, H. (2012). What is the normal small bowel length in humans? First donor-based cohort analysis. *American Journal of Transplantation 12*(Suppl. 4), S49–S54.

Grimstein, M., Yang, Y., Zhang, X., Grillo, J., Huang, S. M., Zineh, I., & Wang, Y. (2019). Physiologically based pharmacokinetic modeling in regulatory science: An update from the U.S. Food and Drug Administration's Office of Clinical Pharmacology. *Journal of Pharmaceutical Sciences 108*, 21–25.

van Groen, B. D., van de Steeg, E., Mooij, M. G., van Lipzig, M. M. H., de Koning, B. A. E., Verdijk, R. M., ... de Wildt, S. N. (2018). Proteomics of human liver membrane transporters: A focus on fetuses and newborn infants. *European Journal of Pharmaceutical Sciences 124*, 217–227.

Hahn, D., Emoto, C., Euteneuer, J. C., Mizuno, T., Vinks, A. A., & Fukuda, T. (2018). Influence of OCT1 ontogeny and genetic variation on morphine disposition in critically ill neonates: Lessons from PBPK modeling and clinical study. *Clinical Pharmacology and Therapeutics 105*, 761–768.

Hahn, D., Emoto, C., Euteneuer, J. C., Mizuno, T., Vinks, A. A., & Fukuda, T. (2019). Influence of OCT1 ontogeny and genetic variation on morphine disposition in critically ill neonates: Lessons from PBPK modeling and clinical study. *Clinical Pharmacology and Therapeutics 105*, 761–768.

Hardiansyah, D., & Ng, C. M. (2018). Effects of the FcRn developmental pharmacology on the pharmacokinetics of therapeutic monoclonal IgG antibody in pediatric subjects using minimal physiologically-based pharmacokinetic modelling. *MAbs*, 1–13.

Hayton, W. L. (2000). Maturation and growth of renal function: Dosing renally cleared drugs in children. *AAPS PharmSci 2*, E3.

Heikkinen, A. T., Lignet, F., Cutler, P., & Parrott, N. (2015). The role of quantitative ADME proteomics to support construction of physiologically based pharmacokinetic models for use in small molecule drug development. *Proteomics. Clinical Applications 9*, 732–744.

Hornik, C. P., Wu, H., Edginton, A. N., Watt, K., Cohen-Wolkowiez, M., & Gonzalez, D. (2017). Development of a pediatric physiologically-based pharmacokinetic model of clindamycin using opportunistic pharmacokinetic data. *Clinical Pharmacokinetics 56*, 1343–1353.

Jamei, M. (2016). Recent advances in development and application of physiologically-based pharmacokinetic (PBPK) models: A transition from academic curiosity to regulatory acceptance. *Current Pharmacology Reports 2*, 161–169.

Jaroch, K., Jaroch, A., & Bojko, B. (2018). Cell cultures in drug discovery and development: The need of reliable in vitro-in vivo extrapolation for pharmacodynamics and pharmacokinetics assessment. *Journal of Pharmaceutical and Biomedical Analysis 147*, 297–312.

Jiang, X. L., Zhao, P., Barrett, J. S., Lesko, L. J., & Schmidt, S. (2013). Application of physiologically based pharmacokinetic modeling to predict acetaminophen metabolism and pharmacokinetics in children. *CPT: Pharmacometrics & Systems Pharmacology 2*, e80.

Johnson, T. N., Bonner, J. J., Tucker, G. T., Turner, D. B., & Jamei, M. (2018). Development and applications of a physiologically-based model of paediatric oral drug absorption. *European Journal of Pharmaceutical Sciences 115*, 57–67.

Johnson, T. N., Cleary, Y., Parrott, N., Reigner, B., Smith, J. R., & Toovey, S. (2018). Development of a PBPK model for Mefloquine and its application alongside a clinical effectiveness model to select an optimal dose for prevention of malaria in young Caucasian children. *British Journal of Clinical Pharmacology 85*, 100–113.

Johnson, T. N., Rostami-Hodjegan, A., & Tucker, G. T. (2006). Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clinical Pharmacokinetics 45*, 931–956.

