Factors affecting successful extrapolation of ibuprofen exposure from adults to paediatric populations after oral administration of a paediatric aqueous suspension

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Ibuprofen exposure: from adults to paediatrics

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ABSTRACT

The importance of physiologically based pharmacokinetic (PBPK) model refinement for adults with data acquired in adults using a paediatric formulation under age-relevant dosing conditions in order to extrapolate drug exposure to infants was recently demonstrated for paracetamol. In the present investigation the aim was to expand the use of PBPK modeling informed by bioavailability data collected in healthy adults under different dosing conditions for a low solubility weak acid, ibuprofen, to simulate exposure across paediatric populations, i.e., infants, pre-school children, and schoolchildren. After developing and evaluating an adult disposition and oral absorption model for the aqueous suspension of ibuprofen, ibuprofen performance was extrapolated to paediatrics simulating exposure as a function of different prandial and dosing conditions: fasted conditions, reference-meal-fed conditions (solid-liquid meal), and infant-formula-fed conditions (homogeneous liquid). Successful predictions were achieved when employing the refined model for fasted or by applying appropriate fed conditions for different age groups, i.e., infant formula for infants and reference meal for children. The present study suggested that ibuprofen performance was primarily guided by gastric emptying events and showed sensitivity towards formulation characteristics and pH changes in the small intestine. Better understanding of luminal conditions' changes in paediatrics and age-dependent ibuprofen post-absorptive processes could improve modeling confidence for ibuprofen, as well as other drugs with similar properties.

Introduction

Across paediatric age groups the oral route of drug administration is preferred, therefore, the development of oral drug formulations that are adapted and acceptable for the needs of the heterogenous paediatric age ranges is of paramount importance. In line with concerns regarding the choice and development of suitable paediatric formulations, testing of paediatric drug formulations still poses a challenge during development of new medicines, primarily based on the ethical limitations to performing clinical investigations in paediatrics. Therefore, tools and methodologies capable of predicting formulations performance in the target paediatric populations can help to reduce clinical burden and thus lead to shorter development timelines and facilitate earlier market access.

To date, bioavailability and food effect studies for orally administered paediatric products are performed in adult volunteers according to regulatory guidelines with application of the suggested fasted and fed conditions, i.e. fasted conditions where the formulation is administered with a glass of water and after the consumption of a high-calorie, high-fat solid-liquid meal with 800 - 1000 kcal and 50 - 60 % fats (herein "the reference meal") (1,2). Based on the variety of foods that different paediatric subpopulations might receive, a recent draft guideline suggests that sponsors can use foods and quantities of food that are commonly consumed with drugs in a particular paediatric population, e.g., infant formula for infants (1,3,4) and results from the food effect investigations in adults can be extrapolated to the paediatric population for which the medication is intended (1). It should be noted that the draft guidance suggests a separate food effect study would not be necessary if the same to-be-marketed paediatric formulation has been approved for use in adults (1). Although paediatric subpopulations, such as young children (2-6 years of age) and schoolchildren (6-12 years of age) (3,5), might receive meals with similar texture as the reference meal, meal caloric content and potions change in an age-dependent manner. Considering the high caloric content of the reference meal, it might not be representative of meal caloric contents for younger populations (3,6).

Understanding oral absorption processes in adults has been greatly improved by the development and application of new *in vitro* and *in silico* tools that enhance the mechanistic understanding of oral drug performance, for the latter in particular physiologically based pharmacokinetic (PBPK) modeling (7,8). The PBPK modeling tool enables the simulation of the interplay between absorption, distribution, metabolism, and elimination (ADME) processes of a given compound in a defined virtual subject based on the compound's physicochemical properties, system parameters representing the human body, and a specific trial design. As PBPK models enable the creation of virtual subjects with different

demographic characteristics and respective physiologies and the ethical challenges accompanying clinical studies in paediatrics, utilization of PBPK modeling in paediatric medicines development has proven to be a valuable tool for modeling age-dependent ADME processes and evaluate possible implications regarding drug exposure (9–11). In the literature, several studies have investigated age-dependent oral drug absorption by employing a mechanistic model of the gastrointestinal tract (GI), such as the Advanced Compartmental Absorption and Transit (ACAT™) model (9,12–16); however only few have attempted to simulate drug performance under different prandial and dosing conditions in paediatrics (17–19). Although different dosing conditions were addressed in these studies, the fed state conditions applied were mostly based on software default parameters (literature-based) for the paediatric subpopulation of interest.

Despite the usefulness and the potential of this *in silico* tool, the modeling process usually requires additional information from *in vitro* and/or *in vivo* studies to refine and/or confirm the suitability of the modeling parameters, commonly referred to as the "middle-out" approach (10,20). The importance of PBPK model refinement for adults with data acquired in adults using the paediatric formulation of interest under age-relevant dosing conditions in order to extrapolate drug exposure to infants was recently demonstrated for paracetamol (***Figure 1***) (19). Three different dosing conditions were modeled and evaluated, i.e., fasted and fed conditions according to regulatory guidelines (2,21), and drug administration during infant formula consumption to mimic drug dosing in infants (4,19).

As natural step towards better understanding and extension of the approach recently presented by Statelova and colleagues (19), the weak acid ibuprofen (pKa ≈ 4.5) was used as a model drug to investigate influences of different dosing and prandial conditions for the extrapolation to paediatric mixed populations including infants (1 month - 2 years) and young children (2 – 6 years) and schoolchildren (6 – 12 years) or populations including children. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that is classified as a Class II drug according to the Biopharmaceutics classification system (BCS) based on its low solubility in acidic media and high intestinal permeability (22). For this purpose, a PBPK model was developed using the GastroPlus™ platform (Simulations Plus, Lancaster, CA), whereby model development was guided by ibuprofen suspension performance in adults under the three different dosing conditions to inform the paediatric oral absorption model, as shown in ***Figure 1*** (4,19). Hence, the purpose of the present study was to extend the application of the previously proposed methodology for food effect extrapolation to a broader paediatric age-range and

85 evaluate the usefulness of food effect data collected in adults to predict drug performance in mixed
86 paediatric populations.

Methods

Clinical data collection

A literature search was performed for pharmacokinetic studies reporting ibuprofen administration following intravenous (i.v.) administration or *per os* administration of a suspension in adults and paediatric populations. Studies not reporting the measured plasma levels, formulations including excipients that alter drug formulation performance or use of ibuprofen salt forms were excluded. A total of 19 datasets were retrieved, with nine performed in adults and ten in paediatric populations. Intravenous ibuprofen dosing in adults was reported in six datasets (23–26), with one of them investigating a high ibuprofen dose, i.e., 800 mg (23). The study by Statelova *et al.* (4) was used to guide modeling of the paediatric ibuprofen suspension (800 mg ibuprofen) administered orally in adults under different dosing conditions, i.e. fasted conditions and fed conditions induced with the reference meal (solid-liquid meal) according to current regulatory guidelines (2,21), and infant-formula-fed conditions mimicking dosing in infants (homogeneous liquid) (4). In paediatrics, two studies (4 datasets) investigated ibuprofen performance following i.v. administration at a dose of 10 mg/kg (27,28), while three datasets were available from investigations of a liquid formulation administered to a paediatric mixed groups, including infants and children at doses 5 mg/kg, 6 mg/kg, and 10 mg/kg (29,30), two datasets were acquired following suspension administration to children at doses 5 mg/kg or 10 mg/kg (31), and one study investigated suspension administration in an infant study group (7.6 mg/kg) (32). As the dataset in the infant population originated from ibuprofen suspension administration in the recovery room under influence of additional drugs used for general anaesthesia (e.g., halothane, vecuronium, phenoperidine, nitrous oxide) altering GI transit times, this dataset was excluded from further investigations. Ibuprofen is low extraction drug that is highly bound to plasma proteins (≈ 99 %), primarily, serum albumin (33–35). Based on the concentration-dependent saturable nature of the plasma binding, non-linear drug exposure has been reported in adults and children (29,33,36). Furthermore, changes in the fraction of unbound drug could result in differences in the apparent volume of distribution and impact drug clearance. Based on this non-linearity and the dose administered (800 mg) in the adult study used to develop the adult disposition model and to inform the oral model (4), only the datasets obtained using high ibuprofen doses (10 mg/kg) in paediatrics were considered within the present PBPK modeling investigation. The datasets acquired at a dose of 10 mg/kg were reported in Brown *et al.* (3 months – 12 years) and Walson *et al.* (2 years – 11 years) (29,31). Additionally, dosing conditions impact was expected to be greater at the higher dose (800 mg in adults, equivalent to 10 mg/kg in paediatrics). Observed ibuprofen mean plasma levels as a function of time and the respective standard deviation (SD) or standard error of the mean (SEM) values were digitized from the publications using the WebPlotDdigitizer software V4.1 (Ankit Rohatgi,

2017). Along with the plasma concentration-time profiles, information regarding dosing conditions and reported study demographics were documented, i.e. number of study participants, age, gender, race, body weight, body height. Ibuprofen is a drug with almost complete absolute bioavailability in adults (23,33) and in neonates (37,38).

Modeling workflow

Modeling of ibuprofen in adults and paediatrics was performed using the GastroPlus™ PBPK modeling platform (V. 9.7, Simulations Plus, Lancaster, CA, USA). The applied modeling workflow is presented in ***Figure 1*** (19). After development and confirmation of the disposition model in adults following i.v. administration, oral ibuprofen absorption in adults was built for a paediatric suspension under different prandial and dosing conditions using the ACAT™ model within the GastroPlus™ platform. As a next step, the model was scaled to paediatrics and its suitability to describe disposition and clearance in paediatrics was confirmed using i.v. data in paediatrics. The three different dosing conditions were then scaled to children and infants and compared to the data observed in the target population.

