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

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Running title:

Ibuprofen exposure: from adults to paediatrics

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1 ABSTRACT

2

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

20 Introduction

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

29

30 To date, bioavailability and food effect studies for orally administered paediatric products are
31 performed in adult volunteers according to regulatory guidelines with application of the suggested
32 fasted and fed conditions, i.e. fasted conditions where the formulation is administered with a glass of
33 water and after the consumption of a high-calorie, high-fat solid-liquid meal with 800 - 1000 kcal and
34 50 - 60 % fats (herein “the reference meal”) (1,2). Based on the variety of foods that different paediatric
35 subpopulations might receive, a recent draft guideline suggests that sponsors can use foods and
36 quantities of food that are commonly consumed with drugs in a particular paediatric population, e.g.,
37 infant formula for infants (1,3,4) and results from the food effect investigations in adults can be
38 extrapolated to the paediatric population for which the medication is intended (1). It should be noted
39 that the draft guidance suggests a separate food effect study would not be necessary if the same to-
40 be-marketed paediatric formulation has been approved for use in adults (1). Although paediatric
41 subpopulations, such as young children (2-6 years of age) and schoolchildren (6-12 years of age) (3,5),
42 might receive meals with similar texture as the reference meal, meal caloric content and portions
43 change in an age-dependent manner. Considering the high caloric content of the reference meal, it
44 might not be representative of meal caloric contents for younger populations (3,6).

45

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

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

63
64 Despite the usefulness and the potential of this *in silico* tool, the modeling process usually requires
65 additional information from *in vitro* and/or *in vivo* studies to refine and/or confirm the suitability of
66 the modeling parameters, commonly referred to as the “middle-out” approach (10,20). The
67 importance of PBPK model refinement for adults with data acquired in adults using the paediatric
68 formulation of interest under age-relevant dosing conditions in order to extrapolate drug exposure to
69 infants was recently demonstrated for paracetamol (**Figure 1**) (19). Three different dosing conditions
70 were modeled and evaluated, i.e., fasted and fed conditions according to regulatory guidelines (2,21),
71 and drug administration during infant formula consumption to mimic drug dosing in infants (4,19).

72
73 As natural step towards better understanding and extension of the approach recently presented by
74 Statelova and colleagues (19), the weak acid ibuprofen ($pK_a \approx 4.5$) was used as a model drug to
75 investigate influences of different dosing and prandial conditions for the extrapolation to paediatric
76 mixed populations including infants (1 month - 2 years) and young children (2 – 6 years) and
77 schoolchildren (6 – 12 years) or populations including children. Ibuprofen is a non-steroidal anti-
78 inflammatory drug (NSAID) that is classified as a Class II drug according to the Biopharmaceutics
79 classification system (BCS) based on its low solubility in acidic media and high intestinal permeability
80 (22). For this purpose, a PBPK model was developed using the GastroPlus™ platform (Simulations Plus,
81 Lancaster, CA), whereby model development was guided by ibuprofen suspension performance in
82 adults under the three different dosing conditions to inform the paediatric oral absorption model, as
83 shown in **Figure 1** (4,19). Hence, the purpose of the present study was to extend the application of the
84 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.

87 Methods

88 Clinical data collection

89 A literature search was performed for pharmacokinetic studies reporting ibuprofen administration
90 following intravenous (i.v.) administration or *per os* administration of a suspension in adults and
91 paediatric populations. Studies not reporting the measured plasma levels, formulations including
92 excipients that alter drug formulation performance or use of ibuprofen salt forms were excluded. A
93 total of 19 datasets were retrieved, with nine performed in adults and ten in paediatric populations.
94 Intravenous ibuprofen dosing in adults was reported in six datasets (23–26), with one of them
95 investigating a high ibuprofen dose, i.e., 800 mg (23). The study by Statelova *et al.* (4) was used to
96 guide modeling of the paediatric ibuprofen suspension (800 mg ibuprofen) administered orally in
97 adults under different dosing conditions, i.e. fasted conditions and fed conditions induced with the
98 reference meal (solid-liquid meal) according to current regulatory guidelines (2,21), and infant-
99 formula-fed conditions mimicking dosing in infants (homogeneous liquid) (4). In paediatrics, two
100 studies (4 datasets) investigated ibuprofen performance following i.v. administration at a dose of
101 10 mg/kg (27,28), while three datasets were available from investigations of a liquid formulation
102 administered to a paediatric mixed groups, including infants and children at doses 5 mg/kg, 6 mg/kg,
103 and 10 mg/kg (29,30), two datasets were acquired following suspension administration to children at
104 doses 5 mg/kg or 10 mg/kg (31), and one study investigated suspension administration in an infant
105 study group (7.6 mg/kg) (32). As the dataset in the infant population originated from ibuprofen
106 suspension administration in the recovery room under influence of additional drugs used for general
107 anaesthesia (e.g., halothane, vecuronium, phenoperidine, nitrous oxide) altering GI transit times, this
108 dataset was excluded from further investigations. Ibuprofen is low extraction drug that is highly bound
109 to plasma proteins ($\approx 99\%$), primarily, serum albumin (33–35). Based on the concentration-dependent
110 saturable nature of the plasma binding, non-linear drug exposure has been reported in adults and
111 children (29,33,36). Furthermore, changes in the fraction of unbound drug could result in differences
112 in the apparent volume of distribution and impact drug clearance. Based on this non-linearity and the
113 dose administered (800 mg) in the adult study used to develop the adult disposition model and to
114 inform the oral model (4), only the datasets obtained using high ibuprofen doses (10 mg/kg) in
115 paediatrics were considered within the present PBPK modeling investigation. The datasets acquired at
116 a dose of 10 mg/kg were reported in Brown *et al.* (3 months – 12 years) and Walson *et al.* (2 years –
117 11 years) (29,31). Additionally, dosing conditions impact was expected to be greater at the higher dose
118 (800 mg in adults, equivalent to 10 mg/kg in paediatrics). Observed ibuprofen mean plasma levels as
119 a function of time and the respective standard deviation (SD) or standard error of the mean (SEM)
120 values were digitized from the publications using the WebPlotDigitizer software V4.1 (Ankit Rohatgi,

121 2017). Along with the plasma concentration-time profiles, information regarding dosing conditions and
122 reported study demographics were documented, i.e. number of study participants, age, gender, race,
123 body weight, body height. Ibuprofen is a drug with almost complete absolute bioavailability in adults
124 (23,33) and in neonates (37,38).

