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## **An update on the use of allometric and other scaling methods to scale drug clearance in children: towards decision tables**

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### **Citation**

Rongen, A. van, Krekels, E. H. J., Calvier, E. A. M., Wildt, S. N. de, Vermeulen, A., & Knibbe, C. A. J. (2022). An update on the use of allometric and other scaling methods to scale drug clearance in children: towards decision tables. *Expert Opinion On Drug Metabolism & Toxicology*, 18(2), 99-113. doi:10.1080/17425255.2021.2027907

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To cite this article: Anne van Rongen, Elke HJ Krekels, Elisa AM Calvier, Saskia N de Wildt, An Vermeulen & Catherijne AJ Knibbe (2022) An Update on the Use of Allometric and Other Scaling Methods to Scale Drug Clearance in Children: Towards Decision Tables, Expert Opinion on Drug Metabolism & Toxicology, 18:2, 99-113, DOI: [10.1080/17425255.2021.2027907](https://doi.org/10.1080/17425255.2021.2027907)

To link to this article: <https://doi.org/10.1080/17425255.2021.2027907>



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REVIEW



## An Update on the Use of Allometric and Other Scaling Methods to Scale Drug Clearance in Children: Towards Decision Tables

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### ABSTRACT

**Introduction:** When pediatric data are not available for a drug, allometric and other methods are applied to scale drug clearance across the pediatric age-range from adult values. This is applied when designing first-in-child studies, but also for off-label drug prescription.

**Areas covered:** This review provides an overview of the systematic accuracy of allometric and other pediatric clearance scaling methods compared to gold-standard PBPK predictions. The findings are summarized in decision tables to provide *a priori* guidance on the selection of appropriate pediatric clearance scaling methods for both novel drugs for which no pediatric data are available and existing drugs in clinical practice.

**Expert opinion:** While allometric scaling principles are commonly used to scale pediatric clearance, there is no universal allometric exponent (i.e. 1, 0.75, or 0.67) that can accurately scale clearance for all drugs from adults to children of all ages. Therefore, pediatric scaling decision tables based on age, drug elimination route, binding plasma protein, fraction unbound, extraction ratio, and/or isoenzyme maturation are proposed to *a priori* select the appropriate (allometric) clearance scaling method, thereby reducing the need for full PBPK-based clearance predictions. Guidance on allometric scaling when estimating pediatric clearance values is provided as well.

### ARTICLE HISTORY

Received 6 October 2021  
Accepted 7 January 2022

### KEYWORDS



Allometric scaling; body size; clearance; decision tables; drug properties; maturation; physiologically-based pharmacokinetic; pediatric clearance scaling

## 1. Introduction


Drug clearance is an important driver of drug dosing in children [1]. Relative differences in drug clearance between populations can be used directly to establish dose differences required to achieve similar exposure. Aiming for similar exposure is appropriate in case a similar exposure-response relation of the drug of interest can be assumed and in case children have similar disease progression compared to adults [2]. Pediatric drug clearance scaling is applied in the design of first-in-child studies, but also in clinical practice for off-label or unlicensed drug prescription. When there are no pediatric pharmacokinetic (PK) data available for a specific drug, a variety of scaling methods with a wide range in complexity are available to scale drug clearance across the pediatric age-range based on adult values. The accuracy of clearance scaling methods depends on their ability to aggregate information on the impact of maturation in various physiological processes

underlying drug elimination in relation to drug properties of the drug of interest across ages.

Figures 1 and 2 illustrate how plasma clearance of, respectively, hepatically metabolized drugs and renally excreted drugs relate to drug-specific- and system-specific parameters. In children, system-specific parameters change non-linearly with age due to growth and maturation in various physiological processes, driving changes in plasma clearance across the pediatric age-range. The extent of the changes in drug clearance depends on drug properties as indicated in the overview below Figures 1 and 2. For hepatic clearance, important physiological parameters are hepatic blood flow ( $Q_h$ ), the unbound drug fraction in plasma ( $f_u$ ), the blood to plasma ratio (B:P), and the intrinsic hepatic metabolic clearance ( $CL_{int,h}$ ).  $Q_h$  is a system-specific parameter, while  $f_u$ , B:P, and  $CL_{int,h}$  are derived from both system-specific and drug-specific parameters (Figure 1). It is known that  $Q_h$  is limiting factor for the clearance of drugs with a high extraction ratio (ER), while  $CL_{int}$  and  $f_u$  are limiting factors for the clearance of drugs with a low ER.

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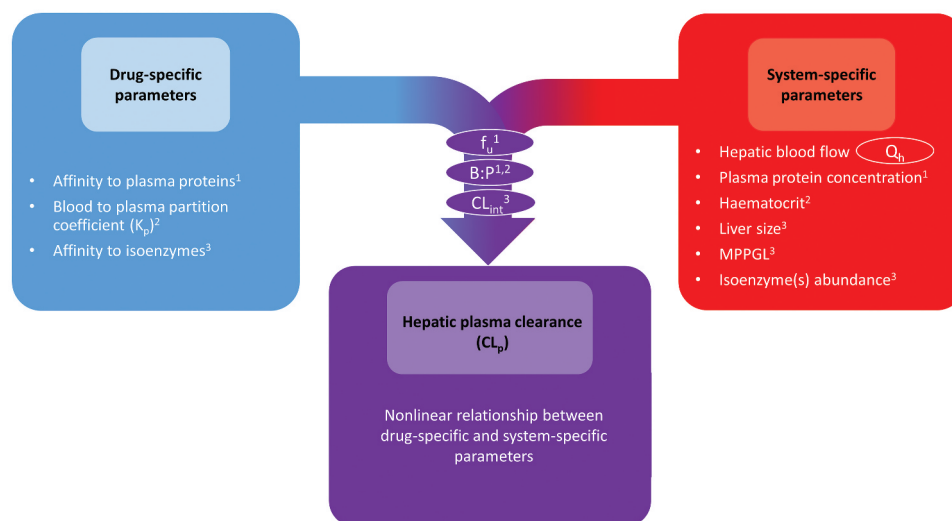
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### Article highlights

- We here propose pediatric scaling decision tables to provide *a priori* guidance on the use of linear bodyweight-based scaling (linearBW) and fixed allometric scaling with an exponent of 0.75 (AS0.75) or, when these two are both not systematically accurate, for age-dependent exponent (ADE) scaling, fixed allometric scaling with maturation function ( $AS0.75 \times MF_{PBPK}$ ), and between-drug extrapolation of pathway-specific pediatric covariate functions (BEPC).
- In children >5 years, both linearBW and AS0.75 can be used to scale clearance with slight differences in accuracy depending on age and drug properties, since scaled pediatric clearance values are hardly sensitive to the allometric exponent in this age-range.
- In children <5 years, additional information regarding drug properties (i.e. elimination route, binding plasma protein, fraction unbound, and/or extraction ratio) and age is required before it can be predicted which scaling method is most appropriate.
- By using the pediatric scaling decision tables, the need for full PBPK modelling to predict drug clearance in pediatrics is reduced for drugs or age-ranges for which accurate scaling can be achieved with allometric or other scaling methods.
- Future pediatric PK studies should focus on accurate clearance predictions throughout childhood instead of identifying an allometric exponent.