Johnson, T. N., Tanner, M. S., Taylor, C. J., & Tucker, G. T. (2001). Enterocytic CYP3A4 in a paediatric population: Developmental changes and the effect of coeliac disease and cystic fibrosis. *British Journal of Clinical Pharmacology 51*, 451–460.

Johnson, T. N., Zhou, D., & Bui, K. H. (2014). Development of physiologically based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents. *Biopharmaceutics & Drug Disposition 35*, 341–352.

Jones, H. M., Mayawala, K., & Poulin, P. (2013). Dose selection based on physiologically based pharmacokinetic (PBPK) approaches. *The AAPS Journal 15*, 377–387.

Jopling, J., Henry, E., Wiedmeier, S. E., & Christensen, R. D. (2009). Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: Data from a multihospital health care system. *Pediatrics 123*, e333–e337.

Kanakoudi, F., Drossou, V., Tzimouli, V., Diamanti, E., Konstantinidis, T., Germenis, A., & Kremenopoulos, G. (1995). Serum concentrations of 10 acute-phase proteins in healthy term and preterm infants from birth to age 6 months. *Clinical Chemistry 41*, 605–608.

Ke, A. B., Greupink, R., & Abduljalil, K. (2018). Drug dosing in pregnant women: Challenges and opportunities in using physiologically based pharmacokinetic modeling and simulations. *CPT: Pharmacometrics & Systems Pharmacology 7*, 103–110.

Kechagia, I. A., Kalantzi, L., & Dokoumetzidis, A. (2015). Extrapolation of enalapril efficacy from adults to children using pharmacokinetic/pharmacodynamic modelling. *The Journal of Pharmacy and Pharmacology 67*, 1537–1545.

Ketharanathan, N., Yamamoto, Y., Rohlwink, U. K., Wildschut, E. D., Mathot, R. A. A., de Lange, E. C. M., ... Figaji, A. A. (2018). Combining brain microdialysis and translational pharmacokinetic modeling to predict drug concentrations in pediatric severe traumatic brain injury: The next step toward evidence-based pharmacotherapy? *Journal of Neurotrauma 36*, 111–117.

Khalil, F., & Laer, S. (2014). Physiologically based pharmacokinetic models in the prediction of oral drug exposure over the entire pediatric age range-sotalol as a model drug. *The AAPS Journal 16*, 226–239.

Kirman, C. R., Suh, M., Proctor, D. M., & Hays, S. M. (2017). Improved physiologically based pharmacokinetic model for oral exposures to chromium in mice, rats, and humans to address temporal variation and sensitive populations. *Toxicology and Applied Pharmacology 325*, 9–17.

Kohlmann, P., Stillhart, C., Kuentz, M., & Parrott, N. (2017). Investigating Oral absorption of carbamazepine in pediatric populations. *The AAPS Journal 19*, 1864–1877.

Konieczna, A., Erdosova, B., Lichnovska, R., Jandl, M., Cizkova, K., & Ehrmann, J. (2011). Differential expression of ABC transporters (MDR1, MRP1, BCRP) in developing human embryos. *Journal of Molecular Histology 42*, 567–574.

Koppen, I. J., Yacob, D., Di Lorenzo, C., Saps, M., Benninga, M. A., Cooper, J. N., ... Thompson, B. P. (2017). Assessing colonic anatomy normal values based on air contrast enemas in children younger than 6 years. *Pediatric Radiology 47*, 306–312.

Kuepfer, L., Niederalt, C., Wendl, T., Schlender, J. F., Willmann, S., Lippert, J., ... Teutonico, D. (2016). Applied concepts in PBPK modeling: How to build a PBPK/PD model. *CPT: Pharmacometrics & Systems Pharmacology 5*, 516–531.

Lam, J., Baello, S., Iqbal, M., Kelly, L. E., Shannon, P. T., Chitayat, D., ... Koren, G. (2015). The ontogeny of P-glycoprotein in the developing human blood-brain barrier: Implication for opioid toxicity in neonates. *Pediatric Research 78*, 417–421.

Le Merdy, M., Fan, J., Bolger, M. B., Lukacova, V., Spires, J., Tsakalozou, E., ... Zhao, L. (2019). Application of mechanistic ocular absorption modeling and simulation to understand the impact of formulation properties on ophthalmic bioavailability in rabbits: A case study using dexamethasone suspension. *The AAPS Journal 21*, 65.