125

126 Modeling workflow

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

135

136 Adult PBPK model

137 Physicochemical and bio-dependent ibuprofen properties used to inform the PBPK model are reported
138 in **Table I**. Within the present model, ibuprofen distribution was predicted using the single Lukacova,
139 Rodgers and Rowland model (45,46) and clearance was incorporated into the model as whole organ
140 intrinsic clearance ($CL_{int,u}$). The clearance was estimated from the PK profile reported for a rapid 5-
141 7 minute infusion of 800 mg of ibuprofen to healthy adults (23) utilizing the PKPlus™ tool within the
142 GastroPlus™ platform. Ibuprofen clearance occurs primarily in the liver with less than 0.5 % of the total
143 ibuprofen dose being recovered unchanged in urine, therefore the whole clearance was attributed to
144 the liver. The $CL_{int,u}$ incorporated into the model was calculated according to the well-stirred model
145 and took into consideration hepatic blood flow, fraction of drug unbound in plasma, clearance
146 observed *in vivo* and the blood to plasma concentration ratio of the drug (**Table I**) (50–52). Virtual
147 physiologies were generated using the Population Estimates for Age-Related (PEAR™) Physiology
148 module within GastroPlus™ (18,52,53). Single simulations were performed using a physiology
149 matching the mean reported demographic parameters for each study, i.e., age, gender, race, body
150 weight, and body height. A default American healthy male physiology (70 kg, 30 years old) was
151 assumed when the demographics for the simulated study were not reported.

152

153 *Oral absorption modeling in adults*

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

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

172
$$\log P_{eff,man} = 0.6795 \times \log P_{app,Caco2} - 0.3036 \quad \text{Eq. 1}$$

173
174 The plasma concentration-time data from the study by Statelova *et al.* were used for confirmation
175 and/or adjustment of the modeling parameters for the paediatric suspension performance under
176 fasted, reference meal-fed, and infant formula-fed conditions (4). Single simulations were performed
177 for a physiology matching the mean study demographics, i.e. 28-year-old male with a body weight of
178 78 kg (population representative). The dosing conditions in the PBPK model matched the conditions
179 applied in the study by Statelova *et al.* (4), whereby a 800 mg dose of ibuprofen was administered as
180 a suspension with a total fluid volume of 250 mL under fasted and reference-meal-fed conditions
181 according to regulatory guidelines (2,21) or without additional water under conditions mimicking drug
182 dosing in infants (4). Under fed conditions, the ibuprofen suspension was administered 30 minutes
183 after the start of the high-fat, high-calorie reference meal consumption (solid-liquid meal, 60 % fat,
184 990 kcal) (2,21), while under infant-formula-fed-conditions, ibuprofen was administered during the
185 consumption of 800 mL of infant formula (homogenous liquid meal, 43 % fat, 520 kcal) (4).

186

187 For fasted state simulations, default settings were used with a gastric transit time (GTT) of 0.1 h and a
188 first order GE process, with GTT representing the mean gastric transit time (MGTT), i.e., the GE half-
189 time ($t_{1/2}$) divided by the $\ln 2$. Model parameter adjustments were needed to match drug performance
190 observed *in vivo* (4). GTT values ranging between 0.1 h and 1.0 h were employed for model refinement
191 to achieve reasonable description of the absorption delay ($t_{1/2}$ 4 to 42 min, respectively). For the
192 reference-meal-fed and infant-formula-fed conditions, liver blood flow was increased by 30 % to
193 simulate the increased blood flow in the GI tract (8). For conditions investigating suspension
194 administration after consumption of the reference meal, simulations were performed using the human
195 fed state physiology following a “user-defined meal” matching the meal used in the study by Statelova
196 *et al.*, i.e. 990 kcal and 60 % fat (4). The GastroPlus™ platform adjusts the GTT according to the caloric
197 content of the meal entered, while bile salt concentration was increased in the simulation related to
198 the fat content in the user-defined meal. First order GE kinetics were employed for the solid-liquid
199 reference meal based on *in vivo* observations in adults following the administration of a similar meal
200 (57). Adjustment of the GTT value was undertaken to match the ibuprofen performance observed *in*
201 *vivo*. Similarly, for infant-formula-fed conditions, the infant formula was defined with 520 kcal and
202 43 % fats within the human fed state physiology with a “user-defined meal”. A zero order GE process
203 was assumed for the infant formula emptying, as known for GE of calories-containing liquids (58). The
204 proposed GTT was adjusted to capture the absorption delay observed under the applied conditions in
205 adults (4). For a zero order GE process the GTT value represents the total gastric transit time. A similar
206 approach has been previously applied for scaling of paracetamol stomach transit from adults to infants
207 (19).