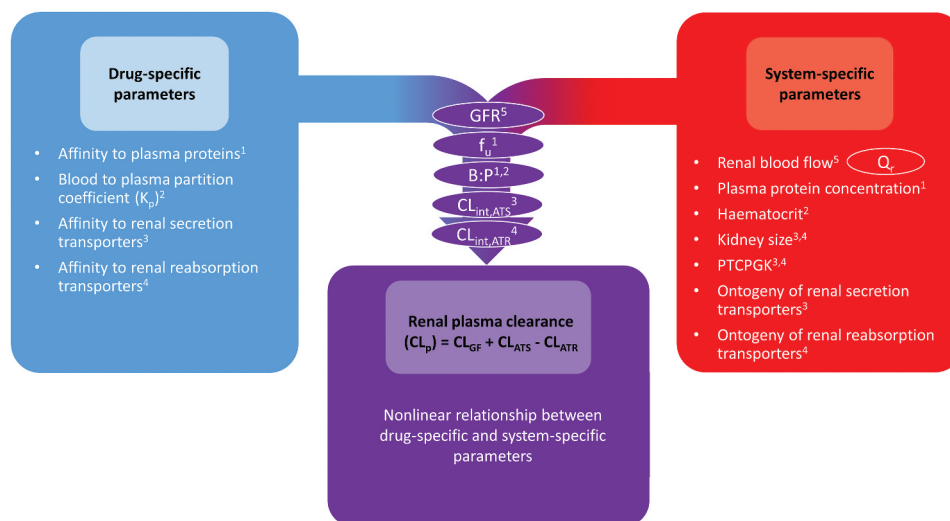
For renally cleared drugs, plasma clearance is impacted by glomerular filtration rate (GFR),  $f_u$ , B:P, and transporter-mediated intrinsic clearance for active tubular secretion ( $CL_{int,ATS}$ ) and/or reabsorption ( $CL_{int,ATR}$ ) (Figure 2).

Physiologically-based pharmacokinetic (PBPK) modeling can accurately integrate all of the above-mentioned information and is the most powerful tool to prospectively predict pediatric drug clearance values, as it accounts for the changes in pediatric physiology in relation to the drug properties across age [3–5]. Given the strong theoretical basis and extensive evidence of the predictive value of this method, PBPK-based simulations of pediatric clearance values can be considered the gold standard for pediatric drug scaling [3,6–12]. However, performing PBPK simulations requires not only time and skilled personnel, they also rely on the availability of data on a range of drug-specific properties which may not be available for all drugs. For these reasons, simplified scaling methods, of which allometric scaling is most commonly applied, are highly sought after [13].



**Figure 1.** Schematic representation of the relationship between drug-specific and system-specific parameters driving hepatic clearance. Parameters in circles are directly used in the physiologically-based hepatic clearance model (e.g. dispersion model). Parameters in circles in the purple arrow represent composite parameters that are derived from the system-specific parameters and the drug-specific parameters indicated by the numbers in superscripts. In children, all of the system-specific parameters change non-linearly with age. The impact of the parameters used in the physiologically-based hepatic clearance model on hepatic clearance is explained in the Table under this figure legend. The influence of transporters on hepatic clearance are not taken into account by the dispersion model. B:P = blood to plasma ratio;  $CL_{int}$  = intrinsic hepatic metabolic clearance; ER = extraction ratio,  $f_u$  = unbound drug fraction in plasma;  $K_p$  = blood to plasma partition coefficient; MPPGL = microsomal protein per gram of liver;  $Q_h$  = hepatic blood flow. Figure is reproduced from Calvier *et al.* [15].

PBPK parameter	Maturation and growth processes driving pediatric changes	Drug-specific impact of maturation and growth on hepatic drug clearance
$Q_h$	<ul style="list-style-type: none"> <li>• Cardiac output (CO)</li> <li>• Percentage of CO directed to liver</li> </ul>	Impact of changes on hepatic metabolic clearance of drugs increases with increasing ER in adults.
$CL_{int,h}$	<ul style="list-style-type: none"> <li>• Liver size</li> <li>• MPPGL</li> <li>• Isoenzyme abundance (specific pattern for each isoenzyme)</li> </ul>	Impact of changes on hepatic metabolic clearance of drugs decreases with increasing ER in adults.
$f_u$	<ul style="list-style-type: none"> <li>• Plasma protein abundance (specific pattern for each plasma protein)</li> </ul>	Impact of changes on hepatic metabolic clearance increases with increasing plasma protein binding in adults and decreases with increasing ER in adults.
B:P	<ul style="list-style-type: none"> <li>• Hematocrit</li> <li>• Plasma protein abundance (specific pattern for each plasma protein)</li> </ul>	Impact of changes on hepatic metabolism increases with increasing partitioning into red blood cells.



**Figure 2.** Schematic representation of the relationship between drug-specific and system-specific parameters driving renal clearance. Renal plasma clearance consists of clearance through glomerular filtration ( $CL_{GF}$ ) and active tubular secretion ( $CL_{ATS}$ ) minus active tubular reabsorption ( $CL_{ATR}$ ). Parameters in circles in the purple arrow represent composite parameters that are derived from the system-specific parameters and the drug-specific parameters indicated by the numbers in superscripts. In children, all of the system-specific parameters change non-linearly with age. The impact of the parameters used in the physiologically-based renal plasma clearance model on renal clearance is explained in the Table under this figure legend. In the physiologically based renal clearance model the influence of renal transporters ( $CL_{ATS}$  and  $CL_{ATR}$  on renal clearance are not taken into account. B:P = blood to plasma ratio;  $CL_{ATS}$  = clearance through active tubular secretion;  $CL_{ATR}$  = clearance through active tubular reabsorption;  $CL_{GF}$  = clearance through glomerular filtration;  $CL_{int,ATS}$  = active tubular secretion transporter-mediated intrinsic clearance;  $CL_{int,ATR}$  = active tubular reabsorption transporter-mediated intrinsic clearance;  $f_u$  = unbound drug fraction in plasma; GFR = glomerular filtration rate (\* note maturation in GFR is generally directly quantified in pediatric PBPK models and not included as a function of the underlying parameters  $Q_r$  and GF);  $K_p$  = blood to plasma partition coefficient; PTCPGK = proximal tubule cells per gram kidney;  $Q_r$  = renal blood flow.

PBPK Parameter	Maturation and growth processes driving pediatric changes	Drug-specific impact of maturation and growth on hepatic drug clearance
$Q_r$	<ul style="list-style-type: none"> <li>Cardiac output (CO)</li> <li>Percentage of CO directed to kidneys</li> </ul>	$Q_r$ impacts GFR and $CL_{ATS}$ no generalizable trends can be defined.
GFR*	<ul style="list-style-type: none"> <li><math>Q_r</math></li> <li>Glomerular function (GF)</li> </ul>	Impact of changes on renal elimination of drugs increases with increasing $f_u$ in adults.
$f_u$	<ul style="list-style-type: none"> <li>Plasma protein abundance (specific pattern for each plasma protein)</li> </ul>	Impact of changes on renal elimination of drugs decreases with increasing $f_u$ in adults.
B:P	Non-linear changes in: <ul style="list-style-type: none"> <li>Hematocrit</li> <li>Plasma protein abundance (specific pattern for each plasma protein)</li> </ul>	Impact of changes on renal elimination of drugs increases with increasing partitioning into red blood cells.
$CL_{int,ATS}$	<ul style="list-style-type: none"> <li>Kidney size</li> <li>PTCPGK</li> <li>Transporter abundance (specific pattern for each transporter)</li> </ul>	Impact of changes on renal secretion increases with increasing affinity for the transporter and with increasing $f_u$ in adults.
$CL_{int,ATR}$	<ul style="list-style-type: none"> <li>Kidney size</li> <li>PTCPGK</li> <li>Transporter abundance (specific pattern for each transporter)</li> </ul>	Impact of changes on renal secretion increases with increasing affinity for the transporter.