Leong, R., Vieira, M. L., Zhao, P., Mulugeta, Y., Lee, C. S., Huang, S. M., & Burckart, G. J. (2012). Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. *Clinical Pharmacology and Therapeutics 91*, 926–931.

Li, A., Yeo, K., Welty, D., & Rong, H. (2018). Development of Guanfacine extended-release dosing strategies in children and adolescents with ADHD using a physiologically based pharmacokinetic model to predict drug-drug interactions with moderate CYP3A4 inhibitors or inducers. *Paediatric Drugs 20*, 181–194.

Li, G. F., Gu, X., Yu, G., Zhao, S. Y., & Zheng, Q. S. (2016). Comment on: "a physiologically based pharmacokinetic drug-disease model to predict carvedilol exposure in adult and Paediatric heart failure patients by incorporating pathophysiological changes in hepatic and renal blood". *Clinical Pharmacokinetics 55*, 133–137.

Lu, C., Holbrook, C. M., & Andres, L. M. (2010). The implications of using a physiologically based pharmacokinetic (PBPK) model for pesticide risk assessment. *Environmental Health Perspectives 118*, 125–130.

Lukacova, V., Goelzer, P., Reddy, M., Greig, G., Reigner, B., & Parrott, N. (2016). A physiologically based pharmacokinetic model for ganciclovir and its prodrug Valganciclovir in adults and children. *The AAPS Journal 18*, 1453–1463.

Maharaj, A. R., Barrett, J. S., & Edginton, A. N. (2013). A workflow example of PBPK modeling to support pediatric research and development: Case study with lorazepam. *The AAPS Journal 15*, 455–464.

Maharaj, A. R., & Edginton, A. N. (2014). Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT: Pharmacometrics & Systems Pharmacology 3*, 1–13.

Maharaj, A. R., & Edginton, A. N. (2016). Examining small intestinal transit time as a function of age: Is there evidence to support age-dependent differences among children? *Drug Metabolism and Disposition 44*, 1080–1089.

Maharaj, A. R., Gonzalez, D., Cohen-Wolkowiez, M., Hornik, C. P., & Edginton, A. N. (2018). Improving pediatric protein binding estimates: An evaluation of alpha1-acid glycoprotein maturation in healthy and infected subjects. *Clinical Pharmacokinetics 57*, 577–589.

Malik, P., & Edginton, A. (2018). Pediatric physiology in relation to the pharmacokinetics of monoclonal antibodies. *Expert Opinion on Drug Metabolism & Toxicology 14*, 585–599.

Malina, R. M. (1969). Quantification of fat, muscle and bone in man. *Clinical Orthopaedics and Related Research 65*, 9–38.

Manolis, E., Osman, T. E., Herold, R., Koenig, F., Tomasi, P., Vamvakas, S., & Saint Raymond, A. (2011). Role of modeling and simulation in pediatric investigation plans. *Paediatric Anaesthesia 21*, 214–221.

Mansoor, N., Ahmad, T., Alam Khan, R., Sharib, S. M., & Mahmood, I. (2019). Prediction of clearance and dose of midazolam in preterm and term neonates: A comparative study between Allometric scaling and physiologically based pharmacokinetic modeling. *American Journal of Therapeutics 26*, e32–e37.

Marshall, J. D., & Kearns, G. L. (1999). Developmental pharmacodynamics of cyclosporine. *Clinical Pharmacology and Therapeutics 66*, 66–75.

Matsumoto, Y., Cabalu, T., Sandhu, P., Hartmann, G., Iwasa, T., Yoshitsugu, H., ... Uemura, N. (2018). Application of physiologically-based pharmacokinetic modeling to predict pharmacokinetics in healthy Japanese subjects. *Clinical Pharmacology and Therapeutics 105*, 1018–1030.

Mirjalili, S. A., Tarr, G., & Stringer, M. D. (2017). The length of the large intestine in children determined by computed tomography scan. *Clinical Anatomy 30*, 887–893.

Mizuno, T., Fukuda, T., Masuda, S., Uemoto, S., Matsubara, K., Inui, K., & Vinks, A. A. (2014). Developmental trajectory of intestinal MDR1/ABCB1 mRNA expression in children. *British Journal of Clinical Pharmacology 77*, 910–912.