Adult PBPK model

Physicochemical and bio-dependent ibuprofen properties used to inform the PBPK model are reported in ***Table I***. Within the present model, ibuprofen distribution was predicted using the single Lukacova, Rodgers and Rowland model (45,46) and clearance was incorporated into the model as whole organ intrinsic clearance ($CL_{int,u}$). The clearance was estimated from the PK profile reported for a rapid 5-7 minute infusion of 800 mg of ibuprofen to healthy adults (23) utilizing the PKPlus™ tool within the GastroPlus™ platform. Ibuprofen clearance occurs primarily in the liver with less than 0.5 % of the total ibuprofen dose being recovered unchanged in urine, therefore the whole clearance was attributed to the liver. The $CL_{int,u}$ incorporated into the model was calculated according to the well-stirred model and took into consideration hepatic blood flow, fraction of drug unbound in plasma, clearance observed *in vivo* and the blood to plasma concentration ratio of the drug (***Table I***) (50–52). Virtual physiologies were generated using the Population Estimates for Age-Related (PEAR™) Physiology module within GastroPlus™ (18,52,53). Single simulations were performed using a physiology matching the mean reported demographic parameters for each study, i.e., age, gender, race, body weight, and body height. A default American healthy male physiology (70 kg, 30 years old) was assumed when the demographics for the simulated study were not reported.

Oral absorption modeling in adults

Oral absorption was mechanistically simulated using the ACAT™ model, depicting dissolved, precipitated, and solid drug transfer and absorption through nine gastrointestinal compartments, represented by the stomach, duodenum, two jejunum, three ileum, and the colon segments (7,8). Default adult physiology-representative system parameters were employed for each compartment, i.e. small-intestinal (SI) length, radius, specific absorption factor (ASF), intraluminal fluid volumes and composition, as well as transit times.

Thermodynamic *in vitro* solubility data were incorporated into the model to estimate solubility and bile-salt solubilization ratios for ibuprofen. Firstly, the solubility in standard buffers with different pH values (pH range 1.0-7.4) measured at 37° C (22) and the reference solubility considered as the lowest measured ibuprofen solubility at pH 1.0 (ibuprofen is expected to be present only in its neutral form, i.e., intrinsic solubility) were used to fit the pKa of ibuprofen (52). Next, the bile salt solubilization ratio representing the drug's affinity to bile salt micelles was estimated (54). Briefly, the thermodynamic solubility of ibuprofen was measured in different media containing defined bile salt levels, i.e., Level III fasted state simulated gastric fluid (FaSSGF), Level II fasted state simulated intestinal fluid (FaSSIF), and fed state simulated intestinal fluid (FeSSIF-V2) (55). Biorelevant solubility was estimated according to the shake-flask method, ***Table I*** (56). Furthermore, human intestinal permeability ($P_{eff,man}$) was estimated according to Eq. 1 from ibuprofen apparent permeability measured in Caco-2 cells ($P_{app,Caco2}$) employing cimetidine as calibrator (41,42).

$$logP_{eff,man} = 0.6795 \times logPapp, Caco2 - 0.3036 \quad \text{Eq. 1}$$

The plasma concentration-time data from the study by Statelova *et al.* were used for confirmation and/or adjustment of the modeling parameters for the paediatric suspension performance under fasted, reference meal-fed, and infant formula-fed conditions (4). Single simulations were performed for a physiology matching the mean study demographics, i.e. 28-year-old male with a body weight of 78 kg (population representative). The dosing conditions in the PBPK model matched the conditions applied in the study by Statelova *et al.* (4), whereby a 800 mg dose of ibuprofen was administered as a suspension with a total fluid volume of 250 mL under fasted and reference-meal-fed conditions according to regulatory guidelines (2,21) or without additional water under conditions mimicking drug dosing in infants (4). Under fed conditions, the ibuprofen suspension was administered 30 minutes after the start of the high-fat, high-calorie reference meal consumption (solid-liquid meal, 60 % fat, 990 kcal) (2,21), while under infant-formula-fed-conditions, ibuprofen was administered during the consumption of 800 mL of infant formula (homogenous liquid meal, 43 % fat, 520 kcal) (4).

For fasted state simulations, default settings were used with a gastric transit time (GTT) of 0.1 h and a first order GE process, with GTT representing the mean gastric transit time (MGTT), i.e., the GE half-time ($t_{1/2}$) divided by the ln2. Model parameter adjustments were needed to match drug performance observed *in vivo* (4). GTT values ranging between 0.1 h and 1.0 h were employed for model refinement to achieve reasonable description of the absorption delay ($t_{1/2}$ 4 to 42 min, respectively). For the reference-meal-fed and infant-formula-fed conditions, liver blood flow was increased by 30 % to simulate the increased blood flow in the GI tract (8). For conditions investigating suspension administration after consumption of the reference meal, simulations were performed using the human fed state physiology following a "user-defined meal" matching the meal used in the study by Statelova *et al.*, i.e. 990 kcal and 60 % fat (4). The GastroPlus™ platform adjusts the GTT according to the caloric content of the meal entered, while bile salt concentration was increased in the simulation related to the fat content in the user-defined meal. First order GE kinetics were employed for the solid-liquid reference meal based on *in vivo* observations in adults following the administration of a similar meal (57). Adjustment of the GTT value was undertaken to match the ibuprofen performance observed *in vivo*. Similarly, for infant-formula-fed conditions, the infant formula was defined with 520 kcal and 43 % fats within the human fed state physiology with a "user-defined meal". A zero order GE process was assumed for the infant formula emptying, as known for GE of calories-containing liquids (58). The proposed GTT was adjusted to capture the absorption delay observed under the applied conditions in adults (4). For a zero order GE process the GTT value represents the total gastric transit time. A similar approach has been previously applied for scaling of paracetamol stomach transit from adults to infants (19).

Paediatric PBPK model

Tissues and organ sizes were scaled to the relevant paediatric age with the PEAR™ physiology module based on the age, body weight, and height of the population representative (52,53); where information used for physiology generation is based on literature sources (52,59–61). Population representatives for each paediatric age group, as reported in the study by Khalil *et al.* (27), were generated, i.e., 11-month-old infant (10.3 kg), a 3-year-old child (16.4 kg), and a 10-year-old child (39.3 kg) (27). For model scaling to paediatrics, Vss was empirically increased for paediatric subjects below the age of 2.5 years (0.20 L/kg) and children (0.15 L/kg) to match the greater volume of distribution reported in infants and children (27,29,47). Based on adult clinical data, the Cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzyme systems are mainly responsible for ibuprofen metabolism (33). Clearance scaling to paediatrics was performed using a previously described routine using allometric scaling taking into consideration age-dependent enzyme maturation (53,62,63) (Detailed description

provided in the Supplementary Information). Paediatric intrinsic clearance values to be incorporated into the paediatric model were calculated as for adults using the scaled paediatric clearance and age-dependent parameters (liver blood flow, fraction unbound in plasma, and blood to plasma ratio) that were adjusted as a function of age according to the physiological parameters for the generated paediatric physiology (50,64). Finally, i.v. administration of 10 mg/kg ibuprofen was simulated for population representatives of the paediatric age groups according to Khalil *et al.* 2017 and compared to individual plasma concentration-time profiles (27,65) and plasma data reported for mixed-age paediatric groups where only one sample was collected per individual (28).

Oral absorption modeling in paediatrics

Modeling in paediatrics was performed in children and infant population representatives from clinical studies in paediatrics following oral administration of ibuprofen liquid formulations administered at an ibuprofen dose of 10 mg/kg. As the clinical studies in paediatrics reported mixed paediatric group or a children group covering a wide range of ages, a bracketing approach was applied (29,31). For the clinical dataset from children population (n = 25), only the age range of the subjects included was reported (2 - 11 years); plasma samples were not available for all time points from each subject, therefore, mean values for each time point were calculated for different sample numbers (11 to 21 samples per time point) (31). Within this study, febrile subjects received a 20 mg/mL orange-flavored paediatric suspension (The Boots Company) as an antipyretic treatment and up to 180 mL of water were allowed to facilitate drug administration (31). For this dataset (ibuprofen performance in children), population representatives included a 2-year-old, a 6 year-old, and an 11-year-old (31). The clinical dataset from a mixed infant/children population included 50 febrile subjects (3 months - 12 years), who received the liquid ibuprofen formulation was given followed by an equal volume of water (29). No food or liquids were allowed one hour after dosing (29). A pre-dose and 2 - 6 post-dose samples were collected per subject (29). Based on the reported age range including infants and children, simulations were performed for paediatric representatives: 12-months-old infant, 6-year-old child, and a 12-year-old child (29).

The three dosing conditions investigated in the study by Statelova *et al*. (4) and simulated in adults (see previous section) were extrapolated to the paediatric populations. Both software-default values and adjusted values for the three dosing conditions were applied. Briefly, default and adjusted fasted and reference meal-fed conditions were simulated for all paediatric ages investigated (29,31), while default and adjusted infant-formula-fed conditions were applied only for population representatives

up to 2.5 years of age. Comparisons of predictions with observed data were performed using the mean data for paediatric mixed and child populations (29,31).

The GI physiology scaling performed when paediatric physiologies are created using the PEAR™ module within GastroPlus™ accounts for changes in volume of GI organs, GI organ blood flows, intestinal length, radius, and surface area, small intestinal transit time (SITT), fluid secretion volume. Values describing the fasted GTT, gastric pH, intestinal pH, bile salt levels, solubility, and permeability at the gut wall are considered unchanged with age in the modeling platform. For the simulation of drug dosing under postprandial conditions, meal caloric content of 170 kcal was assumed for the 12-month-old infant, 200 kcal for a 2-year-old population representative, 260 kcal were employed for the 6-year-old, and a meal containing 340 kcal was used for 12-year-old child. The meal values were calculated based on the average daily energy requirements for children assuming five meals consumed daily (3,6,66). No maturation changes in GE motility were assumed under fasted and fed conditions as meal, but not age, were found to be significant factors defining GE in a meta-analysis investigating of GE times across paediatric age ranges (67).