208

209 Paediatric PBPK model

210 Tissues and organ sizes were scaled to the relevant paediatric age with the PEAR™ physiology module
211 based on the age, body weight, and height of the population representative (52,53); where information
212 used for physiology generation is based on literature sources (52,59–61). Population representatives
213 for each paediatric age group, as reported in the study by Khalil *et al.* (27), were generated, i.e., 11-
214 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
215 scaling to paediatrics, V_{ss} was empirically increased for paediatric subjects below the age of 2.5 years
216 (0.20 L/kg) and children (0.15 L/kg) to match the greater volume of distribution reported in infants and
217 children (27,29,47). Based on adult clinical data, the Cytochrome P450 (CYP) and UDP-
218 glucuronosyltransferase (UGT) enzyme systems are mainly responsible for ibuprofen metabolism (33).
219 Clearance scaling to paediatrics was performed using a previously described routine using allometric
220 scaling taking into consideration age-dependent enzyme maturation (53,62,63) (Detailed description

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

229

230 *Oral absorption modeling in paediatrics*

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

248

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

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

256

257 The GI physiology scaling performed when paediatric physiologies are created using the PEAR™
258 module within GastroPlus™ accounts for changes in volume of GI organs, GI organ blood flows,
259 intestinal length, radius, and surface area, small intestinal transit time (SITT), fluid secretion volume.
260 Values describing the fasted GTT, gastric pH, intestinal pH, bile salt levels, solubility, and permeability
261 at the gut wall are considered unchanged with age in the modeling platform. For the simulation of drug
262 dosing under postprandial conditions, meal caloric content of 170 kcal was assumed for the 12-month-
263 old infant, 200 kcal for a 2-year-old population representative, 260 kcal were employed for the 6-year-
264 old, and a meal containing 340 kcal was used for 12-year-old child. The meal values were calculated
265 based on the average daily energy requirements for children assuming five meals consumed daily
266 (3,6,66). No maturation changes in GE motility were assumed under fasted and fed conditions as meal,
267 but not age, were found to be significant factors defining GE in a meta-analysis investigating of GE
268 times across paediatric age ranges (67).

269

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

278

$$279 \quad Ibuprofen \text{ } GTT_{paediatrics,meal} (h) = \frac{\text{Meal caloric content}_{paediatrics} (kcal) \times Ibuprofen \text{ } GTT_{adult,meal} (h)}{\text{Meal caloric content}_{adults} (kcal)}$$

280

Eq. 2

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

286

287 Model evaluation

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

293
$$AFE = 10^{\left(\frac{1}{n} \sum \log \left(\frac{PRED_i}{OBS_i}\right)\right)}$$
 Eq. 3

294
$$AAFE = 10^{\left(\frac{1}{n} \sum \left| \log \left(\frac{PRED_i}{OBS_i}\right) \right| \right)}$$
 Eq. 4

295

296 where n denoted the number of observed sampling points, PRED_i and OBS_i denoted the predicted
297 and observed plasma concentration, respectively, at the sampling time point i.

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

306

307 Parameter sensitivity analysis

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

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

324 Results

325 Adult model performance

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

341

342 Oral absorption modeling in adults

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

354

355 Simulations following ibuprofen suspension after the reference meal using default settings “user-
356 defined meal” with GTT 3.43 h and a 1st order GE process underpredicted the overall drug performance
357 (*AFE* 0.600) and resulted in inaccurate predictions (*AAFE* 1.882) (**Figure 3C**). Following adjustment of
358 the GTT value to 1.5 h, model performance was improved as shown in **Figure 3D** (*AAFE* 1.266). Under
359 infant-formula-fed conditions, the GTT default values of 1.92 h proposed in the “user-defined meal”
360 option employing a zero order GE process underpredicted the absorption delay, thus resulting in
361 overprediction of the observed early exposure and overprediction of the *C*_{max} (*FD* 1.40). Due to the
362 initial increase in plasma levels prior to the main plasma maximum increase, the *AFE* / *AAFE* metrics
363 could not accurately capture the suitability of the model settings to predict the overall model
364 performance (**Table SVI**, Supplementary Information). The adequacy of the predictions achieved with
365 the adjusted GTT value of 4.5 h was indicated by the *FD* close to unity, i.e. *FD*(AUC) 0.96 and *FD*(*C*_{max})
366 0.9, in addition to visual evaluation (**Figure 3F**).

367

368 Paediatric model performance

369 The simulated plasma concentration-time profiles after i.v. administration of 10 mg/kg ibuprofen for
370 two datasets are presented in **Figure 4**, while simulation evaluation is reported in **Table SVII**,
371 Supplementary Information. In the first study, ibuprofen was administered as an intravenous infusion
372 over 10 minutes to paediatric patients between 6 months and 16 years for fever reduction (27,65) and
373 simulated profiles fell well within the range of the individual observed plasma levels **Figure 4A**. In the
374 second dataset, ibuprofen was administered i.v. over 5 minutes as an analgesic treatment and only
375 one plasma sample was collected per paediatric subject (n = 36 paediatric subjects/samples, mean age
376 4.3 years (range 0.3 - 12.4 years), mean weight 20.5 kg (6 – 54 kg) (28). Simulations for the mean
377 population representatives slightly underpredicted high ibuprofen plasma concentrations at early
378 times, while the elimination phase was well captured **Figure 4B**. Although a certain discrepancy was
379 observed between the simulated and observed datapoints, great underlying variability could be
380 expected based on the wide age range in the observed data, based on observed variability in plasma
381 levels (up to 90 % at 4 h post-dose) in the dataset by Khalil *et al.* (**Figure 4A**), and mainly the availability
382 of only one sample per individual (**Figure 4B**). For the simulations, clearance as a function of age was
383 calculated for population representatives using allometric scaling and, for children younger than 6
384 years, a maturation factor based on the maturation of each ibuprofen metabolizing enzyme reported
385 for the paediatric age. Reported ibuprofen clearance values in different age groups were adequately
386 captured, as the predicted clearance values were within the reported range and were overall close to
387 the reported mean value (27) (**Table SVIII**, Supplementary Information). Due to the higher *V*_{ss} in