Allometry is the study of size and describes quantitative trends in biological variables *versus* bodyweight. Multiple allometric scaling methods are available, but in the context of prospectively scaling pediatric clearance values (i.e. in the absence of pediatric data), the most well-known methods include linear bodyweight-based scaling (linearBW), scaling with a fixed allometric exponent of 0.75 (AS0.75), and age-dependent exponent (ADE) scaling [14]. Other scaling methods relying on additional mechanistic information have also been developed, for example fixed allometric scaling in combination with hepatic enzyme maturation functions ( $AS0.75 \times MF_{PBPK}$ ) and between-drug extrapolation of pathway-specific pediatric

covariate functions (BEPC) [15,16]. Recently, the systematic accuracy of these methods compared to PBPK predictions has been established using the same PBPK simulation workflow [15–20]. However, the performances of these pediatric scaling methods have not been compared against each other in a systematic manner. The aim of this review is therefore to evaluate the use of allometric and other scaling methods to scale drug clearance in children. To this end, we first collate and summarize the predictive performance of the five pediatric scaling methods in decision tables to provide *a priori* guidance on the selection of these scaling methods focusing on linearBW and AS0.75. Then, the pediatric scaling decision tables and the different scaling

methods are discussed. In the last section we provide our opinion about allometric scaling for both prospective pediatric clearance scaling when no pediatric data are available and for estimation of pediatric clearance covariate relationships when analyzing pediatric data.

## 2. Pediatric clearance scaling methods

The scaling methods assessed in this work are presented below in order of increasing complexity or requirements of an increasing number of variables. The first three scaling methods (linearBW, AS0.75, and ADE) are empirical allometric methods that rely on bodyweight. AS0.75 $\times$ MF<sub>PBPK</sub> and BEPC also require knowledge on the elimination route responsible for clearance of the drug of interest and on maturation profiles for the relevant elimination route.

### 2.1. Linear bodyweight-based scaling (linearBW)

LinearBW, also known as isometric scaling, assumes a linear relationship between bodyweight (BW) and clearance (CL) according to equation 1, which represents an allometric equation with an exponent of 1:

$$CL_{pediatric} = CL_{adult} \cdot \frac{BW_{pediatric}}{BW_{adult}} \quad (1)$$

This scaling method is implicitly applied when the adult dose per kilogram bodyweight is directly used for pediatric dosing. The simplicity of this method is one of the reasons why it is commonly used for pediatric drug dosing.

### 2.2. Fixed allometric scaling with an exponent of 0.75 (AS0.75)

In describing the relationship between bodyweight and drug clearance, a bodyweight-based exponential equation with a fixed exponent of 0.75, as described in equation 2, is often proposed [21].

$$CL_{pediatric} = CL_{adult} \cdot \left( \frac{BW_{pediatric}}{BW_{adult}} \right)^{0.75} \quad (2)$$

Originally, a bodyweight-based equation with an exponent of 0.75 was used to describe inter-species differences in basal metabolic rate [22,23], even though also for this purpose this method is not without debate [24–29]. Later, it has been used to also describe the relationship between bodyweight and drug clearance within the human weight-range including children [30,31]. The application of this function in pharmacokinetics is currently applied both for inter-species scaling or to establish first-in-human doses from preclinical data, as well as for within-species scaling. Especially for adolescents there is agreement on the suitability of this approach for clearance scaling independent of drug properties [13,32,33].

### 2.3. Age-dependent exponent (ADE) scaling

From the principles of PBPK it can be deduced that there cannot be one single allometric exponent, be it 1, 0.75, or any other value, that leads to accurate pediatric clearance scaling for all drugs at all ages [16,17]. Age-dependent exponent scaling (ADE) acknowledges this and the relationship between bodyweight and drug clearance is described by an allometric equation in which the exponent is age-dependent. In equation 3, exponents (exp) of 1.1, 1.0, 0.9, or 0.75 are used for ages 0–3 months, 3 months–2 years, 2–5 years, and >5 years, respectively [14,34]:

$$CL_{pediatric} = CL_{adult} \cdot \left( \frac{BW_{pediatric}}{BW_{adult}} \right)^{exp} \quad (3)$$

### 2.4. Fixed allometric scaling with maturation function (AS0.75 $\times$ MF<sub>PBPK</sub>)

In this method, AS0.75 is claimed to account for the impact of size-related changes on drug clearance and this is multiplied by an age-based maturation function derived from a PBPK model (MF<sub>PBPK</sub>), to account for the impact of maturational changes that are not covered by changes in weight, as illustrated in equation 4 [16,35].

$$CL_{pediatric} = CL_{adult} \cdot \left( \frac{BW_{pediatric}}{BW_{adult}} \right)^{0.75} \cdot MF_{PBPK} \quad (4)$$

For drugs cleared through GFR, an empirical function for the MF<sub>PBPK</sub> has been proposed [36]. For hepatically cleared drugs, the MF<sub>PBPK</sub> is similar to isoenzyme-specific functions implemented in PBPK models that describe hepatic isoenzyme maturation as percentage of adult unbound intrinsic clearance per gram of liver. These functions account for maturation in both isoenzyme activity and in MPPGL.

### 2.5. Between-drug extrapolation of pathway-specific pediatric covariate functions (BEPC)

Between-drug extrapolation of pathway-specific pediatric covariate functions (BEPC) directly extrapolates the covariate relationship for plasma clearance obtained in a population pharmacokinetic model for one drug (the model drug), to clearance in the population PK model for another drug that is eliminated through the same pathway (the test drug) [15,37,38]. These covariate relationships can include empirical bodyweight-based equations and/or other equations based on size, age, or disease-related descriptors. This approach is based on similar principles as those applied when using a maturation function for GFR to establish dose adjustments for GFR cleared drugs [39,40].

**Table 1.** Decision table for pediatric scaling methods for renally cleared drugs through glomerular filtration (GF) and active tubular secretion (ATS) for typical children of different ages.

	1 day <sup>1</sup>	1 month <sup>1</sup>	6 months	1 year	2 years	5 years	15 years
GF of drugs binding to albumin	<i>If <math>f_{u,adults} &gt; 0.34</math></i> PBPK	LinearBW	AS0.75	<b>AS0.75</b>	<b>AS0.75</b>	<b>AS0.75</b>	AS0.75
	<i>If <math>f_{u,adults} \leq 0.34</math></i> LinearBW		<b>LinearBW</b>	LinearBW	LinearBW	LinearBW	LinearBW
GF of drugs binding to AAG	<i>If <math>f_{u,adults} &lt; 0.23</math></i> <i>OR <math>f_{u,adults} &gt; 0.78</math></i> PBPK	<i>If <math>f_{u,adults} \leq 0.45</math></i> AS0.75	<i>All <math>f_{u,adults}</math> values</i> AS0.75	<i>All <math>f_{u,adults}</math> values</i> <b>AS0.75</b>	<i>All <math>f_{u,adults}</math> values</i> <b>AS0.75</b>	<b>AS0.75</b>	AS0.75
	<i>If <math>f_{u,adults} 0.23-0.78</math></i> LinearBW	<i>If <math>f_{u,adults} \geq 0.34</math></i> LinearBW	<i>If <math>f_{u,adults} \geq 0.34</math></i> LinearBW	<i>If <math>f_{u,adults} \geq 0.34</math></i> LinearBW	<i>If <math>f_{u,adults} \geq 0.34</math></i> LinearBW	LinearBW	LinearBW
ATS	OCT2	OCT2					
	OAT1	OAT1	OAT1				
	OAT3	OAT3	OAT3	OAT3			
	Pgp	Pgp					

For GF results are split by plasma protein that the drug is binding to; albumin or AAG. When the table refers to two scaling options; **bold font indicates systematically most (reasonably) accurate scaling method**, regular font indicates systematically less accurate, but still (reasonably) accurate scaling option. Both scaling options with regular font indicates both scaling methods perform equally well. In some cases a scaling method can only be applied for drugs with specific properties (depicted in *italic font*).