Mohamed, A. F., Nielsen, E. I., Cars, O., & Friberg, L. E. (2012). Pharmacokinetic-pharmacodynamic model for gentamicin and its adaptive resistance with predictions of dosing schedules in newborn infants. *Antimicrobial Agents and Chemotherapy 56*, 179–188.

Moj, D., Britz, H., Burhenne, J., Stewart, C. F., Egerer, G., Haefeli, W. E., & Lehr, T. (2017). A physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model of the histone deacetylase (HDAC) inhibitor vorinostat for pediatric and adult patients and its application for dose specification. *Cancer Chemotherapy and Pharmacology 80*, 1013–1026.

Mooij, M. G., Schwarz, U. I., de Koning, B. A., Leeder, J. S., Gaedigk, R., Samsom, J. N., ... de Wildt, S. N. (2014). Ontogeny of human hepatic and intestinal transporter gene expression during childhood: Age matters. *Drug Metabolism and Disposition 42*, 1268–1274.

Mooij, M. G., van de Steeg, E., van Rosmalen, J., Windster, J. D., de Koning, B. A., Vaes, W. H., ... de Wildt, S. N. (2016). Proteomic analysis of the developmental trajectory of human hepatic membrane transporter proteins in the first three months of life. *Drug Metabolism and Disposition 44*, 1005–1013.

Mooij, M. G., van Duijn, E., Knibbe, C. A. J., Allegaert, K., Windhorst, A. D., van Rosmalen, J., ... de Wildt, S. N. (2017). Successful use of [(14)C]paracetamol microdosing to elucidate developmental changes in drug metabolism. *Clinical Pharmacokinetics 56*, 1185–1195.

Nicolas, J. M., & de Lange, E. C. M. (2019). Mind the gaps: Ontogeny of human brain P-gp and its impact on drug toxicity. *The AAPS Journal 21*, 67.

Oerlemans, A., Verscheijden, L. F. M., Mol, J. G. J., Vermeulen, R. C. H., Westerhout, J., Roeleveld, N., ... Scheepers, P. T. J. (2019). Toxicokinetics of a urinary metabolite of tebuconazole following controlled oral and dermal administration in human volunteers. *Archives of Toxicology 93*, 2545–2553.

Ogiu, N., Nakamura, Y., Ijiri, I., Hiraiwa, K., & Ogiu, T. (1997). A statistical analysis of the internal organ weights of normal Japanese people. *Health Physics 72*, 368–383.

Ogungbenro, K., & Aarons, L. (2015). Physiologically based pharmacokinetic model for 6-mercpatopurine: Exploring the role of genetic polymorphism in TPMT enzyme activity. *British Journal of Clinical Pharmacology 80*, 86–100.

Ogungbenro, K., Aarons, L., & Cresim, & Epi, C. P. G. (2015). A physiologically based pharmacokinetic model for clobazam and stiripentol in adults and children. *Pharmaceutical Research 32*, 144–157.

Olafuyi, O., Coleman, M., & Badhan, R. K. S. (2017). Development of a paediatric physiologically based pharmacokinetic model to assess the impact of drug-drug interactions in tuberculosis co-infected malaria subjects: A case study with artemether-lumefantrine and the CYP3A4-inducer rifampicin. *European Journal of Pharmaceutical Sciences 106*, 20–33.

Parrott, N., Davies, B., Hoffmann, G., Koerner, A., Lave, T., Prinssen, E., ... Singer, T. (2011). Development of a physiologically based model for oseltamivir and simulation of pharmacokinetics in neonates and infants. *Clinical Pharmacokinetics 50*, 613–623.

Pelekis, M., Gephart, L. A., & Lerman, S. E. (2001). Physiological-model-based derivation of the adult and child pharmacokinetic intraspecies uncertainty factors for volatile organic compounds. *Regulatory Toxicology and Pharmacology 33*, 12–20.

Piepsz, A., Tondeur, M., & Ham, H. (2006). Revisiting normal (51)Cr-ethylenediaminetetraacetic acid clearance values in children. *European Journal of Nuclear Medicine and Molecular Imaging 33*, 1477–1482.

