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Preclinical PK Cheatsheet

Species physiology, IVIVE values, PBPK starter kit, allometric scaling, permeability. Researched, modern, free.

CONTENTS

1. Species physiology

Reference physiological parameters for the 5 most-used preclinical species. Davies & Morris 1993 is the canonical source; modern updates and discrepancies are flagged inline.

Body weight

kg

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
0.02	0.25	10	4 ⚠	70

Reference adult body weight per species. Used to convert per-kg-normalised parameters back to absolute values for PBPK and dose calculations.

⚠ **Monkey (cyno):** Cynomolgus modern lab cohorts cluster 2.5-4 kg (Mandikian 2018, Iwama 2014). Davies & Morris 1993's 5 kg is rhesus-leaning historical default.

Source: Davies B 1993

Cardiac output

L/h/kg

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
24 ⚠	17.8	7.2	13	4.8 ⚠

Total blood pumped per unit body weight per hour. Sets the upper bound on perfusion-limited clearance.

Lidocaine: High-extraction; CL approaches cardiac output

⚠ **Mouse:** Modern conscious-mouse measurements (Janssen 2002) give 14-20 L/h/kg; Davies & Morris value disputed.

⚠ **Human:** Davies & Morris basal value (5.6 L/min for 70 kg). Brown 1997 / ICRP 89 give ~5.2 L/h/kg (~87 mL/min/kg) for moderate activity; rises to ~9-12 L/h/kg under exercise.

Source: Davies B 1993

Liver blood flow (total)

mL/min/kg

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
90	55.2	30.9	43.6	20.7

Sum of hepatic artery + portal vein flow. Sets the upper bound on hepatic clearance for high-extraction drugs ($CL_h \leq Q_h$).

Propranolol: High-extraction; hepatic CL ≈ liver blood flow in human

Source: Davies B 1993

Kidney blood flow

mL/min/kg

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
65	36.8	21.6	27.6	17.7

Both kidneys, total. Upper bound on renal clearance for high-extraction renally cleared drugs.

PAH (para-aminohippurate): PAH clears clinically via near-complete renal extraction. It directly measures renal plasma flow (~600 mL/min in human); renal blood flow is back-calculated as RBF = RPF / (1 – Hct) ≈ 1100-1200 mL/min.

Source: Davies B 1993

Glomerular filtration rate

mL/min/kg

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
14	5.24	6.13	2.08 ⚠	1.79

Plasma volume filtered per minute per kg. Drugs with $CL_{renal} \approx \mathrm{GFR} \cdot fu_p$ are filtered without secretion. $CL_{renal} > \mathrm{GFR} \cdot fu_p$ implies tubular secretion.

Inulin: Used clinically to measure GFR; cleared exclusively by filtration

⚠ **Monkey (cyno):** Davies & Morris (likely rhesus) 2.08; Iwama 2014 cynomolgus iodixanol 3.06 (47% higher)

Source: Davies B 1993

Bile flow

mL/h/kg

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
4.17	3.75	0.5	1.04	0.21 ⚠

Hepatic biliary excretion route. Drugs eliminated via bile rely on this flow rate plus active transport.

Indocyanine green: Cleared almost exclusively in bile; used to assess hepatic function

⚠ **Human:** Davies & Morris basal value (~14.7 mL/h, ~350 mL/day). Stimulated post-prandial flow reaches 0.5-0.7 mL/h/kg (~600-1000 mL/day); use the higher value when modelling fed-state biliary clearance.

Source: Davies B 1993

Total body water

% body weight

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
73	67	60	69	60

Intracellular + extracellular + plasma water. Drugs distributing into total body water (e.g., antipyrine) have $V_d \approx$ this value.

Antipyrine: $V_d \approx$ total body water; classical probe drug

Source: Davies B 1993

Plasma volume

mL/kg

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
50	31	52	45	43

Sets the lower bound for V_d. Drugs that bind tightly to albumin sit a few-fold above plasma volume because albumin is also present in interstitial fluid, not because the drug enters cells. The simple $V_d \approx \mathrm{PV}/fu_p$ estimate overpredicts in this regime.

Warfarin: $V_d \approx 0.14$ L/kg, small but ~3× plasma volume because albumin is also extravascular (PV/fu_p would predict ~8.6 L/kg).

Source: Davies B 1993

Blood volume

mL/kg

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
79	64 ⚠	86	65 ⚠	74

Total blood (plasma + erythrocytes). Used for B/P ratio scaling and PBPK initialization.

⚠ **Rat:** Direct measurements give 48 mL/kg (~25% lower)

⚠ **Monkey (cyno):** Direct cynomolgus measurements give 47.7 mL/kg

Source: Diehl K-H 2001

2. IVIVE scaling values

The conversion factors that turn in vitro intrinsic clearance into a whole-organism prediction. Critical fact-check: Davies & Morris 1993 does NOT contain MPPGL values; the canonical 32 mg/g human value comes from Barter 2007. Human HPGL is genuinely disputed (99 vs 120 vs 139), flagged inline.

MPPGL (microsomal protein per gram liver)

mg/g liver

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
45	45	55 ⚠	49	32 ⚠

Conversion factor that scales in vitro liver microsomal CL_{int} (µL/min/mg protein) up to in vivo CL_h via the well-stirred model. Without this, microsomal data cannot become a clearance prediction.

⚠ **Dog (beagle):** Smith 2008 reports notably higher (~77 mg/g); 55 is the Houston-Galetin compendium consensus.
⚠ **Human:** Modern consensus (Barter 2007 weighted mean, n>50 livers); historical 45 mg/g came from Houston 1994 rat data misapplied to humans. Declines with age (~40 at 30y → ~31 at 60y).