For active tubular secretion (ATS); green color indicates scaling based on GF only is accurate and ATS does not need to be taken into account for accurate pediatric renal clearance scaling. Pink color indicates for which transporters, transporter maturation needs to be taken into account to achieve accurate scaling.

AAG =  $\alpha_1$ -acid glycoprotein; AS0.75 = fixed allometric scaling with an exponent of 0.75; ATS = active tubular secretion;  $f_{u,adults}$  = drug fraction unbound in adults; GF = glomerular filtration; linearBW = linear bodyweight-based scaling; OAT = organic anion transporter; OCT = organic cation transporter; PBPK = physiologically-based pharmacokinetic modeling; Pgp = P-glycoprotein

<sup>1</sup>The decision table applies to term neonates only.

### 3. Guidance for pediatric clearance scaling methods and decision tables

Recently, the various scaling methods were compared to PBPK predictions as gold standard [15–20]. In these studies, systematic accuracy was assessed by studying 20–84,000 hypothetical drugs with realistic ranges of drug properties (i.e. route of elimination, type of binding plasma protein, affinity to the plasma protein, blood to plasma partition coefficient, and the unbound intrinsic clearance value of one microgram of liver microsomes ( $CL_{int,mic}$ )). These drugs cover the entire hypothetical parameter space for small molecule drugs and as such systematic accuracy reflects accurate scaling for all current and future drugs. The scaling is considered to be systematically (reasonably) accurate when the prediction error (PE) between scaled and PBPK-predicted pediatric clearance is 50% or less for all drugs in the analysis. When a scaling method is not systematically (reasonably) accurate, it is still possible that scaling is accurate for some drugs with a particular subset of properties, but it will not be accurate for all drugs. The PBPK simulation workflow used in these analyses is described in Supplementary Material I.

To provide *a priori* guidance on the selection of appropriate pediatric clearance scaling methods, the results of the aforementioned studies are merged and summarized in a set of pediatric scaling decision tables (Tables 1–3). The original studies used the same PBPK simulation workflow, thereby enabling a fair comparison between scaling methods. Due to their ease of implementation, it was first assessed when linearBW and/or AS0.75 systematically yield (reasonably)

accurate pediatric clearance values. Only when this was not the case was it evaluated whether one of the three other scaling methods (ADE,  $AS0.75 \times MF_{PBPK}$ , and/or BEPC), are systematically (reasonably) accurate. The original figures and tables on which the decision tables are based can be found in Supplementary Material II.

For drugs that are fully renally excreted (Table 1), the required information to select the appropriate scaling method for pediatric drug clearance through GF, in addition to age, is:

- Drug binding plasma protein (i.e. exclusive binding to albumin or  $\alpha_1$ -acid glycoprotein (AAG) was tested)
- Fraction unbound of the drug in adults ( $f_{u,adults}$ )

For drugs fully eliminated by hepatic metabolism (Tables 2 and 3), the required information to select the appropriate scaling method for pediatric drug clearance, in addition to age, is:

- Drug binding plasma protein (i.e. albumin or AAG was tested)
- Extraction ratio in adults ( $ER_{adults}$ )
- Isoenzyme responsible for metabolism and maturation of this isoenzyme for the pediatric age

Since the values of ER and  $f_u$  are first available in adults and change with age in children, we took the values of ER and  $f_u$  in adults ( $ER_{adults}$  and  $f_{u,adults}$ ) for the purpose of selecting scaling methods. Isoenzyme maturation for each age is parameterized as percentage of adult abundance and Table 4 provides an overview of enzyme maturation for the most common drug metabolizing

**Table 2.** Decision table for pediatric scaling methods for hepatically cleared drugs binding to *albumin* for typical children of different ages.

	1 day <sup>1,2,3</sup>	1 month <sup>1,3</sup>	6 months	1 year	2 years	5 years	15 years
100% enzyme maturation	AS0.75 <sup>2</sup>	<b>AS0.75</b>	AS0.75	AS0.75	<b>AS0.75</b>	<b>AS0.75</b>	AS0.75
	LinearBW <sup>2,4</sup>	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
Highest % enzyme maturation <sup>5</sup>	AS0.75 <sup>3</sup>	<b>AS0.75<sup>3</sup></b>	<b>AS0.75</b>	<b>AS0.75</b>	<b>AS0.75</b>	<b>AS0.75</b>	AS0.75
	LinearBW <sup>3,4</sup>	LinearBW <sup>3</sup>	LinearBW	LinearBW <sup>4</sup>	LinearBW <sup>4</sup>	LinearBW <sup>4</sup>	LinearBW
Lowest % enzyme maturation <sup>5</sup>	<i>If low + IM ER<sub>adults</sub></i> AS0.75×MF <sub>PBPK</sub>	<i>If low + IM ER<sub>adults</sub></i> AS0.75×MF <sub>PBPK</sub>	<i>If low + IM ER<sub>adults</sub></i> AS0.75×MF <sub>PBPK</sub>	<i>If low + IM ER<sub>adults</sub></i> AS0.75×MF <sub>PBPK</sub>	LinearBW <sup>7</sup>	AS0.75 <sup>7</sup>	AS0.75
			BEPC <sup>6</sup>	BEPC <sup>6</sup>			
	<i>If high ER<sub>adults</sub></i> PBPK	<i>If high ER<sub>adults</sub></i> PBPK	<i>If high ER<sub>adults</sub></i> PBPK	<i>If high ER<sub>adults</sub></i> PBPK			<b>LinearBW<sup>7</sup></b>

AS0.75 and linearBW are considered first, only when these scaling methods are not accurate, other methods are considered.

Results are split by enzyme maturation (100% of adult values, highest and lowest reported enzyme maturation value for each age according to Table 4). When the table refers to two scaling options; **bold font indicates systematically most (reasonably) accurate scaling method**, regular font indicates systematically less accurate, but still (reasonably) accurate scaling option. Both scaling options with regular font indicates both scaling methods perform equally well. In some cases a scaling method can only be applied for drugs with specific properties (depicted in *italic font*).

AS0.75 = fixed allometric scaling with an exponent of 0.75; BEPC = between-drug extrapolation of pathway-specific pediatric covariate functions [15]; ER<sub>adults</sub> = extraction ratio in adults; IM = intermediate; linearBW = linear bodyweight-based scaling; MF<sub>PBPK</sub> = maturation function obtained from PBPK model expressing isoenzyme maturation as percentage of adult values of isoenzyme abundance according to Table 4; PBPK = physiologically-based pharmacokinetic modeling

<sup>1</sup>The decision table applies to term neonates only.

<sup>2</sup>For term neonates of 1 day 100% enzyme maturation is only applicable to SULT1A1, other enzyme maturation values are low (see Table 4), therefore for 1 day old neonates mostly the lowest % enzyme maturation is applicable.

<sup>3</sup>For term neonates of 1 day and 1 month; no isoenzymes with an isoenzyme activity higher than 100% (SULT1A1) exist, so highest enzyme maturation is equal to 100% enzyme maturation.

<sup>4</sup>For drugs with low ER ( $\leq 0.3$ ) few drugs have a PE that is slightly higher than 50% (max 60%).