Poet, T. S., Corley, R. A., Thrall, K. D., Edwards, J. A., Tanojo, H., Weitz, K. K., ... Wester, R. C. (2000). Assessment of the percutaneous absorption of trichloroethylene in rats and humans using MS/MS real-time breath analysis and physiologically based pharmacokinetic modeling. *Toxicological Sciences 56*, 61–72.

Pons, G., Blais, J. C., Rey, E., Plissonnier, M., Richard, M. O., Carrier, O., ... Olive, G. (1988). Maturation of caffeine N-demethylation in infancy: A study using the 13CO2 breath test. *Pediatric Research 23*, 632–636.

Poulin, P., & Theil, F. P. (2000). A priori prediction of tissue:Plasma partition coefficients of drugs to facilitate the use of physiologically-based pharmacokinetic models in drug discovery. *Journal of Pharmaceutical Sciences 89*, 16–35.

Prasad, B., Gaedigk, A., Vrana, M., Gaedigk, R., Leeder, J. S., Salphati, L., ... Unadkat, J. D. (2016). Ontogeny of hepatic drug transporters as quantified by LC-MS/MS proteomics. *Clinical Pharmacology and Therapeutics 100*, 362–370.

Radke, C., Horn, D., Lanckohr, C., Ellger, B., Meyer, M., Eissing, T., & Hempel, G. (2017). Development of a physiologically based pharmacokinetic modelling approach to predict the pharmacokinetics of vancomycin in critically ill septic patients. *Clinical Pharmacokinetics 56*, 759–779.

Rasool, M. F., Khalil, F., & Laer, S. (2015). A physiologically based pharmacokinetic drug-disease model to predict carvedilol exposure in adult and paediatric heart failure patients by incorporating pathophysiological changes in hepatic and renal blood flows. *Clinical Pharmacokinetics 54*, 943–962.

Rasool, M. F., Khalil, F., & Laer, S. (2016). Predicting Stereoselective disposition of carvedilol in adult and pediatric chronic heart failure patients by incorporating pathophysiological changes in organ blood flows-a physiologically based pharmacokinetic approach. *Drug Metabolism and Disposition 44*, 1103–1115.

Rhee, S. J., Chung, H., Yi, S., Yu, K. S., & Chung, J. Y. (2017). Physiologically based pharmacokinetic modelling and prediction of metformin pharmacokinetics in renal/hepatic-impaired young adults and elderly populations. *European Journal of Drug Metabolism and Pharmacokinetics 42*, 973–980.

Rhodin, M. M., Anderson, B. J., Peters, A. M., Coulthard, M. G., Wilkins, B., Cole, M., ... Holford, N. H. (2009). Human renal function maturation: A quantitative description using weight and postmenstrual age. *Pediatric Nephrology 24*, 67–76.

Rodgers, T., Leahy, D., & Rowland, M. (2005). Physiologically based pharmacokinetic modeling 1: Predicting the tissue distribution of moderate-to-strong bases. *Journal of Pharmaceutical Sciences 94*, 1259–1276.

Rodgers, T., & Rowland, M. (2006). Physiologically based pharmacokinetic modelling 2: Predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. *Journal of Pharmaceutical Sciences 95*, 1238–1257.

Rostami-Hodjegan, A. (2012). Physiologically based pharmacokinetics joined with in vitro-in vivo extrapolation of ADME: A marriage under the arch of systems pharmacology. *Clinical Pharmacology and Therapeutics 92*, 50–61.

Roth-Cline, M., & Nelson, R. M. (2015). Microdosing studies in children: A US regulatory perspective. *Clinical Pharmacology & Therapeutics 98*, 232–233.

Sachs, A. N., Avant, D., Lee, C. S., Rodriguez, W., & Murphy, M. D. (2012). Pediatric information in drug product labeling. *JAMA 307*, 1914–1915.

Sadler, N. C., Nandhikonda, P., Webb-Robertson, B. J., Ansong, C., Anderson, L. N., Smith, J. N., ... Wright, A. T. (2016). Hepatic cytochrome P450 activity, abundance, and expression throughout human development. *Drug Metabolism and Disposition 44*, 984–991.

Sager, J. E., Yu, J., Ragueneau-Majlessi, I., & Isoherranen, N. (2015). Physiologically based pharmacokinetic (PBPK) modeling and simulation approaches: A systematic review of published models, applications, and model verification. *Drug Metabolism and Disposition 43*, 1823–1837.