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

390

391 *Oral absorption modeling in paediatrics*

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

396

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

407

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

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

421

422 In the mixed infants-children population, the fasted state default settings employing an GTT value of
423 0.1 h overestimated early exposure as shown in **Figure 5A** and **Table SIX**, Supplementary Information.
424 Simulations performed with the adjusted GTT value of 0.5 h improved the overall predictions (**Figure**
425 **5B**), with *FD* for C_{max} and T_{max}, as well as *AFE* and *AAFE* values close to unity. Fed state conditions
426 and GTT for ibuprofen were firstly investigated using default parameters for infant meals of 170 kcal
427 (1-year-old), child meal of 260 kcal (6-year-old), and 340 kcal (12-year-old) employing 1st order GE
428 process to simulate GE of a solid-liquid meal, as in adults. Based on the individual profiles and the mean
429 simulated plasma concentration-time profile, software default settings led to a greater delay in drug
430 absorption compared to observed data (**Figure 5C**) and resulted in overall model inaccuracy
431 (*AAFE* 1.687), **Table SIX**, Supplementary Information. By employing the adjusted GTT value for the
432 solid-liquid meal, predictions were improved visually (**Figure 5D**) and regarding *FD* values and model
433 accuracy (*AAFE* 1.164), **Table III**. Finally, infant-formula-fed conditions were simulated using the meal
434 caloric content and zero order GE for the youngest population representative, i.e., 1-year-old infant,
435 to evaluate the effects regarding the mean profile of the whole paediatric mixed population. The
436 default software settings resulted in an overall underprediction of ibuprofen plasma levels (**Figure 5E**)
437 and inaccuracy (*AAFE* 1.621). The employment of the adjusted GTT value for the infant-formula-fed
438 conditions in combination with the refined fed conditions in children led to more accurate predictions
439 compared to the default settings (*AAFE* 1.244) and captured adequately the mean profile shape,
440 **Figure 5F**.

441

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

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

459

460 Parameter sensitivity analysis

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

472

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

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

489

490 Regarding physiological and anatomical parameters influencing ibuprofen absorption, GTT
491 prolongation led to delayed absorption with increased Tmax up to twofold compared to simulations
492 with the adjusted GTT 0.5 h, while peak concentrations were up to 30 % lower under fasted conditions
493 (**Figure S7**, Supplementary Information). Meal-dependent GTT increase resulted in prolonged times to
494 maximum ibuprofen levels and lowered Cmax values under fed conditions within the range of 70-
495 120 kcal, while higher caloric content of the meals resulted in changes within 10% range of the
496 baseline. Under infant-formula-fed conditions, different caloric contents of the meals led to changes
497 in Tmax with limited influence on Cmax (< 15%). Overall a greater absorption delay with prolonged
498 Tmax and lowered Cmax were observed for the same caloric contents when employing default settings
499 (**Figure S7**, Supplementary Information). Furthermore, Cmax values decrease and Tmax increase were
500 observed as SI radius increased in the population representatives. Finally, in line with the acidic nature
501 of the compound and its low solubility under acidic conditions, pH lowering in the absorption
502 compartments resulted in absorption delay (**Figure S7**, Supplementary Information). Duodenal pH
503 changes resulted in a Tmax delay that was one third slower than the baseline. Lowering the jejunal pH
504 resulted in greater Cmax reduction from baseline (20 %) compared to duodenal pH, while pH lowering
505 was less pronounced regarding Tmax in the rank order (most to least pronounced): fasted (GTT 0.5 h)
506 > fed > infant-formula-fed conditions (**Figure S7**, Supplementary Information). Differences in gastric
507 pH under all prandial conditions had limited impact on ibuprofen absorption in all paediatric
508 subpopulations. Lastly, small intestinal length, small intestinal transit time, and gastric volume had no
509 substantial impact on ibuprofen absorption across the paediatric populations regardless of the dosing
510 conditions investigated.

511 Discussion

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

529

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

541

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

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

563

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

572

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

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

590

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

611

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

638

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

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

650

651 [Concluding remarks](#)