For the fasted conditions two scenarios were explored employing default GTT values of 0.1 h and GTT values from the refined adult model for suspension performance in the study by Statelova *et al*. (4). Under reference-meal-fed conditions, the caloric content of the "user-defined meal" was adjusted to the relevant age, the fat content was matched to the reference meal, and GE followed a 1st order process, as in adults. Adjusted GTT values for paediatrics according to the study by Statelova *et al.* (4) were obtained by normalizing the meal caloric content assumed for the paediatric age representative, the caloric meal content administered in adults, and the GTT value used in the adult refined model Eq. 2 (19).

$$Ibuprofen\ GTT_{paediatrics,meal}\ (h) = \frac{Meal\ caloric\ content\ _{paediatrics}\ (kcal) \times Iburpofen\ GTT_{adult,meal}\ (h)}{Meal\ caloric\ content\ _{adults}\ (kcal)}$$

Eq. 2

To simulate infant-formula-fed conditions default software settings and adjusted GTT values according to the study by Statelova *et al*. (4) were employed with zero order GE emptying process, as in adults. The default software settings were obtained using the user-defined meal option and assuming a 170-kcal meal for a 12-month-old infant or 200 kcal for 2-year-old child with 43 % fat content. The adjusted GTT values for the infant and the 2-year-old child were obtained according to Eq. 2.

Model evaluation

Pharmacokinetic parameters describing ibuprofen exposure were compared using the Fold Difference (FD) ratio of the predicted vs. observed parameters, i.e., area under the plasma concentration-time curve (AUC), maximum plasma concentration (Cmax), and time to reach Cmax (Tmax). The predicted plasma concentration-time profiles were compared to observed plasma data using the Average Fold Error (*AFE*) and the Absolute Average Fold Error (*AAFE*) according to Eq. 3 and Eq. 4, respectively.

$$AFE = 10^{\left(\frac{1}{n}\sum \log\left(\frac{PREDi}{OBSi}\right)\right)} \quad \text{Eq. 3}$$

$$AAFE = 10^{\left(\frac{1}{n}\sum \left|\log\left(\frac{PREDi}{OBSi}\right)\right|\right)} \quad \text{Eq. 4}$$

where n denoted the number of observed sampling points, PREDi and OBSi denoted the predicted and observed plasma concentration, respectively, at the sampling time point i.

For the paediatric studies in a mixed population or children populations following oral dosing of ibuprofen, for which a bracketing approach was applied, PK and model evaluation parameters were calculated for the mean predicted profiles, i.e. *FDpred/obs*, *AFE*, and *AAFE*. *AFE* values indicated the trend of the simulated data to underpredict (*AFE* < 1) or overpredict (*AFE* > 1) the observed plasma concentrations, while an *AAFE* value close to unity signified the precision of the simulations. Predictions resulting in $FD_{pred/obs}$ and *AAFE* values less than two were considered adequate (68), while stricter evaluation criteria was set for $FD_{pred/obs}$; between 0.66-1.5 and for *AAFE* below 1.5 indicated a successful prediction (69).

Parameter sensitivity analysis

A parameter sensitivity analyses (PSA) were performed according to a one-factor-at-a-time methodology for population representatives including adults (mean demographics of study by Statelova et al. (4)), a 12-months-old infant, 6- and 12-year-old children (***Table SII***, Supplementary Information). For adults, PSA investigations aimed to understand the impact of parameters bringing uncertainty into the model and the impact under the three different dosing conditions, i.e., drug particle size, effective permeability, and GTT values. The three dosing conditions were investigated in infants, however, conditions mimicking infant drug dosing were not investigated in the PSA for children. The following parameters were considered for the PSA: drug-related properties such as solubility, drug particle size, and effective permeability, and physiology parameters, such as gastric and intestinal pH, intraluminal fluid volumes, GTT, SITT, intestinal radius, length, and surface area. The influence of meal fat content changes on ibuprofen performance was investigated for the fed conditions following the reference meal and infant formula (adjusted model). Lastly, applying the

software predicted or the refined model settings based on adult observations, the impact of the caloric content for each meal was evaluated over a feasible range, i.e. 70-200 kcal for infants, and 150-300 kcal in 6-year-old children, and 250-400 kcal for 12-year-old children (***Table SII***, Supplementary Information).

Results

Adult model performance

The PBPK model developed for adults was able to adequately describe the observed plasma concentrations following a 800 mg ibuprofen dose administered as an i.v. rapid infusion over 5-7 min to a healthy population representative matching the mean study demographics (23), i.e., $AAFE$ 1.136 (***Figure 2***A). Clearance and Vss values reported from i.v. administration of ibuprofen in adults were in agreement with the parameters employed for model development in the present study (**Table SIII**, Supplementary Information). The additional 5 study datasets used as external verification of the developed model were adequately described by the developed model as shown in ***Figure S1*** and ***Table SIV***, Supplementary Information. As demonstrated in ***Figure 2***B and C, representing selected external verification datasets, the i.v. administration of 200 mg and 400 mg in healthy adults was adequately described by the developed model with $AAFE$ 1.170 and $AAFE$ 1.205, respectively. In all cases the AFE and $AAFE$ values remained within the ranges 0.788-1.109 and 1.136-1.268, respectively, indicating a good agreement between the simulated and observed profiles (***Table SIV***, Supplementary Information). Nevertheless, prediction inaccuracies were observed at low plasma concentrations for studies investigating low ibuprofen doses (150 mg) as shown in ***Figure S2*** and ***Table SIV***, Supplementary Information (26).

Oral absorption modeling in adults

The performance of default and the adjusted model settings for the three different dosing conditions are presented in ***Figure 3***, while model evaluation parameters are reported in ***Table SV***, Supplementary Information. Model refinement was needed for all three dosing conditions investigated to capture the observed drug performance (4). Under fasted conditions, all simulations were able to predict total exposure ($AUC_{0\text{-}10h}$) regardless of the GTT value applied within the range 0.1 - 1 h (***Table SVI*** and ***Figure S2***, Supplementary Information). The default conditions (GTT 0.1 h) for the fasted state overpredicted early exposure, as indicated by a FD(Cmax) of 1.53 (***Figure 3***A). As noted from the mean profile, a pronounced double peak phenomenon can be observed in the mean profile and cannot be accurately captured by a single GE event (Supplementary Information). The simulation with GTT resulting in FD(Cmax) and FD(Tmax) close to unity was considered as most suitable to describe the fasted state performance in adults, i.e. GTT of 0.5 h resulting in a FD(Cmax) of 1.33 and FD(Tmax) of 1.4 (***Figure 3***B).

Simulations following ibuprofen suspension after the reference meal using default settings "user-defined meal" with GTT 3.43 h and a 1st order GE process underpredicted the overall drug performance (AFE 0.600) and resulted in inaccurate predictions ($AAFE$ 1.882) (***Figure 3***C). Following adjustment of the GTT value to 1.5 h, model performance was improved as shown in ***Figure 3***D ($AAFE$ 1.266). Under infant-formula-fed conditions, the GTT default values of 1.92 h proposed in the "user-defined meal" option employing a zero order GE process underpredicted the absorption delay, thus resulting in overprediction of the observed early exposure and overprediction of the Cmax (FD 1.40). Due to the initial increase in plasma levels prior to the main plasma maximum increase, the $AFE / AAFE$ metrics could not accurately capture the suitability of the model settings to predict the overall model performance (***Table SVI***, Supplementary Information). The adequacy of the predictions achieved with the adjusted GTT value of 4.5 h was indicated by the FD close to unity, i.e. FD(AUC) 0.96 and FD(Cmax) 0.9, in addition to visual evaluation (***Figure 3***F).

Paediatric model performance

The simulated plasma concentration-time profiles after i.v. administration of 10 mg/kg ibuprofen for two datasets are presented in ***Figure 4***, while simulation evaluation is reported in ***Table SVII***, Supplementary Information. In the first study, ibuprofen was administered as an intravenous infusion over 10 minutes to paediatric patients between 6 months and 16 years for fever reduction (27,65) and simulated profiles fell well within the range of the individual observed plasma levels ***Figure 4***A. In the second dataset, ibuprofen was administered i.v. over 5 minutes as an analgesic treatment and only one plasma sample was collected per paediatric subject (n = 36 paediatric subjects/samples, mean age 4.3 years (range 0.3 - 12.4 years), mean weight 20.5 kg (6 – 54 kg) (28). Simulations for the mean population representatives slightly underpredicted high ibuprofen plasma concentrations at early times, while the elimination phase was well captured ***Figure 4***B. Although a certain discrepancy was observed between the simulated and observed datapoints, great underlying variability could be expected based on the wide age range in the observed data, based on observed variability in plasma levels (up to 90 % at 4 h post-dose) in the dataset by Khalil *et al*. (***Figure 4***A), and mainly the availability of only one sample per individual (***Figure 4***B). For the simulations, clearance as a function of age was calculated for population representatives using allometric scaling and, for children younger than 6 years, a maturation factor based on the maturation of each ibuprofen metabolizing enzyme reported for the paediatric age. Reported ibuprofen clearance values in different age groups were adequately captured, as the predicted clearance values were within the reported range and were overall close to the reported mean value (27) (***Table SVIII***, Supplementary Information). Due to the higher Vss in

infants than distribution in children (29), suitable adjustments were undertaken for these age-groups, i.e., Vss 0.20 L/kg for infants and 0.15 L/kg in children (47).

Oral absorption modeling in paediatrics

Default ACAT™ settings and settings adjusted according to the refined adult model were applied to simulate different dosing conditions mixed groups including infants and children or exclusively children. The paediatric studies used for comparison of the predictions were performed at an ibuprofen dose level of 10 mg/kg (29,31).