<sup>5</sup>The lowest and highest values for every age are: 10% and 100% at 1 day and 1 month, 21% and 122% at 6 months, 13% and 153% at 1 year, 18% and 159% at 2 years, 32% and 152% at 5 years, and 79% and 125% at 15 years (see Table 4 for reference).

<sup>6</sup>BEPC is possible from model drugs with low ER to drugs with low and intermediate (0.3–0.7) ER. And for model drugs with intermediate ER to test drugs with low and intermediate ER.

<sup>7</sup>Exception for drugs mainly metabolized by UGT2B7; for 2-5-year-old children the same scaling methods as 1 year should be used (AS0.75×MF<sub>PBPK</sub>, BEPC or PBPK), because of very low UGT2B7 enzyme maturation at these ages.

isoenzymes at various ages that were used in the original PBPK simulation workflow [17]. As maturation patterns for different drug metabolizing enzymes drive clearance changes across the pediatric age-range, scaling accuracy for drugs eliminated by hepatic metabolism is provided for drugs metabolized by mature isoenzymes (100% of adult value) and the extremes of isoenzyme maturation values, i.e. the lowest and highest % enzyme maturation compared to adult value for every age (Tables 2 and 3). When for some isoenzymes in the very young, extremely low or absent enzyme activity is reported, a lower cutoff of 10% was used to account for the fact that in these cases other elimination routes generally take over (Table 4).

For renally cleared drugs undergoing active tubular secretion, accurate system-specific information needed to inform PBPK models is scarce, limiting the reliability of the gold standard PBPK predictions. As a result, for drugs that are substrate for renal transporters, pediatric scaling accuracy against PBPK predictions was not used to systematically assess these drugs, and instead PBPK models using maturation functions derived from limited data on the OCT2, OAT1, OAT3, and P-gp transporters were used to assess in what cases active tubular secretion can be ignored without yielding unacceptable prediction bias for pediatric drug clearance [20]. Table 1 summarizes these results by showing for which ages scaling based on GF alone results in (reasonably) accurate clearance predictions for all drugs, meaning transporter maturation can

be ignored, and in which cases transporter maturation cannot be ignored. Maturation functions for other active renal transporters have not been published, but various hypothetical scenarios have been evaluated. For detailed information related to this, we refer to the work of Cristea *et al.* [20].

Generally, without information on drug properties, clearance can be (reasonably) accurately scaled from adults to children of 5 years and older using linearBW and AS0.75 (Tables 1–3). In some cases, these methods can even be used for younger ages, however, for children under 5 years of age, additional information regarding elimination route of the drug, binding plasma protein, ER<sub>adults</sub>, f<sub>u,adults</sub>, and/or isoenzyme maturation is required to select the appropriate scaling methods. For instance, for drugs undergoing GF, linearBW and AS0.75 can be used as scaling method from adults to infants of 6 months, except for drugs binding to AAG for children for 2 years and younger for which the applicability of linearBW is dependent on the value of f<sub>u,adults</sub> (see Table 1). For drugs undergoing hepatic metabolism, binding to AAG and metabolism by an isoenzyme with the highest maturation, AS0.75 can be used in children below 2 years for drugs with high or intermediate ER<sub>adults</sub> (Table 3). However, for drugs with low ER<sub>adults</sub>, AS0.75×MF<sub>PBPK</sub> or BEPC are required in children below 2 years. The decision tables show that in case none of these methods lead to accurate predictions, PBPK-based clearance predictions are required to scale drug clearance in pediatrics.

Table 3. Decision table for pediatric scaling methods for hepatically cleared drugs binding  $\alpha_1$ -acid glycoprotein for typical children of different ages.

	1 day <sup>1,2,3</sup>	1 month <sup>1,3</sup>	6 months	1 year	2 years	5 years	15 years
100% enzyme maturation	PBPK <sup>2</sup>	If high + IM $ER_{adults}$ AS0.75	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
		If low $ER_{adults}$					
		AS0.75×MF <sub>PBPK</sub>					
		BEPC					
Highest % enzyme maturation <sup>5</sup>	PBPK <sup>3</sup>	If high + IM $ER_{adults}$ AS0.75 <sup>3</sup>	If high + IM $ER_{adults}$ AS0.75	If high + IM $ER_{adults}$ AS0.75	If high + IM $ER_{adults}$ AS0.75	AS0.75	AS0.75
		If low $ER_{adults}$					
		AS0.75×MF <sub>PBPK</sub> <sup>3</sup>					
		BEPC <sup>3</sup>					
Lowest % enzyme maturation <sup>5</sup>	PBPK	If low + IM $ER_{adults}$ AS0.75×MF <sub>PBPK</sub>	If low + IM $ER_{adults}$ AS0.75×MF <sub>PBPK</sub>	If low + IM $ER_{adults}$ AS0.75×MF <sub>PBPK</sub>	AS0.75 <sup>6</sup>	AS0.75 <sup>6</sup>	AS0.75
		If high $ER_{adults}$ PBPK					
		If high $ER_{adults}$ PBPK					
		LinearBW <sup>6</sup>					

AS0.75 and linearBW are considered first, only when these scaling methods are not accurate, other methods are considered.

Results are split by enzyme maturation (100% of adult values, highest and lowest reported enzyme maturation value for each age according to Table 4). When the table refers to two scaling options; **bold font indicates systemically most (reasonably) accurate scaling method**, regular font indicates systemically less accurate, but still (reasonably) accurate scaling option. Both scaling options with regular font indicates both scaling methods perform equally well. In some cases a scaling method can only be applied for drugs with specific properties (depicted in *italic font*).

AS0.75 = fixed allometric scaling with an exponent of 0.75; BEPC = between-drug extrapolation of pathway-specific pediatric covariate functions [15];  $ER_{adults}$  = extraction ratio in adults; IM = intermediate; linearBW = linear bodyweight-based scaling; MF<sub>PBPK</sub> = maturation function obtained from PBPK model expressing isoenzyme maturation as percentage of adult values of isoenzyme abundance according to Table 4; PBPK = physiologically-based pharmacokinetic modelling

<sup>1</sup>The decision table applies to term neonates only.

<sup>2</sup>For term neonates of 1 day 100% enzyme maturation is only applicable to SULT1A1, other enzyme maturation values are low (see Table 4), therefore for 1 day old neonates mostly the lowest % enzyme maturation is applicable. <sup>3</sup>For term neonates of 1 day and 1 month; no isoenzymes with an isoenzyme activity higher than 100% (SULT1A1) exist, so highest enzyme maturation is equal to 100% enzyme maturation.

<sup>4</sup>For drugs with low  $ER$  ( $\leq 0.3$ ) few drugs have a PE that is slightly higher than 50% (max 60%).

<sup>5</sup>The lowest and highest values for every age are: 10% and 100% at 1 day and 1 month, 21% and 122% at 6 months, 13% and 153% at 1 year, 18% and 159% at 2 years, 32% and 152% at 5 years, and 79% and 125% at 15 years (see Table 4 for reference).

<sup>6</sup>Exception for drugs mainly metabolized by UGT2B7; for 2-5-year-old children the same scaling methods as 1 year should be used (AS0.75×MF<sub>PBPK</sub> or PBPK), because of very low UGT2B7 enzyme maturation at these ages.

**Table 4.** Published hepatic isoenzyme maturation values, expressed as percentage of adult values, for each pediatric age. In the PBPK simulation workflow, these values were taken to represent unbound intrinsic clearance per gram of liver, accounting for maturation in both isoenzyme activity and in MPPGL.