Salar-Behzadi, S., Wu, S., Mercuri, A., Meindl, C., Stranzinger, S., & Frohlich, E. (2017). Effect of the pulmonary deposition and in vitro permeability on the prediction of plasma levels of inhaled budesonide formulation. *International Journal of Pharmaceutics 532*, 337–344.

Salem, F., Johnson, T. N., Abduljalil, K., Tucker, G. T., & Rostami-Hodjegan, A. (2014). A re-evaluation and validation of ontogeny functions for cytochrome P450 1A2 and 3A4 based on in vivo data. *Clinical Pharmacokinetics 53*, 625–636.

Salem, F., Johnson, T. N., Barter, Z. E., Leeder, J. S., & Rostami-Hodjegan, A. (2013). Age related changes in fractional elimination pathways for drugs: Assessing the impact of variable ontogeny on metabolic drug-drug interactions. *Journal of Clinical Pharmacology 53*, 857–865.

Salerno, S. N., Burckart, G. J., Huang, S. M., & Gonzalez, D. (2019). Pediatric drug-drug interaction studies: Barriers and opportunities. *Clinical Pharmacology and Therapeutics 105*, 1067–1070.

Samant, T. S., Lukacova, V., & Schmidt, S. (2017). Development and qualification of physiologically based pharmacokinetic models for drugs with atypical distribution behavior: A Desipramine case study. *CPT: Pharmacometrics & Systems Pharmacology 6*, 315–321.

Schalkwijk, S., Buaben, A. O., Freriksen, J. J. M., Colbers, A. P., Burger, D. M., Greupink, R., & Russel, F. G. M. (2018). Prediction of fetal Darunavir exposure by integrating human ex-vivo placental transfer and physiologically based pharmacokinetic modeling. *Clinical Pharmacokinetics 57*, 705–716.

Schmidt, A. R., Buehler, P., Seglias, L., Stark, T., Brotschi, B., Renner, T., ... Schmitz, A. (2015). Gastric pH and residual volume after 1 and 2 h fasting time for clear fluids in childrendagger. *British Journal of Anaesthesia 114*, 477–482.