For the mixed populations modeling, a population representative of each paediatric subpopulation was simulated under relevant conditions: fasted, reference-meal-fed, and infant-formula-fed conditions were simulated in a 12-month-old infant and a 2-year-old child, while only fasted and reference-meal fed-conditions were simulated in children. Caloric content of an average meal for each population representative were calculated according to the daily average caloric requirements for each age group (***Table II***). Initially, using the default software settings, simulation of ibuprofen plasma profiles for each paediatric population representative were performed under the relevant dosing conditions. Next, for the purpose of extrapolating the fed conditions and the infant-formula-fed conditions to paediatric representatives of different ages, adjusted GTT values for infants/children were calculated based on the recommended calories for each population representative ***Table II*** (19).

Simulations for the study group with subjects between 3 months and 12 years receiving 10 mg/kg ibuprofen (29) are presented in ***Figure 5***, while simulations for the study group between 2 and 11 years receiving 10 mg/kg are presented in ***Figure 6***. Observed and predicted PK parameters along with model evaluation metrics for the paediatric age groups (29,31) are reported in ***Table III*** and ***Table SIX*** (Supplementary Information). Overall, the model was able to adequately capture total exposure reported in both studies for the 10 mg/kg dose, as shown in ***Table III*** (29,31). Within the simulations, minor bioavailability changes (< 3%) were observed as a function of age when compared to ibuprofen bioavailability in adults, i.e., 93 %, 92 %, 93 %, and 95 % drug reaching the systemic circulation in an 1-year-old infant, 6-year-old child, 12-year-old child, and an adult, respectively. Slight increase of bioavailability (1.5 %) was observed under postprandial conditions in all population representatives. The lowered bioavailability was attributed to first pass liver metabolism, as the whole drug dose was

dissolved in the GI lumen and absorbed in the age groups studied in the simulations (simulated fraction of drug dissolved and fraction of drug absorbed were 1).

In the mixed infants-children population, the fasted state default settings employing an GTT value of 0.1 h overestimated early exposure as shown in ***Figure 5***A and ***Table SIX***, Supplementary Information. Simulations performed with the adjusted GTT value of 0.5 h improved the overall predictions (***Figure 5***B), with FD for Cmax and Tmax, as well as AFE and $AAFE$ values close to unity. Fed state conditions and GTT for ibuprofen were firstly investigated using default parameters for infant meals of 170 kcal (1-year-old), child meal of 260 kcal (6-year-old), and 340 kcal (12-year-old) employing 1st order GE process to simulate GE of a solid-liquid meal, as in adults. Based on the individual profiles and the mean simulated plasma concentration-time profile, software default settings led to a greater delay in drug absorption compared to observed data (***Figure 5***C) and resulted in overall model inaccuracy ($AAFE$ 1.687), ***Table SIX***, Supplementary Information. By employing the adjusted GTT value for the solid-liquid meal, predictions were improved visually (***Figure 5***D) and regarding FD values and model accuracy ($AAFE$ 1.164), ***Table III***. Finally, infant-formula-fed conditions were simulated using the meal caloric content and zero order GE for the youngest population representative, i.e., 1-year-old infant, to evaluate the effects regarding the mean profile of the whole paediatric mixed population. The default software settings resulted in an overall underprediction of ibuprofen plasma levels (***Figure 5***E) and inaccuracy ($AAFE$ 1.621). The employment of the adjusted GTT value for the infant-formula-fed conditions in combination with the refined fed conditions in children led to more accurate predictions compared to the default settings ($AAFE$ 1.244) and captured adequately the mean profile shape, ***Figure 5***F.

A similar approach was applied for the second dataset describing ibuprofen suspension administration from the study by Walson *et al.*, whereby the youngest and oldest population representatives were 2- and 11-year-old (31) and the meal caloric content used for the fed state simulations were adjusted according to the respective ages (***Table II***). As for the first clinical dataset, overall exposure was not majorly affected by the dosing conditions investigated (***Table III*** and ***Table SIX***, Supplementary Information). Default simulations of ibuprofen administration under fasted conditions overpredicted early exposure and led to overall inaccuracy ($AAFE$ 1.436), while adjusted settings successfully captured Cmax and Tmax, and observed plasma levels ($AAFE$ 1.184), ***Figure 6***A vs. B. Default conditions following a solid-liquid meal underpredicted early and total exposure ($AAFE$ 1.452), while using the adjusted GTT values based on the ibuprofen reference-meal-dependent GE in adults generated mean

predicted profiles close to clinical observations ($AAFE$ 1.235), ***Figure 6***C vs. D, ***Table SIX***, Supplementary Information. As for the reference-meal-fed conditions, consideration of a liquid homogeneous meal for the 2-year old population representative to predict mean ibuprofen exposure in the children population overpredicted drug absorption delay (***Figure 6***E) with $AAFE$ 1.368, ***Table SIX***, Supplementary Information. The inclusion of the adjusted infant-formula-fed conditions for the 2-year-old population representative together with the adjusted reference-meal-fed conditions for 6 and 11-year-olds improved predictions of the mean predicted profile ($AAFE$ 1.171), as shown in ***Figure 6***F.

Parameter sensitivity analysis

One-factor-at-a-time PSA was performed to understand the impact of drug/drug formulation parameter uncertainties regarding the performance of ibuprofen suspension in adults under the three dosing conditions. The influence of formulation particle size and effective permeability employed in the refined adult model are shown regarding the resulting plasma concentration-time profiles and Cmax and Tmax values, ***Figure S4*** and ***Figure S5***, Supplementary Information. Sensitivity for both parameters was more pronounced under fasted and fed conditions compared to infant-formula-fed conditions. Drug particle size increase and permeability decrease led to slower ibuprofen absorption and prolonged Tmax and reduced Cmax values. Additionally, as part of the adult model refinement process under fasted conditions, a sensitivity analysis was performed for the GTT value employed in the model (***Figure S2***, Supplementary Information) and had the greatest impact of the tested sensitivity parameters.

In paediatrics, PSA was performed for three population representatives under relevant dosing conditions, i.e., 1-year-old, 6-year-old, and 12-year-old. For the parameters investigated, total exposure remained substantially unchanged, while Cmax and most notably Tmax values were affected. Drug solubility, formulation particle size, and effective permeability were identified as sensitive drug/drug formulation-related parameters. Particle size increase resulted in most pronounced decrease in Cmax for infants, while Tmax values were prolonged for all population representatives under all dosing conditions (***Figure S6,*** Supplementary Information). Effects of effective permeability regarding peak exposure were within 10 % of the baseline simulations (***Figure S6,*** Supplementary Information), while Tmax delay with decreasing permeability was observed for all population representatives under fasted and fed conditions but was not pronounced under infant-formula-fed conditions for infants. Reference solubility and bile salt solubilization ratio changes within the investigated ranges (***Table SII***, Supplementary Information) had limited influence on ibuprofen PK in

paediatrics. Furthermore, ibuprofen suspension performance across paediatric ages appeared robust towards variations in volumes used for administration of ibuprofen suspensions under the three different dosing conditions and variations in fat contents of the meals under both fed conditions (***Table SII***, Supplementary Information).

Regarding physiological and anatomical parameters influencing ibuprofen absorption, GTT prolongation led to delayed absorption with increased Tmax up to twofold compared to simulations with the adjusted GTT 0.5 h, while peak concentrations were up to 30 % lower under fasted conditions (***Figure S7,*** Supplementary Information). Meal-dependent GTT increase resulted in prolonged times to maximum ibuprofen levels and lowered Cmax values under fed conditions within the range of 70-120 kcal, while higher caloric content of the meals resulted in changes within 10% range of the baseline. Under infant-formula-fed conditions, different caloric contents of the meals led to changes in Tmax with limited influence on Cmax (< 15%). Overall a greater absorption delay with prolonged Tmax and lowered Cmax were observed for the same caloric contents when employing default settings (***Figure S7,*** Supplementary Information). Furthermore, Cmax values decrease and Tmax increase were observed as SI radius increased in the population representatives. Finally, in line with the acidic nature of the compound and its low solubility under acidic conditions, pH lowering in the absorption compartments resulted in absorption delay (***Figure S7,*** Supplementary Information). Duodenal pH changes resulted in a Tmax delay that was one third slower than the baseline. Lowering the jejunal pH resulted in greater Cmax reduction from baseline (20 %) compared to duodenal pH, while pH lowering was less pronounced regarding Tmax in the rank order (most to least pronounced): fasted (GTT 0.5 h) > fed > infant-formula-fed conditions (***Figure S7,*** Supplementary Information). Differences in gastric pH under all prandial conditions had limited impact on ibuprofen absorption in all paediatric subpopulations. Lastly, small intestinal length, small intestinal transit time, and gastric volume had no substantial impact on ibuprofen absorption across the paediatric populations regardless of the dosing conditions investigated.

Discussion

Although food effect studies for paediatric formulations are usually performed in adults in order to predict their performance to paediatric population, agreement on the suitability of commonly applied dosing conditions in food effect studies for paediatric medicines is required. A recent bioavailability study in healthy adults revealed differences in the performance of paediatric suspension formulations containing paracetamol and ibuprofen under three dosing conditions, i.e. fasted, fed, and infant-formula-fed conditions (4). Furthermore, paracetamol data collected under these three different dosing conditions were used to inform a paracetamol PBPK model to simulate exposure in infants, demonstrating that fasted conditions and/or infant-formula fed conditions resulted in successful predictions but not the reference-meal-fed conditions (19). To address the suitability of data under different dosing conditions to inform PBPK modeling for a mixed population group (infants and children, 0.3-12 years) and to a children group (2-11 years) using a BCS class II drug, *in vivo* data collected under the three different dosing conditions was used to inform the adult PBPK model, which was then scaled to the target paediatric groups. The successful prediction of ibuprofen performance in the mixed paediatric group confirmed the usefulness of bioavailability data collected under fasted and fed conditions in adults and additionally investigated the impact of including different meal types, i.e., infant formula, for the evaluation of product performance in mixed paediatric groups that include infants.