	1 day	1 month	6 months	1 year	2 years	5 years	15 years	Reference
CYP1A2	0.022	3	25	47	70	90	98	[10]
CYP1A2	5	20	29	35	NA	NA	100	[45]
CYP1A2	27	41	122	153	159	152	123	[46]
CYP2B6	0.22	6	30	46	65	85	98	[10]
CYP2C8	39	88	99	100	101	101	102	[10]
CYP2C9	39	94	101	102	103	103	103	[10]
CYP2C18_19	23	30	52	66	80	95	103	[10]
CYP2D6	6	49	88	95	100	103	104	[10]
CYP2E1	11	26	41	49	57	71	90	[10]
CYP2E1	21	40	46	100	100*	100*	100	[45]
CYP3A4	20	50	110	130	130	NA	100	[45]
CYP3A4	10	NA	43	54	72	101	100	[11]
CYP3A4_5	2	29	64	76	85	92	97	[10]
UGT2B7	8	9	11	13	18	32	79	Simcyp
UGT1A6	10	16	36	50	NA	NA	100	[45]
SULT1A1	100	100	100	100	100	100	100	[47]

Numbers within cells corresponds to the value of enzyme maturation, expressed as percentage of adult isoenzyme abundance. NA was used when no data on enzyme maturation for the corresponding age and isoenzyme were reported. \* Indicates replacement of missing enzyme maturation values (NA) by 100% when reported values in younger and older children were equal to 100%. CYP = cytochrome P450; SULT = sulfotransferase; UGT = UDP-glucuronosyltransferase.

Table is adapted from Calvier *et al.* [15,17].

#### 4. Discussion

By unraveling for each age and elimination route the minimum amount of information required for selecting an accurate scaling method of clearance from adults to children of various ages, the pediatric scaling decision tables aid in determining when the use of simple scaling methods is justifiable over full PBPK modeling. Balancing simplicity and generalizability, the focus was on keeping the tables as simple as possible. The use of allometric and other scaling methods as alternative to PBPK methods through these tables may reduce resources required to select the initial dose for first-in-child trials and can be used as a structured approach to pediatric dose selection [41]. Additionally, these scaling methods can be used to optimize informative sampling times based on the scaled clearance [42,43]. Finally, as for off-label or unlicensed drug prescription in children, most dosing guidelines, even in neonates and infants, are still based on linear extrapolation combined with expert consensus, the use of our decision tables for clearance and dose scaling may provide more robust support for these dosing guidelines for researchers, pharmacists, pediatricians, the developers of (national) Children's Formularies and regulators.

The decision tables show that above the age of 5 years, both linearBW and AS0.75 perform well. An explanation for this finding is that in these ages scaled pediatric clearance values based on allometric principles are not sensitive to the allometric exponent that is used [17,44]. In these older children and adolescents, physiological differences compared to adults are not that extensive. In adolescents, AS0.75 for clearance scaling is widely accepted, even by regulatory agencies, while support for linearBW in this population is emerging as well [32,33,44]. Tables 2 and 3 show that for young children, 100% enzyme maturation is a requirement for the applicability of AS0.75 for hepatically cleared drugs, which was also reported by other investigators [11,45–52], but as can be seen in Table 4, a large number of isoenzymes take up to

5 years or more to reach maturity [53,54]. LinearBW, on the other hand, can lead to underprediction when enzyme maturation is close to adult values, which was also described by other investigators [18,55–57]. Especially for neonates, infants and children under 2 years of age and for drugs with certain drug properties, linearBW scaling can lead to underprediction with prediction errors of more than 50% [18]. Although linearBW and AS0.75 may yield accurate predictions for some drugs for ages below 5 years, the impact of physiological changes in this young pediatric population may impact drugs with different properties differently. Therefore, absence of systematic accuracy implies that it cannot be known *a priori* whether scaling will be accurate for a particular drug without knowledge regarding drug properties and/or enzyme maturation. The same holds true for ADE, which was found to be generally less accurate than  $AS0.75 \times MF_{PBPK}$  in the young [16]. Although ADE acknowledges that different exponents may be used at different ages, no distinction is made between drugs with different properties.

An important drug-specific parameter to select the appropriate pediatric clearance scaling method is the type of plasma protein to which a drug binds. Especially in the first days of life, the difference in maturation of abundance between albumin and AAG is large and a steep maturation of AAG abundance in the first days of life leads to a wide variation in clearance predictions for drugs binding to AAG with different affinities. This limits the systematic accuracy of scaling methods for hepatically cleared drugs binding to AAG in neonates of 1 day.

For hepatically metabolized drugs, an important parameter to select the appropriate pediatric clearance scaling method is the level of enzyme maturation. Differences in maturation patterns of isoenzymes in the very young lead to a wide variation in clearance maturation between drugs, and therefore scaling methods accounting for the maturation of the isoenzyme or pathway of interest, like  $AS0.75 \times MF_{PBPK}$  or BEPC, are generally most suitable for pediatric clearance

scaling in younger ages. This particularly applies to drugs with a low and intermediate  $ER_{adults}$ , since for these drugs isoenzyme maturation is one of the main determinants for changes in clearance. Here, it is emphasized that the ER of drugs will decrease with decreasing  $CL_{int,hr}$ , meaning that a drug that has a high ER in adults may have an intermediate or low ER in children when enzyme maturation is low [58,59]. As such in young children, changes in clearance of drugs that have a high ER in adults, will not solely reflect changes in hepatic blood flow, like it would in adults, but also reflect isoenzyme maturation [16]. This ultimately leads to an increasingly wide variation in clearance maturation of these drugs [16]. As this shift in the contribution of hepatic blood flow to clearance maturation is not taken into account by  $AS0.75 \times MF_{PBPK}$  and BEPC, PBPK modeling is required for clearance scaling of drugs with a high  $ER_{adults}$  for children below 1 year. For  $AS0.75 \times MF_{PBPK}$  it is of great importance to pay attention to the maturation function that is being used. The reported results are based on functions taken from PBPK models that account for isoenzyme maturation per gram of liver, accounting for maturation in both isoenzyme abundance and in MPPGL. Isoenzyme maturation per microgram microsomes does not take MPPGL maturation into account and should be avoided as the use of this parameter was found to lead to considerable scaling bias [16].

The extrapolation potential of pediatric covariate functions, and as such the applicability of BEPC, is found to be restricted by the degree of similarity between the model drug (for which the covariate function was developed) and test drug (to which the covariate function is extrapolated), regarding  $f_u$ , ER, the type of plasma protein the drug binds to, and the fraction of the model and test drug metabolized by the specified isoenzyme [15]. The reason for this dependence is that pediatric covariate functions describing maturation in plasma clearance describe the net influence of all underlying physiological changes on drug clearance, aggregating information on system-specific and drug-specific properties. This finding contradicts the often implicitly made assumption that clearance maturation for substrates of the same isoenzyme is drug independent and highlights the importance of maturation processes other than isoenzyme maturation on pediatric clearance scaling [60,61]. Detailed information on the applicability of BEPC can be found in the original publication of Calvier *et al.* [15], but as a rule of thumb BEPC is mostly applicable in children of 6 months and older, for drugs with a low or intermediate ER in adults that are mainly metabolized by a single isoenzyme and that bind to albumin [15].

In addition to this theoretical assessment, Brussee *et al.* indeed showed that a pediatric covariate function for midazolam clearance (a CYP3A substrate) could accurately scale pediatric clearance for 6 out of 8 CYP3A substrates that were theoretically expected to scale accurately [62]. Moreover, BEPC was found to yield accurate scaling in children younger than 3 years for morphine (model drug) and zidovudine (test drug), both predominantly metabolized by UGT2B7 [37]. According to the report of Calvier *et al.*, BEPC for these drugs was not systematically accurate in children below 5 years of age [15].