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

678

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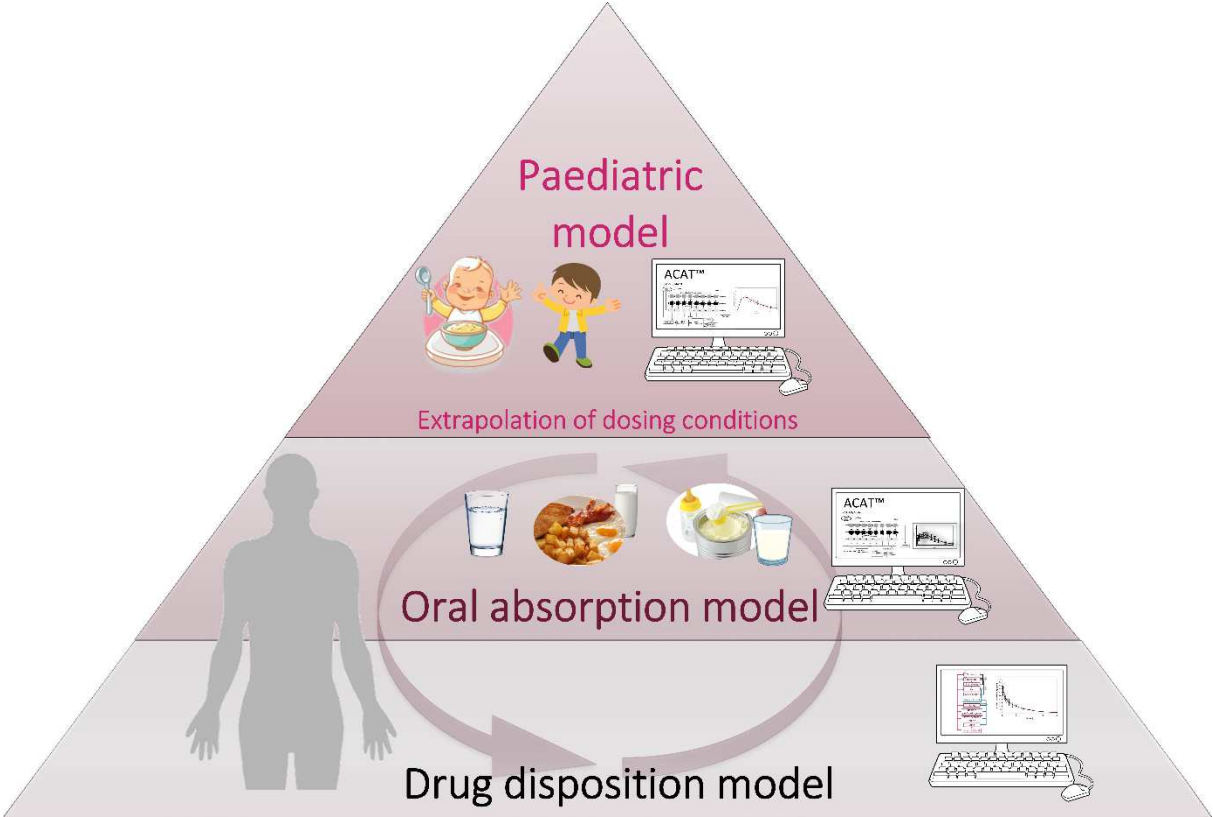
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887

Graphical abstract



List of Figures

Figure 1 Model development strategy for the evaluation of food effects in infants and children based on *in vivo* data in adults. Reproduced with permission from (19)

Figure 2 Simulation of ibuprofen plasma concentrations following i.v. administration in healthy adults. The disposition model was developed according to data observed at a high dose, 800 mg (A) (23). Model verification was performed with clinical data sets not used during model development at lower doses, i.e. 200 mg (B) and 400 mg (C) doses (25). Symbols and error bars denote observed mean data and standard deviation, while continuous lines represent the simulated plasma concentration-time profile.

Figure 3 Predicted plasma concentration-time profiles (purple lines) following oral administration of ibuprofen paediatric suspension under different dosing conditions fasted conditions employing default GTT value 0.1 h (A) and adjusted GTT value of 0.5 h according to *in vivo* observations (B); Reference meal fed conditions employing calorie-based software estimated GTT of 3.43 h (C) and adjusted GTT of 1.5 h according to *in vivo* observations (D) with first order GE; and infant formula fed conditions simulating infant dosing employing calorie-based software estimated GTT 2.03 (E). and adjusted GTT of 4.5 h (F) with zero order GE. Grey lines denote individual observed data and symbols and error bars denote mean observed plasma levels and the standard deviation [n=8 healthy male adult volunteers, (4)].

Figure 4 Simulation of ibuprofen plasma concentration-time profiles (purple lines) following i.v. administration of 10 mg/kg ibuprofen as a 10-minute infusion (27) (A) and 5-minute injection in paediatric population representatives (28) (B), with purple continuous lines 11-month-old population representative (group 6-24 months), purple dashed lines 3-year-old population representative (group 2-6 years), purple dotted lines 10-year-old population representative (group 6-16 years). Grey lines denote individual plasma concentration-time profiles (A), symbols denote individual plasma concentrations from the paediatric study with one sample collected per subject, i.e., circles (○) 3-24 months, (□) squares 2-6 years, triangles (Δ) 6-12 years (B).

Figure 5 Predicted plasma concentration-time profiles (lines) following oral administration of ibuprofen under different dosing conditions. Thin light blue continuous line (—) 12-month-old infant, blue dashed line (---) 6-year-old child, dark blue dotted line (···) 12-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 12 year-olds) and infant-formula-fed (12-month-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 12-year-olds) and infant-formula-fed conditions (12-