To date, PBPK modeling in paediatrics has been considered to have reached its maturation (10), however, the PBPK modeling investigation using paracetamol as a model drug (19) and the present modeling exercise employing ibuprofen demonstrated that informing the model based on formulation performance in adults was crucial to achieve successful predictions in three clinical data sets from mixed paediatric age groups, as shown in ***Figure 5***, ***Figure 6*** and ***Table III***. In the present study, when using the default GTT value for liquid formulations, early exposure was overestimated in all cases, while simulated Tmax occurred earlier than clinically observed; adjustment based on the refined adult model (GTT 0.5 h) led to close prediction of Cmax and Tmax (***Table III***). Confirmatory of our findings for ibuprofen, a reported PBPK-PD model for ibuprofen in children indicated that observed Tmax was underpredicted and Cmax overpredicted using GTT values to represent rapid gastric emptying, while employing a greater GTT value improved Cmax and Tmax predictions (47).

Adult simulations under reference-meal-fed conditions required ibuprofen GTT adjustment (GTT 1.5 h), as the software default GTT values overpredicted the GE delay observed *in vivo*. The

shorter ibuprofen transit time in the stomach may be explained by the partial emptying of the liquid formulation/drug independently from the ingested reference meal (4) due to incomplete mixing of the formulation with meal bolus, as observed for heterogeneous solid-liquid meals (57,70). The shorter stomach transit times in adults for the reference-meal-fed conditions translated in minor GE delay in the paediatric simulations based on the refined adult model (***Table II***). Additionally, based on the caloric-dependent nature of the GE process, it could be expected that with the lower caloric content recommended for younger populations compared to adults, the meal GE times would be shorter than observed for the reference meal containing high-calorie content (***Table II***). When employing software default values for the fed state simulations in paediatrics, a delayed drug absorption was predicted contrary to clinical observations, while mean simulated profiles based on the adjusted GTT vales for the fed state better described the data observed mean profile in paediatrics. According to previous investigations, physiological parameters influencing GE, i.e., motility, were reported to be similar in older children, adolescent and adults, whereas no evidence could be found regarding age influence on GE from birth until adolescents (67). According to this meta-analysis (67), the type of food, i.e., formula, semi-solid, or solid food, majorly determined GE in different age groups; investigation of the caloric influence was not performed due to data scarcity. Nevertheless, recently, a scintigraphy study performed in a large dataset collected over a period of 12 years in paediatric patients < 5 years of age (n = 2 273) using milk and/or infant formula indicated decreased % liquid emptied from the stomach with increasing feeding volumes and, therefore, meal caloric content (67,71).

Consideration of an additional meal type, such as infant formula for infants, can be useful for simulation of the distinct meal types in mixed paediatric groups that cover broad age ranges from infants to adolescents, as is often the case in paediatric clinical studies (3,6). In the present study, the inclusion of the infant-formula-fed conditions improved the predictions of the mean observed profile, however, dosing conditions in the studies used as observed data were not stated (29,31). Despite the uncertainties in the proportion of infants relative to the whole study group (29,31), representation of the infant population under common dosing conditions typical for the group could be crucial to capture gastric mixing events and the subsequent arrival at the drug absorption site (19).

According to the recent draft guideline by the FDA no additional food effect study is needed for the paediatric formulation, when the same to be marketed paediatric formulation has been approved for use in adults (1), indicating that food effect data in adults following the reference meal could be used to understand food impact on a paediatric population. In line, the present investigation achieved

successful simulation of ibuprofen exposure both under fasted and fed conditions adjusted to *in vivo* observations in adults and taking into consideration the average caloric needs of children (***Table II***). Based on the texture similarity of the reference meal and meals for paediatric populations receiving heterogenous solid-liquid feeds, the impact on gastric mixing processes between meal and formulation, the resulting GE and appearance in the SI might not differ profoundly between children and adults. For compounds whose appearance in the systemic circulation is limited by GE and partly dissolution, as in the case for BCS class II weak acids (47,72), the extrapolation of data already available in adults could be beneficial for accelerating paediatric development timelines and reduction of clinical burden. Nevertheless, it should be noted that meal fat contents might vary across paediatric populations and differ from the high fat content of the reference meal that might overestimate bile-salt-mediated drug solubilization for other highly lipophilic compounds; although such effect was not observed for ibuprofen, the extrapolation based on the high fat reference meal should be evaluated cautiously in each situation.

The performed PSA (***Table SII***, Supplementary Information) revealed greatest sensitivity to formulation particle size from the drug/drug formulation-related parameters tested (***Figure S4***, ***Figure S5***, ***Figure S6,*** Supplementary Information). The utility of PBPK modeling in the evaluation of formulation strategies could be particularly beneficial for paediatric product development, e.g. in the evaluation of impact of particle size changes on pediatric suspension performance. Regarding physiology-related factors, greatest sensitivity was observed regarding GTT, duodenal and jejunal pH, as well as SI radius under all dosing conditions investigated and paediatric population representatives of different age groups (***Figure S7,*** Supplementary Information). Lowering of the intraluminal pH, especially in the jejunum, where major part of the drug is absorbed, would result in lower peak exposure and prolonged absorption times for ibuprofen based on the acidic properties of ibuprofen that can negatively impact ibuprofen dissolution. Considering the knowledge gaps in age-dependent changes in intraluminal fluid composition (3), i.e., pH and buffer capacity, further investigations are needed to better understand and conclude on the age-dependent faith of ibuprofen in the SI lumen. Nevertheless, the ibuprofen absorption delay observed in the study by Statelova *et al.* was explained by GE delay under all dosing conditions investigated (4). Additionally, the dominating role of GTT on ibuprofen performance could be corroborated by the fact that the same delay was observed and used for modeling of the GE of paracetamol that was co-administered in the clinical investigation by Statelova *et al.* (4,19). The results from the present investigation and PSA revealed that GE rather than dissolution was the limiting step for the weak acid ibuprofen given as an aqueous suspension. Similar tendencies were shown for the weak acid naproxen, where PK parameters showed greatest sensitivity to GE times (72).

The extensive and saturable plasma protein (albumin) binding of ibuprofen (34,65) can influence drug distribution and clearance in a concentration-dependent manner, leading to non-linear AUC increase in adults (73). As the current model was developed for a high dose of ibuprofen (10 mg/kg) and disposition modeling was based on i.v. data following the same dose in adults, some inaccuracies of the simulations for lower ibuprofen doses in adult i.v. studies were observed (***Figure S1***, Supplementary Information). To ensure adequate scaling of disposition and clearance parameters to paediatrics, only paediatric datasets utilizing similar doses were selected (29,31). Furthermore, ibuprofen's distribution volume appears to be higher in children compared to adults (33,47) and appeared greater in children below the age of 2.5 years compared to older children (29). Despite accounting for developmental changes of plasma proteins across paediatrics, the model was not able to reflect ibuprofen disposition changes observed *in vivo* (27–29). Based on the scarcity of information regarding ibuprofen age-dependent plasma protein binding and the resulting impact on drug disposition, an empirical adjustment of the volume of distribution was undertaken according to clinical observations (27–29,47). Although some of the observations of age-dependent disposition changes originated from oral dosing, changes in fraction of drug absorbed have been considered unlikely to explain the differences observed (47). The empirical adjustment of Vss poses a limitation to the present model regarding extrapolation only to similar doses and limits the incorporation of variability originating in fraction of drug unbound. In addition to the quantitative ontogeny changes in plasma proteins, age-dependent differences in binding dynamics and drug affinity to albumin could introduce additional model uncertainty. High ibuprofen concentrations were underpredicted in one of the paediatric datasets following intravenous administration (***Figure 4B***), which was explained in changes of free drug in plasma and the high interindividual variability in the samples (up to 60 %) (28). Finally, most of the paediatric studies were performed in febrile paediatric patients, which could lead to changes in ibuprofen fraction unbound, and could have contributed to the disposition differences reported among studies (27–29). Studies of ibuprofen plasma protein binding regarding age-dependent changes and health status deserve further attention.

It should be noted that paediatric model evaluation of the current investigation focused on a children study population and a mixed infant/children population, as the paediatric clinical studies did not stratify the subjects according to age groups (3). Data from a well-defined study population including solely infants would be beneficial for the evaluation of the usefulness of the different dosing conditions, especially to simulate drug performance when administered with infant formula, which is the typical type of food for this subpopulation. Although a clinical study in 11 infants (6 - 18 months)

has been published in the literature (32), the ibuprofen suspension was administered after general anaesthesia in the recovery room and was therefore excluded from the present work. In line with this, in order to improve and validate the biopharmaceutics tools and methodologies currently available for paediatric medicines evaluation, generation and reporting of reliable, high-quality clinical data in different paediatric populations are imperative (3,4).

Concluding remarks

In the present investigation, we evaluated the importance of PBPK model refinement for adults with data acquired in adults using a paediatric formulation under age-relevant dosing conditions in order to extrapolate ibuprofen exposure to paediatrics. Compared with our recent relevant attempt that covered paracetamol dosing under age-relevant conditions in infants (19), the present study focused on mixed paediatric populations ranging from infants to school children. As previously observed for paracetamol, default software settings failed to predict drug performance in paediatrics, while the employment of adjusted settings extrapolated from the adult study under different prandial conditions resulted in successful predictions in paediatric populations (29,31). The present PBPK modeling exercise demonstrated the need of high-quality data in adults designed to inform the modeling workflow for extrapolation in paediatrics under different prandial conditions. As recently suggested in a draft FDA guideline on the investigation of food effects for paediatric formulations (1), the reference meal appeared appropriate for extrapolation to children, while the consideration of the ibuprofen infant-formula-dependent GE for paediatric subjects below the age of 2.5 years, led to improvement of ibuprofen exposure in mixed paediatric groups including infants. No major differences were observed among predictions based on the adjusted model for the three different dosing conditions investigated. Gastric emptying rather than dissolution appeared to define the absorption of the weak acid ibuprofen. Nevertheless, the present model exercise highlighted several areas where further investigations were required to drive model refinement forward. For instance, implications of intraluminal age-dependent pH and buffer capacity changes regarding drug intraluminal performance are yet to be investigated and understood in paediatrics. Furthermore, although modeling drug disposition in paediatrics has been considered to reach maturity, challenges regarding capturing non-linear PK behavior due to concentration-dependent plasma protein binding should be addressed with relevant *in vivo* investigations to exploit the vast capabilities of PBPK modeling and improve modeling of complex PK processes. Finally, the proposed methodology deserves further verification and investigations using a broader spectrum of drugs and drug formulations, whereby efforts should be focused on collecting well-designed and recorded clinical data in paediatrics and in adults.

