2. Decision tables from van Rongen et al., 2022

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[1]	1 month[1]	6 months	1 year	2 years	5 years	15 years
GF of drugs binding to albumin	*If $f_{u,adults}$ > 0.34* PBPK	LinearBW	AS0.75	**AS0.75**	**AS0.75**	**AS0.75**	AS0.75
	If $f_{u,adults}$ ≤0.34 LinearBW		**LinearBW**	LinearBW	LinearBW	LinearBW	LinearBW
GF of drugs binding to AAG	*If $f_{u,adults}$ < 0.23 OR $f_{u,adults}$ > 0.78* PBPK	*If $f_{u,adults}$ ≤0.45* AS0.75	*All $f_{u,adults}$ values* AS0.75	*All $f_{u,adults}$ values* **AS0.75**	*All $f_{u,adults}$ values* **AS0.75**	**AS0.75**	AS0.75
	If $f_{u,adults}$ 0.23-0.78 LinearBW	*If $f_{u,adults}$ ≥ 0.34* LinearBW	*If $f_{u,adults}$ ≥ 0.34* LinearBW	*If $f_{u,adults}$ ≥ 0.34* LinearBW	*If $f_{u,adults}$ ≥ 0.34* 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 = α_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

[1]The decision table applies to term neonates only.

Figure 2A. Reprinted from van Rongen et al., 2022; *Expert opinion on drug metabolism & toxicology*; https://doi.org/10.1080/17425255.2021.2027907

2. Decision tables from van Rongen et al., 2022

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

	1 day [1,2,3]	1 month [1,3]	6 months	1 year	2 years	5 years	15 years
100% enzyme maturation	AS0.75[2]	**AS0.75**	AS0.75	AS0.75	**AS0.75**	**AS0.75**	AS0.75
	LinearBW[2,4]	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
Highest % enzyme maturation[5]	AS0.75[3]	**AS0.75[3]**	**AS0.75**	**AS0.75**	**AS0.75**	**AS0.75**	AS0.75
	LinearBW[3,4]	LinearBW[3]	LinearBW	LinearBW[4]	LinearBW[4]	LinearBW[4]	LinearBW
Lowest % enzyme maturation[5]	*If low + IM* ER_{adults} AS0.75×MF_{PBPK}	*If low + IM* ER_{adults} AS0.75×MF_{PBPK}	*If low + IM* ER_{adults} AS0.75×MF_{PBPK} BEPC[6]	*If low + IM* ER_{adults} AS0.75×MF_{PBPK} BEPC[6]	LinearBW[7]	AS0.75[7]	AS0.75
	If high ER_{adults} PBPK	*If high* ER_{adults} PBPK	*If high* ER_{adults} PBPK	*If high* ER_{adults} PBPK		**LinearBW[7]**	LinearBW

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_{adults} = extraction ratio in adults; IM = intermediate; linearBW = linear bodyweight-based scaling; MF_{PBPK} = 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

[1]The decision table applies to term neonates only.

[2]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.

[3]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.

[4]For drugs with low ER (≤ 0.3) few drugs have a PE% that is slightly higher than 50% (max 60%).

[5]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).

[6]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.

[7]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_{PBPK}, BEPC or PBPK), because of very low UBT2B7 enzyme maturation at these ages.

Figure 2B. Reprinted from van Rongen et al., 2022; *Expert opinion on drug metabolism & toxicology*; https://doi.org/10.1080/17425255.2021.2027907

2. Decision tables from van Rongen et al., 2022

Table 3. Decision table for pediatric scaling methods for hepatically cleared drugs binding *α_1-acid glycoprotein* for typical children of different ages.

	1 day[1,2,3]	1 month[1,3]	6 months	1 year	2 years	5 years	15 years
100% enzyme maturation	PBPK[2]	*If high + IM ER_{adults}* AS0.75	AS0.75	AS0.75	**AS0.75**	**AS0.75**	AS0.75
		If low ER_{adults}			LinearBW[4]	LinearBW	LinearBW
		AS0.75×MF_{PBPK}					
		BEPC					
Highest % enzyme maturation[5]	PBPK[3]	*If high + IM ER_{adults}* AS0.75[3]	*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}	*If low ER_{adults}*	*If low ER_{adults}*	*If low ER_{adults}*		LinearBW
		AS0.75×MF_{PBPK}[3]	AS0.75×MF_{PBPK}	AS0.75×MF_{PBPK}	AS0.75×MF_{PBPK}		
		BEPC[3]	BEPC	BEPC	BEPC		
Lowest % enzyme maturation[5]	PBPK	*If low + IM ER_{adults}* AS0.75×MF_{PBPK}	*If low + IM ER_{adults}* AS0.75×MF_{PBPK}	*If low + IM ER_{adults}* AS0.75×MF_{PBPK}	LinearBW[6]	**AS0.75[6]**	AS0.75
		If high ER_{adults} PBPK	*If high ER_{adults}* PBPK	*If high ER_{adults}* PBPK		LinearBW[6]	LinearBW

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_{adults} = extraction ratio in adults; IM = intermediate; linearBW = linear bodyweight-based scaling; MF_{PBPK} = 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

[1]The decision table applies to term neonates only.

[2]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.[3] 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.

[4]For drugs with low ER (≤ 0.3) few drugs have a PE% that is slightly higher than 50% (max 60%).

[5]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).

[6]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_{PBPK} or PBPK), because of very low UBT2B7 enzyme maturation at these ages.

Figure 2C. Reprinted from van Rongen et al., 2022; *Expert opinion on drug metabolism & toxicology*; https://doi.org/10.1080/17425255.2021.2027907