This illustrates that absence of systematic accuracy does not mean that accuracy cannot be obtained for a single specific drug within a specific category, only that the accuracy cannot be established *a priori*.

The decision tables were developed using PBPK-based predictions for typical individuals and they may not apply to pediatric sub-populations such as preterm neonates, obese or undernourished children, critically-ill children, or children with diseases or comedication that impact drug disposition [63–67]. Due to deviating maturation patterns in preterm neonates compared to term neonates, drug clearance cannot simply be scaled from term neonates to preterm neonates. For obese children, the relationship between clearance and total bodyweight are likely to differ from children with normal weight [68,69]. Moreover, for some situations in which clearance maturation is impacted by disease or drug effects, physiological parameters and/or demographic values that drive drug clearance can be altered. For instance, plasma protein binding can be reduced due to uremia and hypoalbuminemia, which can significantly alter clearance of drugs with high plasma protein binding and low ER or drugs undergoing glomerular filtration [70–72]. Also, in some other complex cases, for example with drug–drug interactions or in children with different diseases compared to adults, PBPK remains the preferred tool for clearance scaling compared to the other (allometric) scaling approaches [67].

Also with respect to drug properties, limitations apply. Due to a lack of available information, drugs that are substrates for hepatic or renal transporters [73], drugs binding to lipoproteins or drugs with saturable plasma protein binding were not considered in the work underlying the decision tables [15–18]. In addition, only drugs that are fully renally- or fully hepatically cleared and drugs exclusively binding to albumin or exclusively binding to AAG were investigated. Further investigations are therefore needed for classes of drugs eliminated by both elimination routes or binding to both albumin and AAG. In addition, scaling accuracy of drugs eliminated by multiple hepatic isoenzymes or drugs with known shifts in dominant metabolizing isoenzymes (e.g. paracetamol of which metabolism is shifting from mainly sulfation in neonates to glucuronidation in older children or CYP3A substrates with shifting contributions from the CYP3A4/5 isoenzymes to CYP3A7 in early life) need further investigation [54,74,75].

## 5. Conclusion

From this review, it can be concluded that the accuracy of allometric and other pediatric clearance scaling methods is dependent on drug properties and the age of interest. For children above 5 years of age, both linearBW and  $AS0.75$  scaling can be used for accurate scaling, with slight differences in accuracy depending on age and drug properties. In children below 5 years of age, additional information regarding age and drug properties (elimination pathway, binding plasma protein,  $f_{u,adults}$ ,  $ER_{adults}$ ) is required before the

appropriate scaling method can be selected. Use of the pediatric scaling decision tables that uses all of this information may provide *a priori* guidance on the selection of appropriate clearance scaling methods both for designing first-in-child studies and for off-label or unlicensed drug prescription in clinical practice, thereby reducing the need for full PBPK-based clearance predictions. While there are some gaps yet on drugs eliminated via multiple pathways or transporters, these decision tables can be used by pharmacists, pediatricians, developers of (national) Children's Formularies, researchers, and regulators as support for dosing guidelines for new and existing drugs.

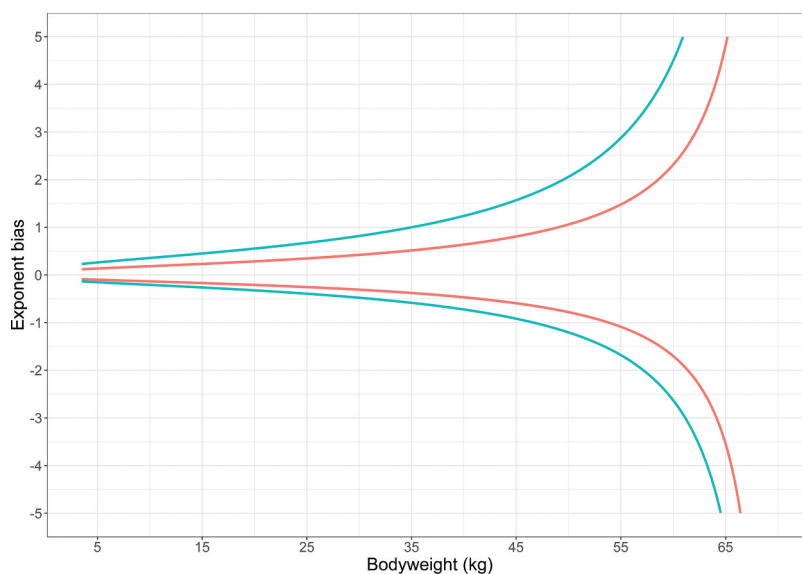
## 6. Expert opinion

### 6.1. The future of allometric scaling

The most common method for clearance scaling in the pediatric age-range is allometric scaling, assuming a linear or exponential relationship between bodyweight and clearance [76]. Clearance scaling is sometimes also performed using body surface area (BSA), particularly in oncology, however, as BSA cannot be directly measured and has to be derived from bodyweight, length, and sex, it is more complicated and error prone than bodyweight-based scaling [76]. Age is also an intuitive descriptor of maturation that is highly correlated with bodyweight in children. However, population PK analyses regularly show that bodyweight shows a stronger correlation than BSA or age in describing inter-individual differences in clearance between pediatric patients [77,78]. Allometric scaling principles can be used both for prospective pediatric clearance scaling in absence of pediatric data and for the development of pediatric covariate relationships in population pharmacokinetic data analyses of (sparse) pediatric datasets. In this section, we discuss both topics separately.

#### 6.1.1. Allometric scaling for prospective pediatric clearance scaling

When allometric scaling is applied for scaling of clearance, the value of the allometric exponent is often topic of debate. Exponents of 1, 0.75, or 0.67 are most commonly used, while in the very young values higher than 1 are advocated to account for the rapid increase in clearance [34,48,79,80]. LinearBW, i.e. with an allometric exponent of 1, is often applied for reasons of simplicity. A value of 0.67 ( $2/3$ ) for the allometric exponent is said to yield a function between bodyweight and clearance that is similar to a linear function between BSA and clearance [81]. Although evidence that (pediatric) drug clearance scales linearly with BSA is lacking, dosing based on BSA is common practice in some clinical areas. Proponents of AS0.75 claim that there is a sound theoretical basis for an exponent of 0.75 [30,31,57]. AS0.75 would only account for changes in size, and the bias in scaled pediatric clearance values resulting from AS0.75 in the younger age-ranges is subsequently attributed to maturation, which is where AS0.75 with an estimated maturation function finds its origin [30,31,82]. PBPK-based simulations, however, dispute this, as simulations which only include size-related changes (i.e. changes in liver weight, hepatic blood flow, and GFR) without including maturation in abundance of isoenzymes, plasma proteins, and in hematocrit (i.e.  $CL_{int}$ ,  $f_u$ , and B:P being 100% of the adult value), show that AS0.75 can lead to very large errors (up to 278%) in scaled clearance values in children younger than 6 months of age [17]. Nevertheless, the European Medicines Agency (EMA) recommends AS0.75 for clearance scaling for all pediatric ages for all drugs, albeit with the use of empirically age-based maturation function for younger aged children derived from pediatric data instead of a PBPK-based maturation function ( $MF_{PBPK}$ ) that we use in our decision tables [83].



**Figure 3.** Bias in allometric exponent (estimated allometric exponent compared to 'true' PBPK exponent) leading to  $\pm 30\%$  (red) or to  $\pm 50\%$  (green) clearance prediction error (CL PE) versus bodyweight. The clearance is scaled from adult values and a median adult bodyweight of 70 kg. The figure shows that with increasing bodyweight, increasing exponent bias will lead to similar PE in clearance. Figure is taken from Calvier *et al.* [85].