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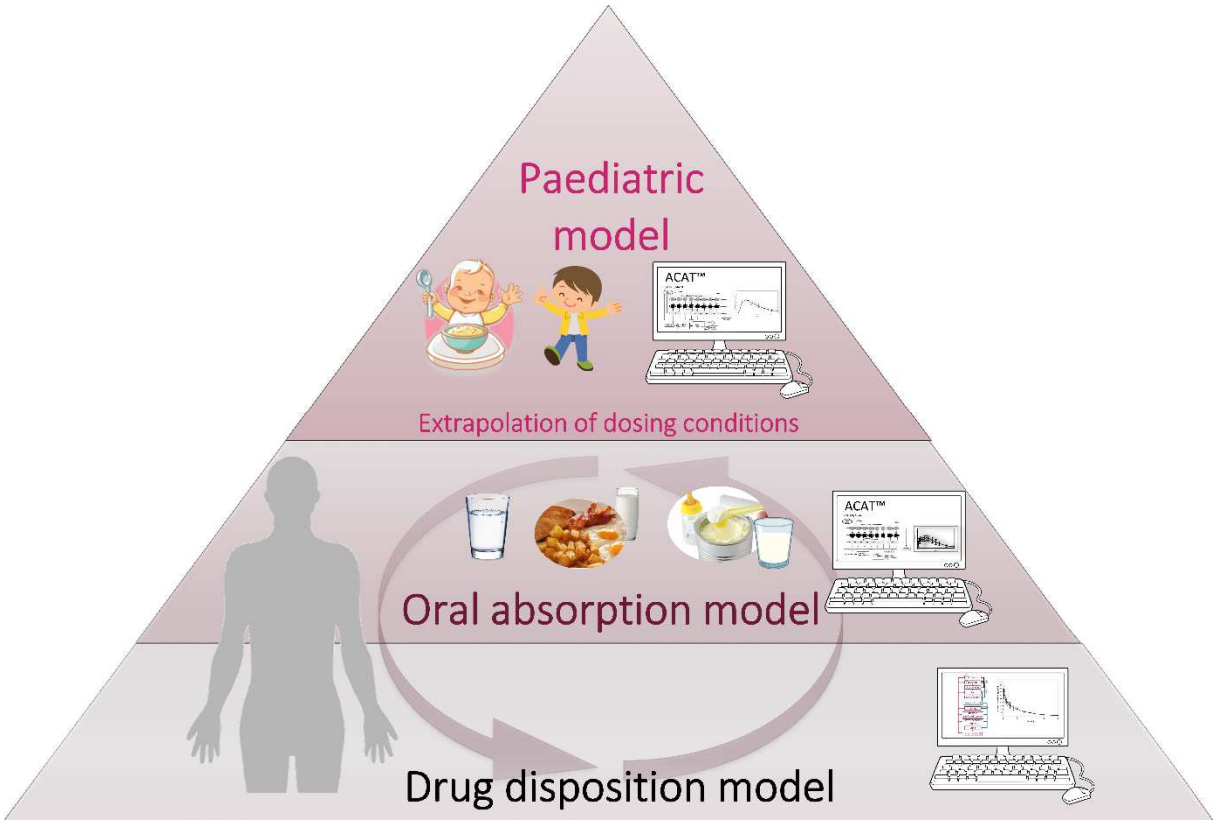
Graphical abstract



List of Figures

month-old) based on the ibuprofen meal-dependent GE from adult refined model for infant formula (F). Symbols and error bars denote mean observed plasma levels and the standard deviation of Brown et al., 1992 (n=49 paediatric subjects) (29).

Figure 6 Predicted plasma concentration-time profiles (lines) following oral administration of ibuprofen under different dosing conditions. Thin light blue continuous line (–) 2-year-old child, blue dashed line (---) 6-year-old child, dark blue dotted line (···) 11-year-old child, bold purple continuous lines (**–**) mean profiles for the three age groups. Fasted conditions employing default GTT values 0.1 h (A) and adjusted GTT value of 0.5 h (B) according to *in vivo* observations in adults; Reference-meal-fed conditions with first order GE employing calorie-based default software GTT (C) or adjusted GTT based on ibuprofen meal-dependent GE from adult refined model (D); reference meal-fed (6 and 11- year-olds) and infant-formula-fed (2-year-old) conditions simulating dosing employing calorie-based default software GTT (zero order GE for infant formula) (E) or adjusted GTT values for reference-meal-fed conditions (6 and 11-year-olds) and infant-formula-fed conditions (2-year-old) based on the ibuprofen meal-dependent GE from adult refined model with zero-order GE for infant formula (F). Symbols and error bars denote mean observed plasma levels and the standard deviation of Walson et al., 1989 (n=11-21 paediatric subjects), (31).

Figure 1

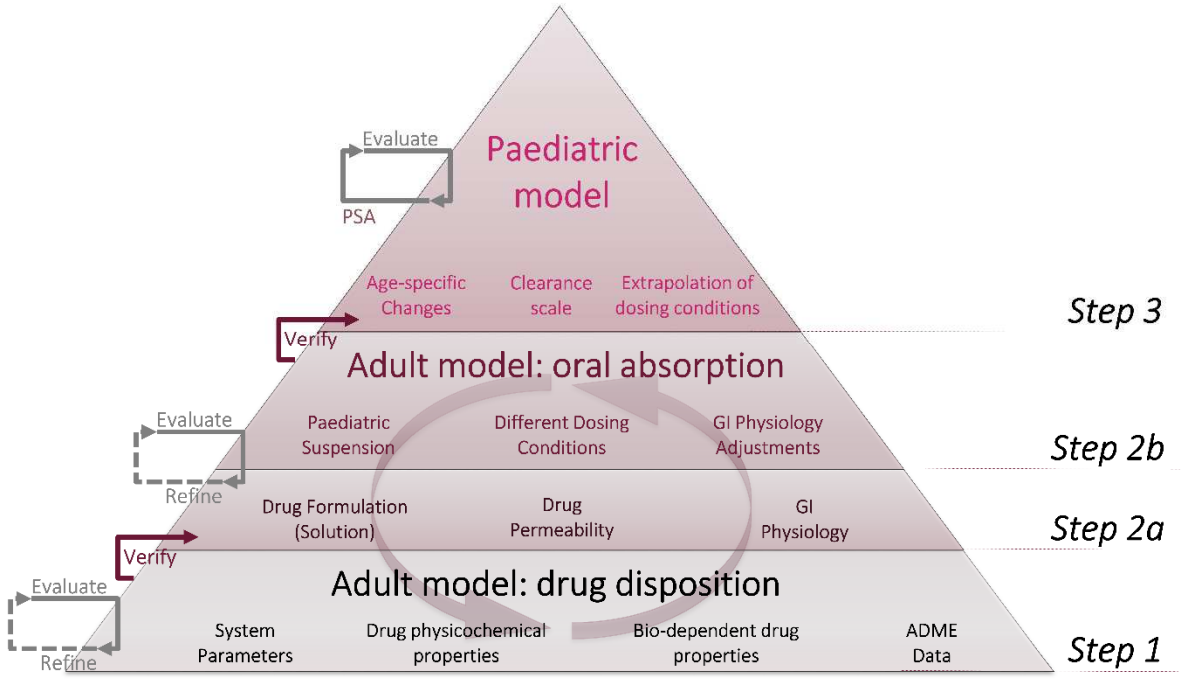

Evaluate
PSA
Paediatric model
Age-specific Changes
Clearance scale
Extrapolation of dosing conditions
Step 3
Verify
Adult model: oral absorption
Evaluate
Refine
Paediatric Suspension
Different Dosing Conditions
GI Physiology Adjustments
Step 2b
Drug Formulation (Solution)
Drug Permeability
GI Physiology
Step 2a
Verify
Evaluate
Refine
Adult model: drug disposition
System Parameters
Drug physicochemical properties
Bio-dependent drug properties
ADME Data
Step 1

Figure 2

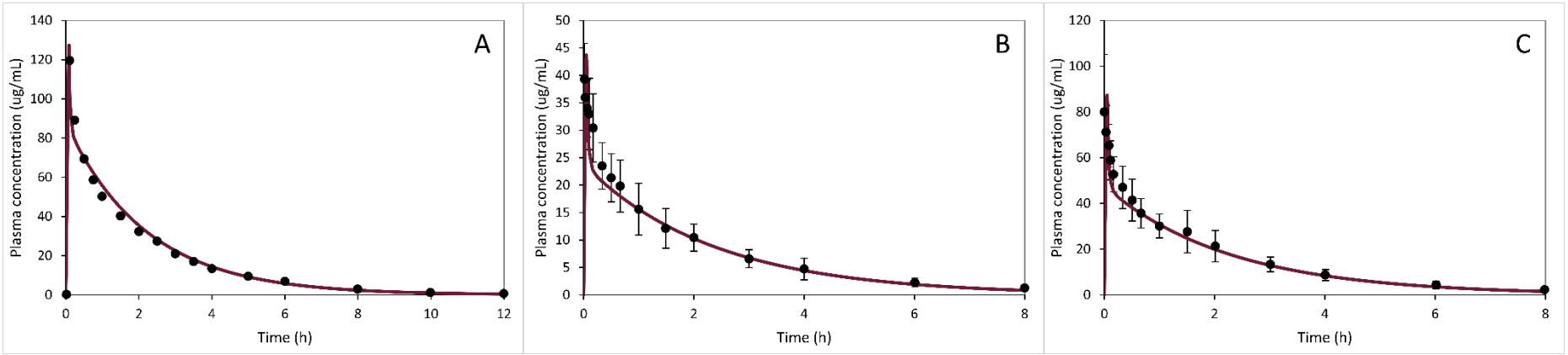

A
Plasma concentration (ug/mL)
Time (h)
B
Plasma concentration (ug/mL)
Time (h)
C
Plasma concentration (ug/mL)
Time (h)