Schoning, M., & Hartig, B. (1996). Age dependence of total cerebral blood flow volume from childhood to adulthood. *Journal of Cerebral Blood Flow and Metabolism 16*, 827–833.
Schwartz, G. J., Haycock, G. B., Edelmann, C. M., Jr., & Spitzer, A. (1976). A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics 58*, 259–263.
Scotcher, D., Jones, C., Posada, M., Rostami-Hodjegan, A., & Galetin, A. (2016). Key to opening kidney for in vitro-in vivo extrapolation entrance in health and disease: Part I: In vitro systems and physiological data. *The AAPS Journal 18*, 1067–1081.
Sethi, P. K., White, C. A., Cummings, B. S., Hines, R. N., Muralidhara, S., & Bruckner, J. V. (2016). Ontogeny of plasma proteins, albumin and binding of diazepam, cyclosporine, and deltamethrin. *Pediatric Research 79*, 409–415.
Shebley, M., Sandhu, P., Emami Riedmaier, A., Jamei, M., Narayanan, R., Patel, A., ... Rowland, M. (2018). Physiologically based pharmacokinetic model qualification and reporting procedures for regulatory submissions: A consortium perspective. *Clinical Pharmacology and Therapeutics 104*, 88–110.
Smith, J. N., Hinderliter, P. M., Timchalk, C., Bartels, M. J., & Poet, T. S. (2014). A human lifestage physiologically based pharmacokinetic and pharmacodynamic model for chlorpyrifos: Development and validation. *Regulatory Toxicology and Pharmacology 69*, 580–597.
Sokol, P. P. (1991). Mechanism of vancomycin transport in the kidney: Studies in rabbit renal brush border and basolateral membrane vesicles. *The Journal of Pharmacology and Experimental Therapeutics 259*, 1283–1287.
Song, G., Sun, X., Hines, R. N., McCarver, D. G., Lake, B. G., Osimitz, T. G., ... Yoon, M. (2017). Determination of human hepatic CYP2C8 and CYP1A2 age-dependent expression to support human health risk assessment for early ages. *Drug Metabolism and Disposition 45*, 468–475.
Struijs, M. C., Diamond, I. R., de Silva, N., & Wales, P. W. (2009). Establishing norms for intestinal length in children. *Journal of Pediatric Surgery 44*, 933–938.
Templeton, I. E., Jones, N. S., & Musib, L. (2018). Pediatric dose selection and utility of PBPK in determining dose. *The AAPS Journal 20*, 31.
Thompson, E. J., Wu, H., Maharaj, A., Edginton, A. N., Balevic, S. J., Cobbaert, M., ... Cohen-Wolkowiez, M. (2019). Physiologically based pharmacokinetic modeling for trimethoprim and sulfamethoxazole in children. *Clinical Pharmacokinetics 58*, 887–898.
T'Jollyn, H., Vermeulen, A., & Van Bocxlaer, J. (2018). PBPK and its virtual populations: The impact of physiology on pediatric pharmacokinetic predictions of tramadol. *The AAPS Journal 21*, 8.
Tohon, H., Valcke, M., & Haddad, S. (2019). An assessment of the impact of multi-route co-exposures on human variability in toxicokinetics: A case study with binary and quaternary mixtures of volatile drinking water contaminants. *Journal of Applied Toxicology 39*, 974–991.
Tucker, G. T. (2017). Personalized drug dosage - closing the loop. *Pharmaceutical Research 34*, 1539–1543.
Upreti, V. V., & Wahlstrom, J. L. (2016). Meta-analysis of hepatic cytochrome P450 ontogeny to underwrite the prediction of pediatric pharmacokinetics using physiologically based pharmacokinetic modeling. *Journal of Clinical Pharmacology 56*, 266–283.
Upton, R. N., Foster, D. J., & Abuhelwa, A. Y. (2016). An introduction to physiologically-based pharmacokinetic models. *Paediatric Anaesthesia 26*, 1036–1046.
Valcke, M., & Krishnan, K. (2010). An assessment of the interindividual variability of internal dosimetry during multi-route exposure to drinking water contaminants. *International Journal of Environmental Research and Public Health 7*, 4002–4022.
Verscheijden, L. F. M., Koenderink, J. B., de Wildt, S. N., & Russel, F. G. M. (2019). Development of a physiologically-based pharmacokinetic pediatric brain model for prediction of cerebrospinal fluid drug concentrations and the influence of meningitis. *PLoS Computational Biology 15*, e1007117.
Villiger, A., Stillhart, C., Parrott, N., & Kuentz, M. (2016). Using physiologically based pharmacokinetic (PBPK) modelling to gain insights into the effect of physiological factors on Oral absorption in Paediatric populations. *The AAPS Journal 18*, 933–947.
Wagner, C., Zhao, P., Pan, Y., Hsu, V., Grillo, J., Huang, S. M., & Sinha, V. (2015). Application of physiologically based pharmacokinetic (PBPK) modeling to support dose selection: Report of an FDA public workshop on PBPK. *CPT: Pharmacometrics & Systems Pharmacology 4*, 226–230.
Walsh, C., Bonner, J. J., Johnson, T. N., Neuhoff, S., Ghazaly, E. A., Gribben, J. G., ... Veal, G. J. (2016). Development of a physiologically based pharmacokinetic model of actinomycin D in children with cancer. *British Journal of Clinical Pharmacology 81*, 989–998.