The above findings break through the beliefs and misconceptions about a universal allometric exponent to scale clearance for all drugs from adults to children of all ages [16,17,84]. In children of 5 years and older, almost all allometric exponents will result in (reasonably) accurate scaling predictions, as scaled pediatric clearance values are not sensitive to the allometric exponent [17,44,85]. This is illustrated in Figure 3 in which the bias in the estimated allometric exponent compared to the 'true' (PBPK-based) exponent *versus* bodyweight leading to 30% or 50% prediction error in clearance is displayed for scenarios where clearance is scaled from adult values. This figure shows that for older children of higher bodyweights, the bias in the allometric exponent can be much higher than for younger children while still reaching the same clearance prediction error [85]. Comparable conclusions were published by Sinha *et al.* reporting that the prediction error of clearance prediction when various false values of the exponents are chosen result in a larger impact in young children compared to older children [86]. As such, below the age of 5 years, when maturation in underlying physiological processes is becoming increasingly relevant, it is impossible to define a single empirical function based on bodyweight alone to scale pediatric clearance, because the changes in the various physiological processes impact drugs with different properties differently [16].

### 6.1.2. Allometric exponent for estimating pediatric covariate relationships for clearance

When pediatric concentration-time data are available for a drug, pharmacokinetic parameters can be estimated for children, preferably using the population approach allowing for optimal statistical power [87]. Also in the context of data-analysis, concepts of allometric scaling are often applied and the debate on the allometric exponent is still ongoing [31,44,88]. In population pharmacokinetics analyses, investigators may either adhere to a data-driven systematic covariate analyses or to an approach based on the theory of AS0.75. A data-driven analysis uses formal statistical tests to select the most predictive covariates in estimated covariate relationships that are supported by the data. Using an approach based on AS0.75, clearance is *a priori* assumed to change with bodyweight in an exponential relationship with an exponent of 0.75 without formal assessments of statistical significance. In case this does not yield an adequate fit, an additional maturation function based on age is estimated [30,89]. However, this maturation function cannot be compared to maturation functions of an isoenzyme ( $MF_{PBPK}$ ), but should rather be considered a mathematical residue of variability that is remaining after inclusion of the correlated covariate bodyweight and/or as a correction factor for the bias introduced by this function in case the true exponent is different from 0.75. Strougo *et al.* indeed showed that maturation functions estimated with this method also represent changes in size-related physiological processes (i.e. liver blood flow), that they may be dependent on drug properties (i.e. ER and lipophilicity) and that they do not only represent ontogeny

of enzyme activity [35,54]. Likewise, Mahmood illustrated that these maturation functions correct for bias introduced by the *a priori* inclusion of an allometric equation with an exponent of 0.75 [90]. Moreover, it has been shown that unless the true underlying covariate relationships are included, a data-driven systematic covariate modeling approach yields the best fit of data when highly correlated covariates are assessed [91]. In addition to the findings of the PBPK-based analyses described in this paper, a large number of studies refute the theoretical basis of AS0.75 for its applicability to scale clearance between and within species (including in children) either through observational data or through theoretical arguments [24–29,53,92–95]. Based on these considerations, a data-driven systematic covariate analysis should in general be preferred over AS0.75 in pediatric pharmacokinetic modeling (i.e. 'let the data speak' as stated in Fisher *et al.* [44]).

Arguments against a data-driven systematic covariate analysis have been put forward as well. Recently, Germovsek *et al.* compared published models for midazolam (a CYP3A substrate with intermediate  $ER_{adults}$  and low  $f_{u,adults}$ ) and gentamicin (a renally excreted drug with high  $f_{u,adults}$ ), with fitted models for these two drugs based on AS0.75 with an estimated PMA-based sigmoidal maturation function [82]. They concluded that no model was statistically better than the fitted models, based on which they propose to use this method as a standardized approach for modeling clearance in children, which is in line with suggestions of other investigators [31,96,97]. However, case examples of a limited number of drugs cannot be used as general proof for the applicability of the underlying theoretical basis. Another argument that is used is that there is insufficient power in pediatric datasets to estimate the exponent in a data-driven systematic covariate analysis. By way of contrast, investigators using AS0.75 with an estimated age-based maturation function are also estimating one or more model parameter(s) from the data introducing a similar or sometimes even higher degree of freedom in the fit compared to directly estimating an exponent for the allometric function. Higher degrees of freedom will improve the descriptive properties of the model, as illustrated by Germovsek *et al.*, but may also have a negative impact on the power to estimate each parameter from the data.

It should also be kept in mind that obtaining the value of an allometric exponent in pediatric population is not an aim in itself and that focus should rather be on the accuracy of the clearance estimation throughout childhood. As the allometric function may not always be sensitive to the estimated exponent (see Figure 3), clearance functions with different exponents may not deviate much from one another, particularly in older children. In this regard, Sinha *et al.* showed that when simulations are based on AS0.75 and a deviating allometric exponent is re-estimated, the resulting bias in clearance prediction is negligible in children older than 3 years [86]. Moreover, these authors showed that 20 children and adults are sufficient for an unbiased estimation of the allometric exponent with a study power of more than 80% [86]. As such, estimated allometric exponent values should not be

misinterpreted as incorrect or biased, nor should it erroneously be claimed that the confidence interval of the estimated allometric exponent estimate should always include 0.75 [30]. As derived from previous PBPK modeling work, 'true' allometric exponents accounting for both size- and age-related changes can range from 0.57 to 2.07 for drugs undergoing hepatic metabolism, and vary with age and drug properties [16]. A similar range in the allometric exponents has been reported in population PK data analyses [48,50,95,98]. As an alternative to the estimation of a single exponent for a certain population, more flexible functions could also be used in model development using bodyweight only [48–50,80]. For example, the bodyweight-dependent exponent (BDE) model, in which the allometric exponent changes in a sigmoidal fashion with bodyweight, is taking the rapid physiological changes in young children into account by using a higher exponent, while leveling off to adult values in the older ages [48,80].

Irrespective of whether AS0.75 or data-driven systematic covariate analysis is chosen, when a model is developed based on pediatric PK data that is used for predictive purposes, model validation is imperative. Particularly in the youngest age ranges this requires additional attention as due to the heterogeneity of this special population, the scarcity of datasets, variation in drug administration and variable sampling times, additional diagnostic and validation tools are required (i.e. Goodness-of-Fit, ETA (random effects), and CWRES (conditional weighted residuals) plots that are stratified for weight or age or NPDE (normalized prediction distribution errors)) [99]. Moreover, as population modeling is an empirical data analysis approach, caution with respect to extrapolations to other age groups will always be required.

In conclusion, for pediatric drug clearance the mechanistic value of allometric functions is proven to be limited, however for descriptive purposes they have pragmatic merit. The pediatric scaling decision tables can now be used to identify scenarios for which these functions are systematically accurate for predicting pediatric drug clearance, reducing the need for full PBPK modeling. In those cases, confirmatory PK data through sparse sampling could be sufficient and reduce costs and burden for participating children [13]. In the case of adolescents, PK studies do not even have to be performed as there is sufficient evidence on the predictive value of allometric scaling from adults to this pediatric subpopulation [32]. In addition to investigating scenarios, future efforts should also focus on improving the general acceptance of these tables for pharmacists, pediatricians, developers of (national) Children's Formularies, researchers, and regulators so that this knowledge can be routinely used for pediatric pharmacology both in drug development and in the clinic.

## Funding

The author(s) reported there is no funding associated with the work featured in this article.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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