Figure 3

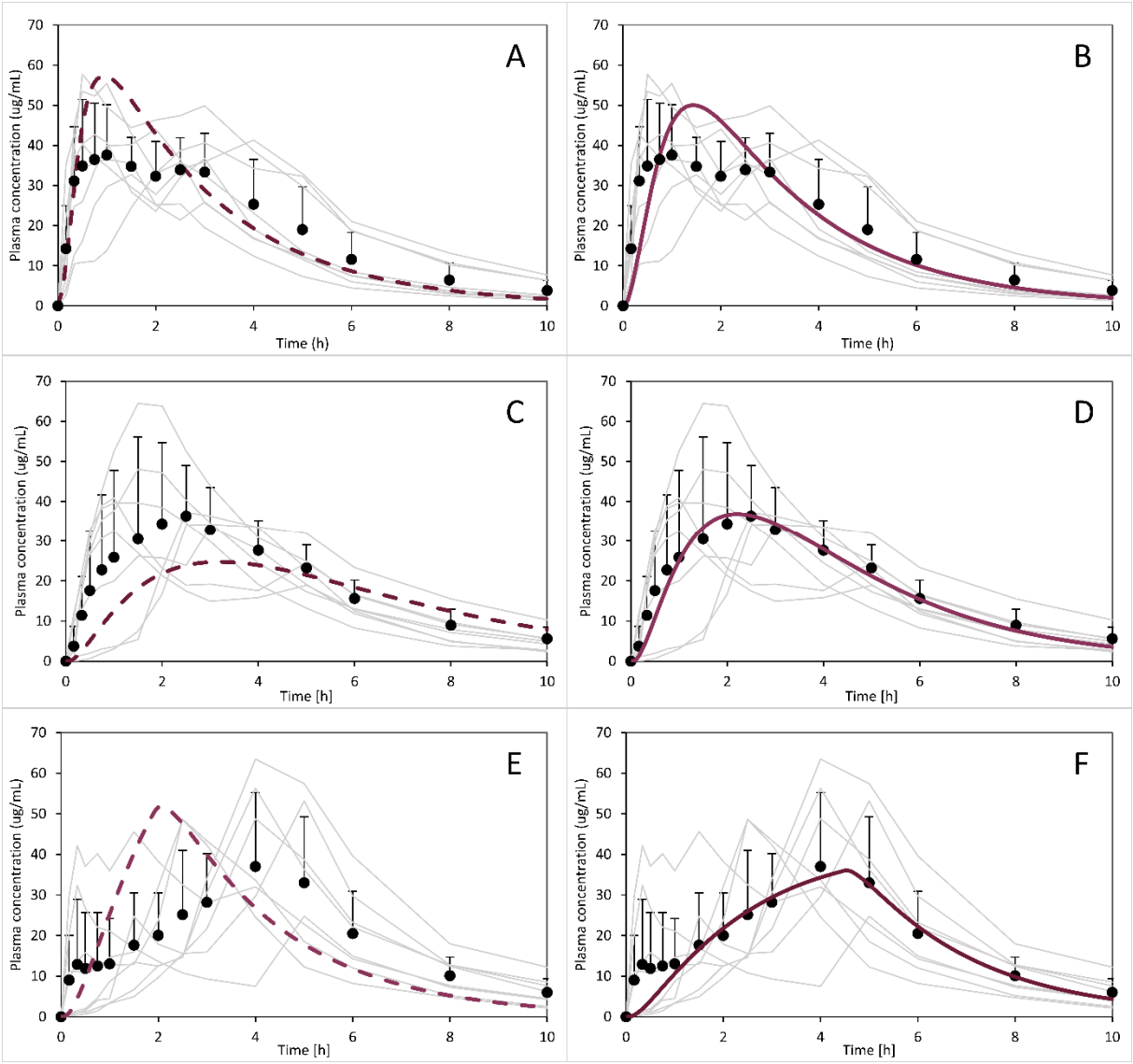

A
B
C
D
E
F
Plasma concentration (ug/mL)
Time (h)
Time [h]
0
10
20
30
40
50
60
70
0
2
4
6
8
10

Figure 4

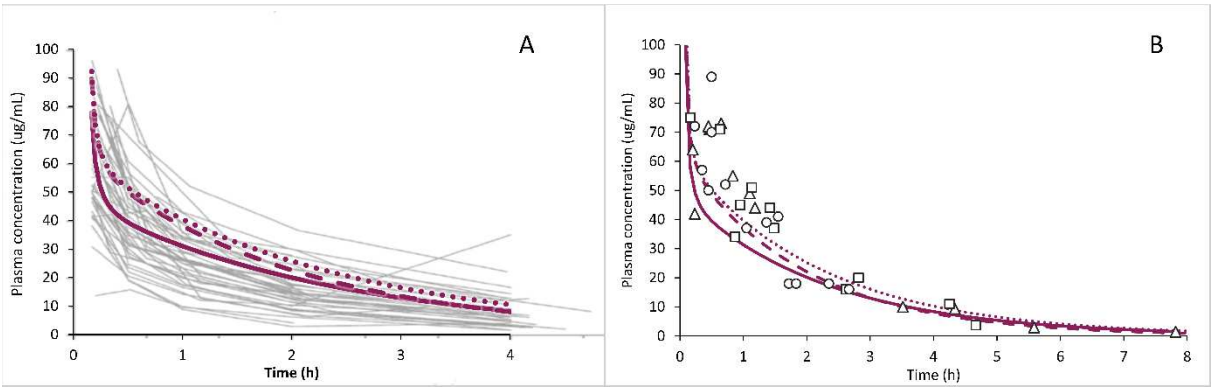

A
Plasma concentration (ug/mL)
Time (h)
B
Plasma concentration (ug/mL)
Time (h)

Figure 5

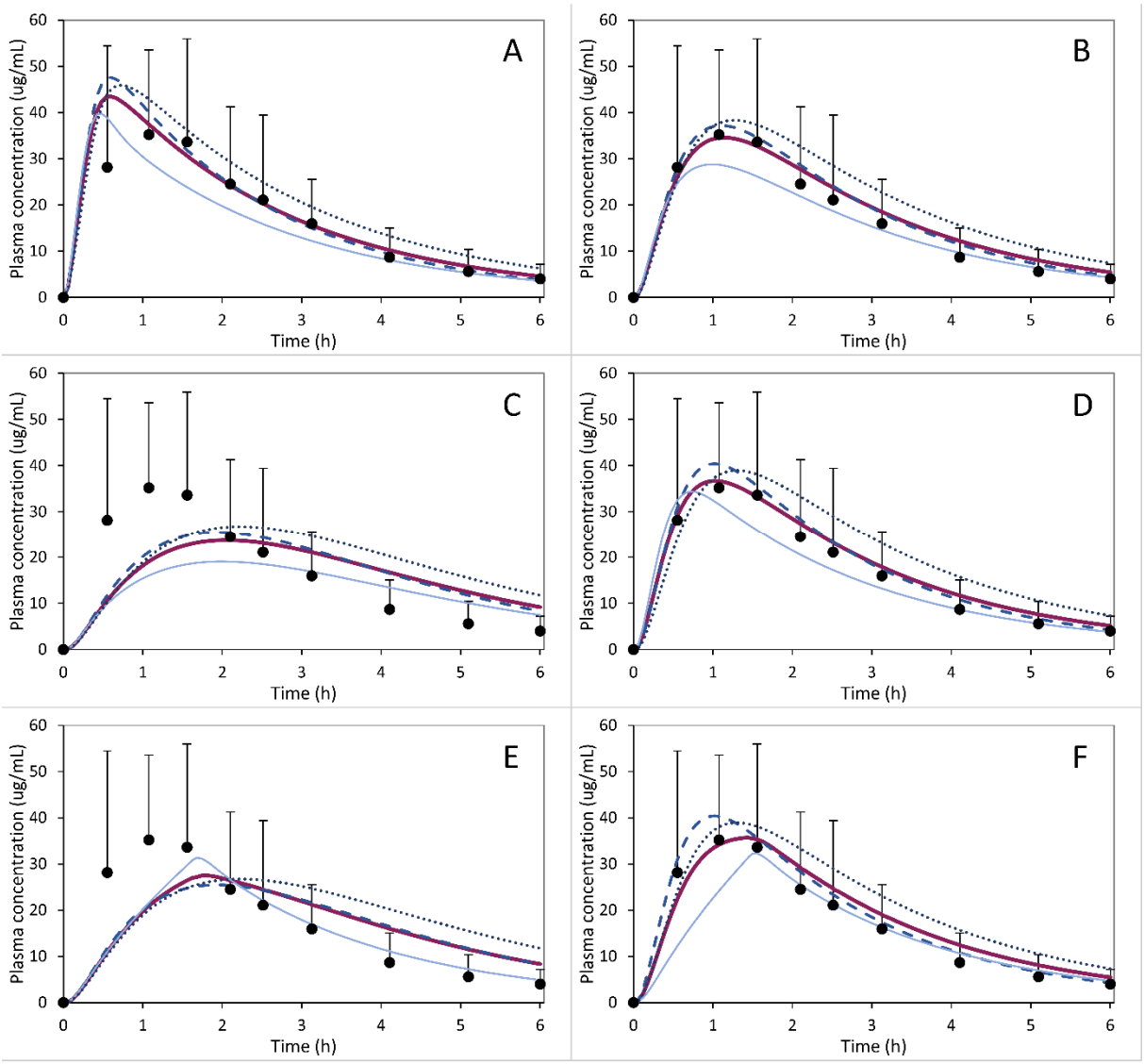

A
B
C
D
E
F
Plasma concentration (ug/mL)
Time (h)
0
10
20
30
40
50
60
0
1
2
3
4
5
6