Watt, K. M., Cohen-Wolkowiez, M., Barrett, J. S., Sevestre, M., Zhao, P., Brouwer, K. L. R., & Edginton, A. N. (2018). Physiologically based pharmacokinetic approach to determine dosing on extracorporeal life support: Fluconazole in children on ECMO. *CPT: Pharmacometrics & Systems Pharmacology 7*, 629–637.
Weaver, L. T., Austin, S., & Cole, T. J. (1991). Small intestinal length: A factor essential for gut adaptation. *Gut 32*, 1321–1323.
Whetstine, L. J., Hulsey, T. C., Annibale, D. J., & Pittard, W. B. (1995). Supplemental oxygen and gastric pH in unfed preterm infants. *Southern Medical Journal 88*, 458–461.
Williams, L. R., & Leggett, R. W. (1989). Reference values for resting blood flow to organs of man. *Clinical Physics and Physiological Measurement 10*, 187–217.
Willmann, S., Becker, C., Burghaus, R., Coboeken, K., Edginton, A., Lippert, J., ... Muck, W. (2014). Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. *Clinical Pharmacokinetics 53*, 89–102.
Willmann, S., Thelen, K., Kubitza, D., Lensing, A. W. A., Frede, M., Coboeken, K., ... Lippert, J. (2018). Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: An EINSTEIN-Jr phase I study. *Thrombosis Journal 16*, 32.
Yamamoto, Y., Valitalo, P. A., van den Berg, D. J., Hartman, R., van den Brink, W., Wong, Y. C., ... de Lange, E. C. (2017). A generic multi-compartmental CNS distribution model structure for 9 drugs allows prediction of human brain target site concentrations. *Pharmaceutical Research 34*, 333–351.
Yamamoto, Y., Valitalo, P. A., Wong, Y. C., Huntjens, D. R., Proost, J. H., Vermeulen, A., ... de Lange, E. C. M. (2018). Prediction of human CNS pharmacokinetics using a physiologically-based pharmacokinetic modeling approach. *European Journal of Pharmaceutical Sciences 112*, 168–179.
Yee, K. L., Li, M., Cabalu, T., Sahasrabudhe, V., Lin, J., Zhao, P., & Jadhav, P. (2017). Evaluation of model-based prediction of pharmacokinetics in the renal impairment population. *Journal of Clinical Pharmacology 58*, 364–376.
Yellepeddi, V., Rower, J., Liu, X., Kumar, S., Rashid, J., & Sherwin, C. M. T. (2018). State-of-the-art review on physiologically based pharmacokinetic modeling in pediatric drug development. *Clinical Pharmacokinetics 58*, 1–13.
Yun, Y. E., & Edginton, A. N. (2019). Model qualification of the PK-Sim(R) pediatric module for pediatric exposure assessment of CYP450 metabolized compounds. *Journal of Toxicology and Environmental Health. Part A 82*, 789–814.
Zakaria, Z., & Badhan, R. K. S. (2018). The impact of CYP2B6 polymorphisms on the interactions of efavirenz with lumefantrine: Implications for paediatric antimalarial therapy. *European Journal of Pharmaceutical Sciences 119*, 90–101.
Zane, N. R., & Thakker, D. R. (2014). A physiologically based pharmacokinetic model for voriconazole disposition predicts intestinal first-pass metabolism in children. *Clinical Pharmacokinetics 53*, 1171–1182.
Zaya, M. J., Hines, R. N., & Stevens, J. C. (2006). Epirubicin glucuronidation and UGT2B7 developmental expression. *Drug Metabolism and Disposition 34*, 2097–2101.
Zhang, Z., Imperial, M. Z., Patilea-Vrana, G. I., Wedagedera, J., Gaohua, L., & Unadkat, J. D. (2017). Development of a novel maternal-fetal physiologically based pharmacokinetic model I: Insights into factors that determine fetal drug exposure through simulations and sensitivity analyses. *Drug Metabolism and Disposition 45*, 920–938.
Zhang, Z., & Unadkat, J. D. (2017). Development of a novel maternal-fetal physiologically based pharmacokinetic model II: Verification of the model for passive placental permeability drugs. *Drug Metabolism and Disposition 45*, 939–946.
Zhou, L., Tong, X., Sharma, P., Xu, H., Al-Huniti, N., & Zhou, D. (2019). Physiologically based pharmacokinetic modelling to predict exposure differences in healthy volunteers and subjects with renal impairment: Ceftazidime case study. *Basic & Clinical Pharmacology & Toxicology 125*, 100–107.
Zhou, W., Johnson, T. N., Bui, K. H., Cheung, S. Y. A., Li, J., Xu, H., ... Zhou, D. (2018). Predictive performance of physiologically based pharmacokinetic (PBPK) modeling of drugs extensively metabolized by major cytochrome P450s in children. *Clinical Pharmacology and Therapeutics 104*, 188–200.
Zhou, W., Johnson, T. N., Xu, H., Cheung, S., Bui, K. H., Li, J., ... Zhou, D. (2016). Predictive performance of physiologically based pharmacokinetic and population pharmacokinetic modeling of Renally cleared drugs in children. *CPT: Pharmacometrics & Systems Pharmacology 5*, 475–483.