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

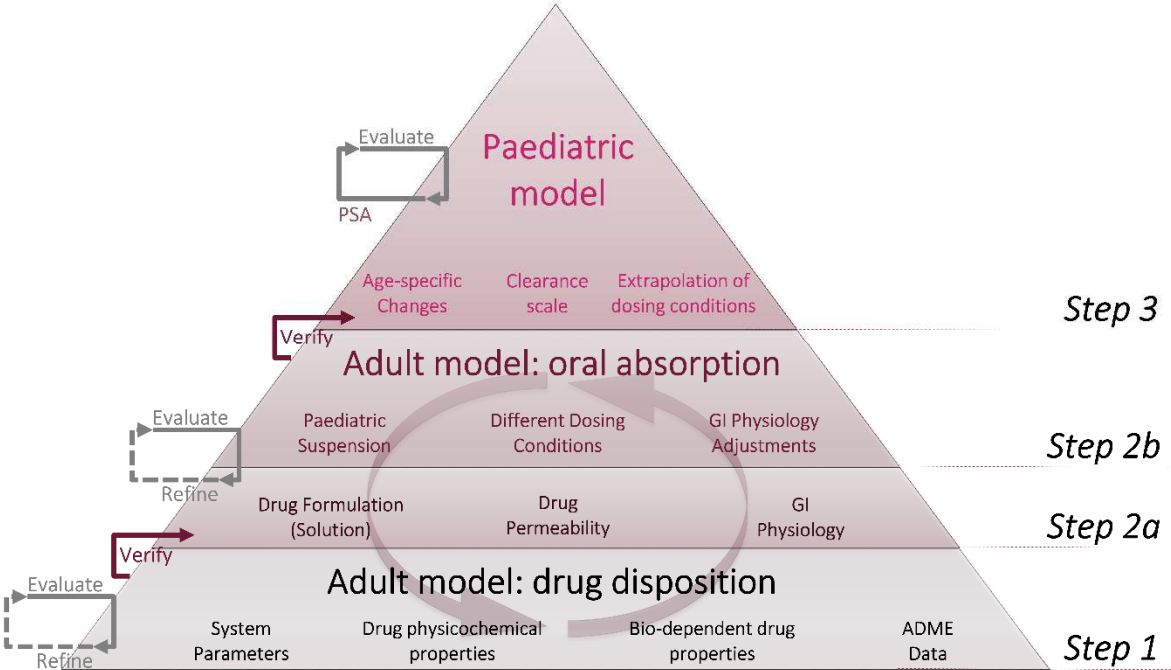


Figure 2

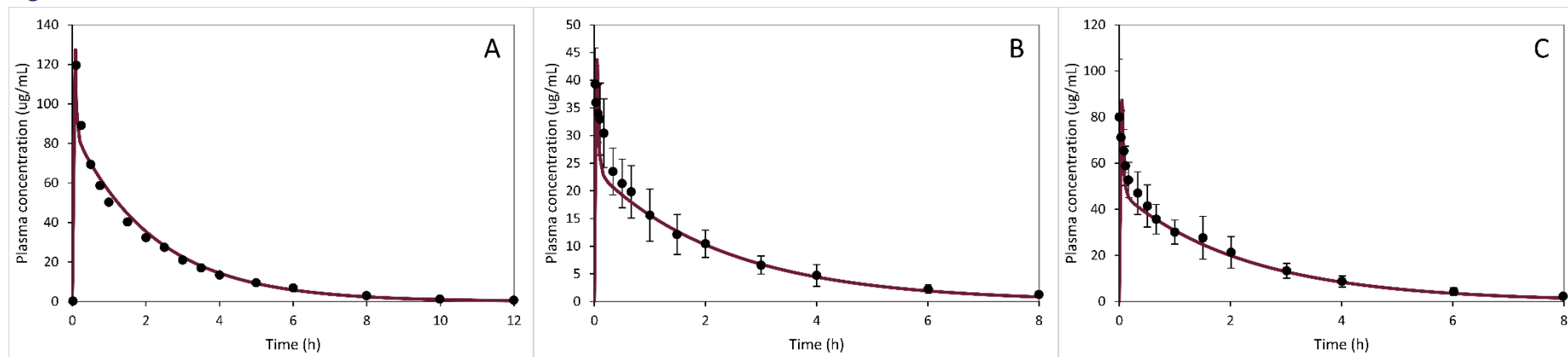


Figure 3

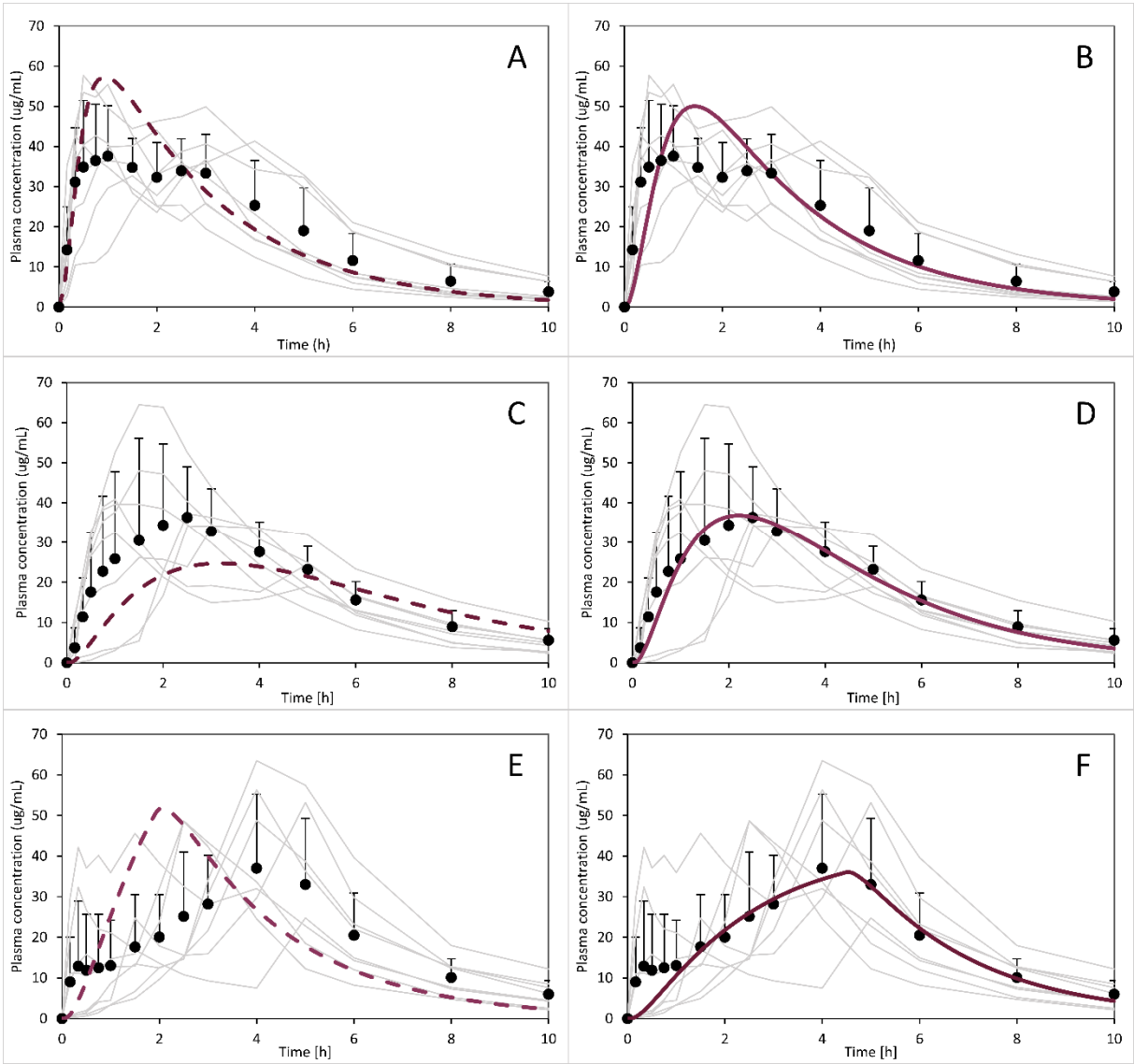


Figure 4

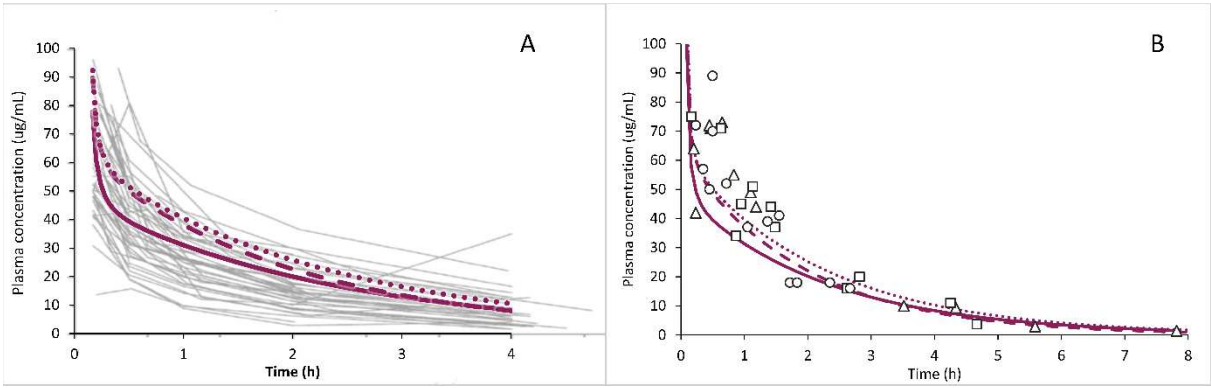


Figure 5

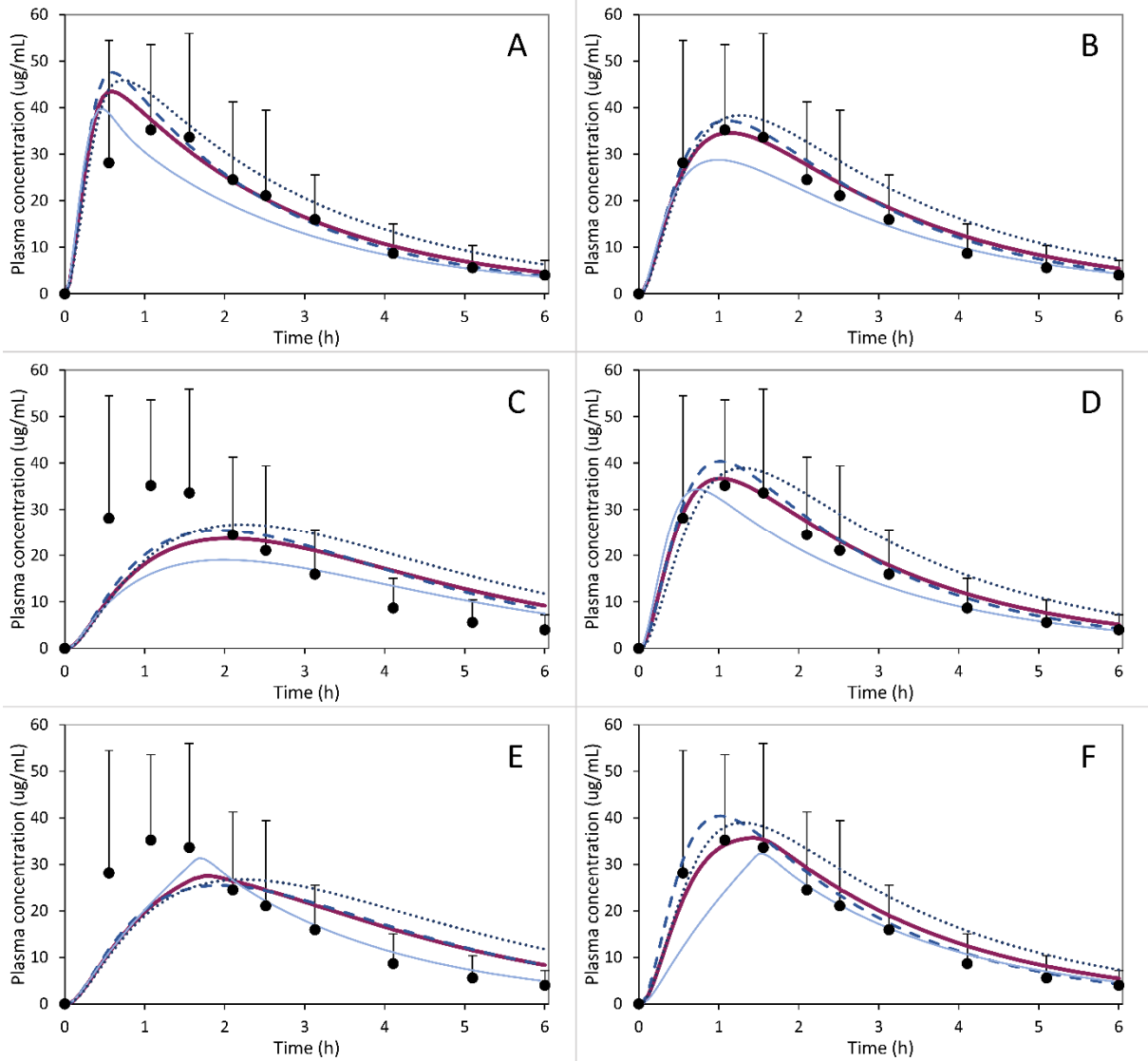


Figure 6

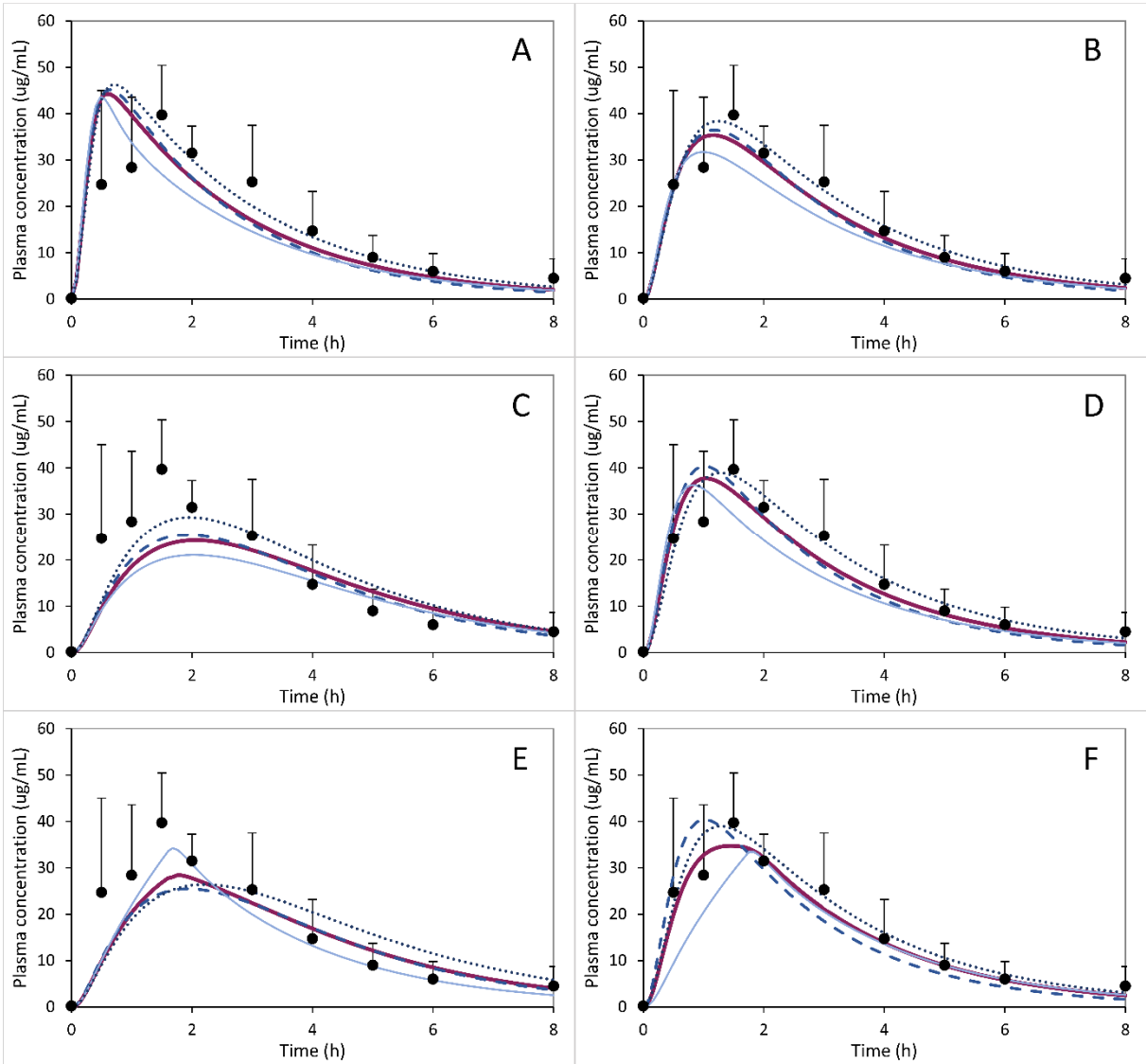


Table I Input parameters used to build the PBPK model for ibuprofen

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)		In house data
Level III FaSSGF	0.048	
Level II FaSSIF	1.953	
Level II FeSSIF-V2	2.290	
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)
V _{ss} (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 <i>et al.</i> (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 Stelova *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 Stelova 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 <i>et al.</i> 1992 (29)	AUC _{0-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 <i>et al.</i> 1989 (31)	AUC _{0-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 Stelova *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-t} (ug/mL·h)

^f Maximum plasma concentration Cmax (ug/mL)

^g Time to reach Cmax (h)