Figure 6

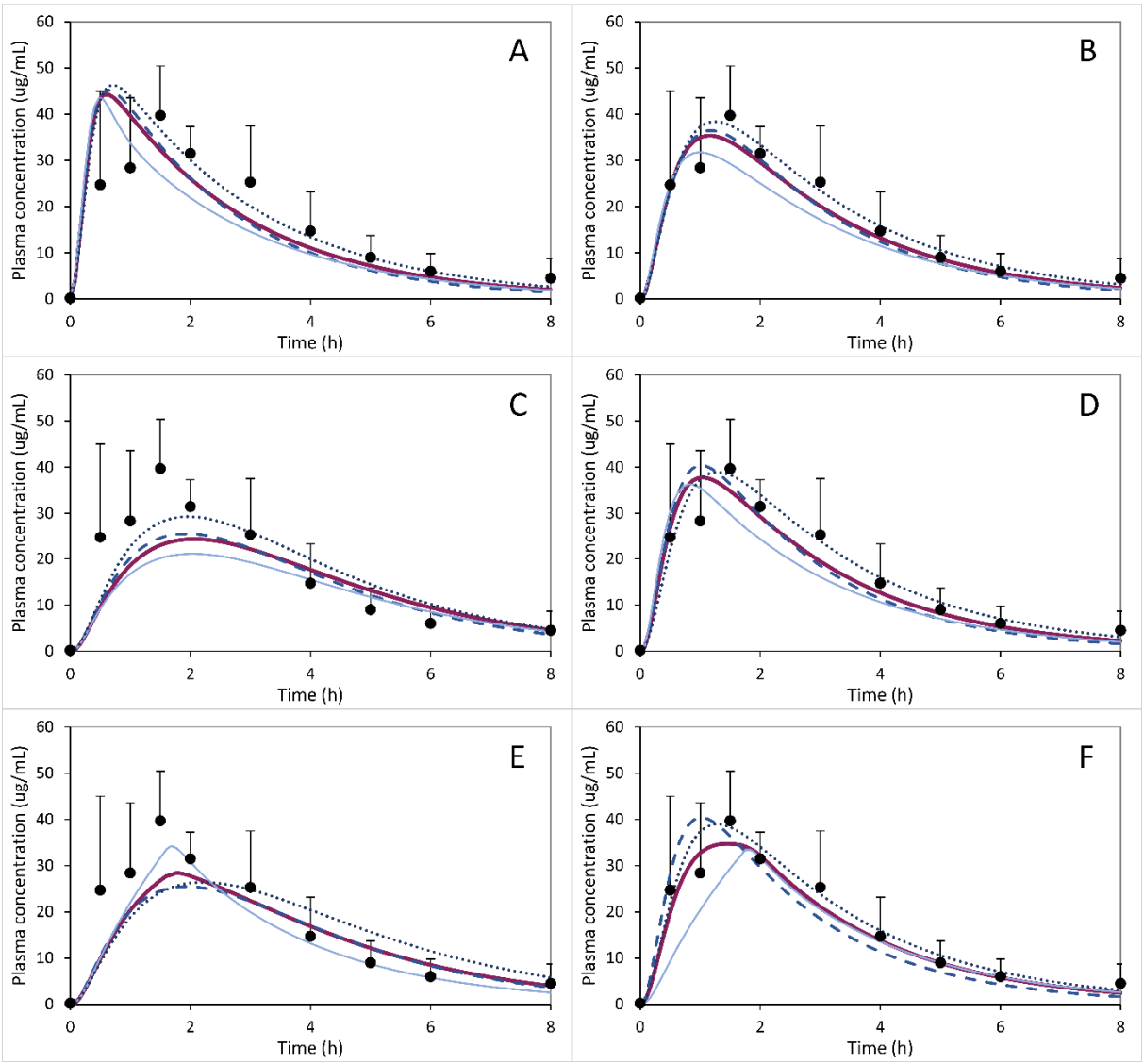

A
B
C
D
E
F
Plasma concentration (ug/mL)
Time (h)
0
10
20
30
40
50
60
0
2
4
6
8

Table I Input parameters used to build the PBPK model for ibuprofen

Parameter		Source
Physicochemical properties		
Molecular weight (g/mol)	206.29	(39)
pKa	4.42 (acidic)	(40)
Compound type	Monoprotic weak acid	
clogP*	3.65	Predicted GastroPlus™
Reference solubility (mg/mL)	0.038	(22)
Aqueous solubility in mg/mL (pH)	0.038 (1.0)	(22)
	0.043 (3.0)	
	0.084 (4.5)	
	0.685 (5.5)	
	3.37 (6.8)	
	3.44 (7.4)	
Absorption		
Model	ACAT™	
Effective permeability, human (cm/s ×10^4)	6.6	Calculated based on (41,42)
Solubility in biorelevant media (mg/mL) Level III FaSSGF Level II FaSSIF Level II FeSSIF-V2	 0.048 1.953 2.290	In house data
Dissolution model	Johnson	GastroPlus™, (43)
Particle size, radius (µm)	25	Default GastroPlus™
Distribution		
Fraction unbound, fu	0.0155	(34)
Blood-plasma ratio	1.55	(44)
Vss (L/kg) [a]	0.11	Predicted using the Lukacova, Rodgers and Rowland method (45,46)
Clearance		
Clearance (L/h)	3.81	Adjusted based on Pavliv *et al*. (23)

*calculated/predicted logP (octanol/water) by GastroPlus™, experimental logP range 3.23-4.13 (40,47–49)

Table II Adjusted gastric transit time (GTT) values for ibuprofen gastric emptying in paediatric population representatives according to recommended meal calories for age calculated based on GTT values employed in the refined adult model for the reference meal and infant formula used for inducing fed and infant-formula-fed conditions and their respective caloric contents (4).

Test Meal and ibuprofen gastric emptying process	Adult		Infant		Infant/Child		Child			
	28-years-old male, 78 kg body weight [a]		12-month-old, 9.5 kg body weight [b]		2-year-old, 12.9 kg body weight [c]		6-year-old, 23 kg body weight [b, c]		11-[c]/12-[b] year-old, 43.6/48.6 kg body weight [d]	
	Caloric content (kcal)	GTT (h)	Caloric content (kcal)	GTT (h)	Caloric content (kcal)	GTT (h)	Caloric content (kcal)	GTT (h)	Caloric content (kcal)	GTT (h)
Reference meal (Solid-liquid) 1st order gastric emptying	990	1.5	170	0.26	200	0.30	260	0.38	340	0.58
Infant formula (Liquid homogeneous) Zero order gastric emptying	520	4.5	170	1.47	200	1.73	-	-	340	-

[a] mean adult population representative of the study by Statelova *et al*. (4)

[b] population representative of the study by Brown *et al*. (29)

[c] population representative of the study by Walson *et al*. (31)

[d] the recommended average daily needs for the 11- and 12-year-old population representatives were the same, resulting in the same caloric content per meal and adjusted GTT value for these population representatives

Table III Observed and predicted ibuprofen pharmacokinetic (PK) parameters in studies performed in two infant/children or children mixed populations, i.e., 0.3-12 years (29) and 2-11 years (31) at a dose 10 mg/kg. The PK parameters were estimated from the mean profile obtained from single simulations in infant/2-year-old, 6-year-old, and 12-year-old population representatives. Results are presented for model settings (GTT values) extrapolated from the refined adult model for fasted, reference-meal-fed conditions, or reference meal and infant-formula-fed conditions as described in Statelova et al. (4).

Paediatric Study	Parameter	Observed	Fasted state [a] Adjusted GTT			Fed state [a] (reference meal) Adjusted GTT			Fed State [a] (reference meal and infant formula) Adjusted GTT		
			Predicted	FD [b]	AFE [c]/ AAFE [d]	Predicted	FD [b]	AFE [c]/ AAFE [d]	Predicted	FD [b]	AFE [c]/ AAFE [d]
Brown *et al*. 1992 (29)	AUC $_{0\text{-}t}$ [e] (ug/mL·h)	100.9	110.5	1.09	1.164/ 1.196	111.5	1.10	1.161/ 1.164	111.3	1.10	1.175/ 1.244
	Cmax [f] (ug/mL)	35.21	34.60	0.98		36.70	1.04		35.72	1.01	
	Tmax (h) [g]	1.08	1.14	1.06		1.02	0.95		1.44	1.34	
Walson *et al*. 1989 (31)	AUC $_{0\text{-}t}$ [e] (ug/mL·h)	132.6	120.6	0.91	0.884/ 1.184	121.4	0.92	0.879/ 1.235	121.8	0.92	0.886/ 1.171
	Cmax [f] (ug/mL)	39.70	35.35	0.89		37.79	0.95		34.72	0.87	
	Tmax (h) [g]	1.50	1.12	0.75		1.04	0.69		1.44	0.96	

[a] Conditions simulated based on the refined adult model for different dosing condition as described in Statelova *et al.* (4)

[b] $FD_{pred/obs}$: Fold difference predicted/observed

[c] AFE average fold error

[d] $AAFE$ absolute average fold error

[e] Area under the plasma concentration-time curve from 0h until the last observed time point (t) $AUC_{0\text{-}t}$ (ug/mL·h)

[f] Maximum plasma concentration Cmax (ug/mL)

[g] Time to reach Cmax (h)