Source: Barter ZE 2007

HPGL (hepatocellularity per gram liver)

×10⁶ cells/g liver

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
120 ⚠	120	215 ⚠	120	99 ⚠

Scales in vitro hepatocyte CL_{int} (µL/min/10⁶ cells) up to in vivo. Hepatocyte assays preserve more of the metabolic machinery than microsomes (UGTs, conjugations, transporters), so HPGL-based IVIVE is preferred for non-CYP-dominated drugs.

⚠ **Mouse:** Sohlenius-Sternbeck 2006 reports ~135; 120 is a software-default rounding.
⚠ **Dog (beagle):** Sohlenius-Sternbeck 2006 protein-ratio method = 215 ± 45; Smith 2008 ~215; Houston-Galetin compendium ~168; some software defaults to 120-130 but primary measurements consistently support the higher value.
⚠ **Human:** Genuinely disputed: 99 (Barter 2007 weighted direct counts) vs 120 (round-number default) vs 139 (Sohlenius-Sternbeck protein-ratio back-calc). Modal Simcyp/GastroPlus default = 99.

Source: Barter ZE 2007

Liver weight

% body weight

MOUSE	RAT	DOG (BEAGLE)	MONKEY (CYNO)	HUMAN
5.5	3.6	3.29	2.5 ⚠	2.57

Combined with MPPGL or HPGL, gives mg microsomal protein per kg body weight (or 10⁶ cells/kg) — the final scaling factor for IVIVE.

⚠ **Monkey (cyno):** Brown 1997 covers rhesus only (~2.16%); cynomolgus literature reports 2.5-3.0%.

Source: Brown RP 1997

Well-stirred model

$$CL_h = \frac{Q_h \cdot fu_b \cdot CL'_{int}}{Q_h + fu_b \cdot CL'_{int}}$$

where $CL'_{int} = CL_{int} \cdot \mathrm{MPPGL} \cdot W_{liver}$. For $B/P \approx 1$, $fu_p \approx fu_b$; for high-B/P drugs (cyclosporine, tacrolimus, sirolimus) convert: $fu_b = fu_p/(B/P)$.

3. PBPK starter kit

Tissue volumes (% body weight)

Tissue	Mouse	Rat	Dog (beagle)	Monkey (cyno)	Human
Skeletal muscle Adult human male; elderly populations 25-30%, lean athletes up to 50%	38.4	40.4	45.7	40	40
Adipose tissue Single most BMI-variable tissue; always document body composition assumption	7	7.6	15	6.5	21.4 ⚠
Liver	5.5	3.6	3.29	2.5 ⚠	2.57
Kidney	1.67	0.73	0.55	0.48	0.44
Heart	0.5	0.33	0.78	0.27	0.47
Lung	0.73	0.5	0.94	0.53	0.76
Brain	1.65	0.57	0.8	1.5	2
Skin (dermis) Human is dermis only (~3.7%); subcutaneous fat is counted in the adipose row. If you need a "whole-skin" parameter (e.g., topical PBPK), use ~16% (dermis 3.7% + subcutaneous ~12%). Rodent/dog/monkey values follow Brown 1997's broader skin definition and already include subcutaneous — do not double-count adipose for those species.	16.5	19	9.1	8	3.7 ⚠
Bone (skeleton) "Skeleton" (incl. marrow) ~14%; "bone mineral" alone ~5%	10.7	7.3	8.8	6	14.3
GI tract Wall only; if including lumen contents, +2-4% in fed state	4.2	2.7	4.6	4	1.7
Spleen	0.35	0.2	0.27	0.25	0.26

⚠ **Adipose tissue, Human:** Brown 1997 reference adult male; ICRP 89 gives 18% (M)/27% (F); modern PBPK uses 18% lean, 30-45% obese

⚠ **Liver, Monkey (cyno):** Brown 1997 covers rhesus (~2.16%); cynomolgus literature reports 2.5-3.0%.

⚠ **Skin (dermis), Human:** Dermis-only convention (ICRP 89 ~4.5%; Brown 1997 dermis 3.71%). Brown 1997's broader "skin" of 11.1% includes hypodermis/subcutaneous, which double-counts vs the separate adipose row above.

fu_p ladder (human)

Verified human fu_p values from Obach 2008 + Lombardo 2018. Method-dependent for highly-bound drugs ($fu_p < 0.01$).

Very high (> 0.9): Gabapentin (1) – Negligible PPB; Atenolol (0.94); Metformin (0.99)

High (0.5 – 0.9): Caffeine (0.65); Theophylline (0.6); Antipyrine (0.95) – Free-distribution probe drug; minimal binding

Moderate ($0.10 \leq fu_p < 0.50$): Phenobarbital (0.45) – Reported 0.40-0.55 across sources (Obach 2008, Lombardo 2018); sits at the high/moderate boundary.; Lidocaine (0.3); Propranolol (0.13); Quinidine (0.13); Verapamil (0.1); Phenytoin (0.1) – 0.20+ in uremic patients

Low ($0.01 \leq fu_p < 0.10$): Sildenafil (0.04); Diazepam (0.02); Atorvastatin (0.02)

Very low (< 0.01): Warfarin (0.005) – Equilibrium-dialysis values 0.005–0.008 (Obach 2008); textbook compilations sometimes round to 0.01. Free fraction rises in hypoalbuminemia and on albumin-displacement DDIs.; Ibuprofen (0.005) – Equilibrium-dialysis values 0.005–0.01 (Obach 2008 / Lombardo 2018); the lower end is concentration-dependent because albumin sites saturate at therapeutic doses.; Naproxen (0.0017); Itraconazole (0.002)

B/P ladder (human)

Hinderling 1997 is the canonical theory; Lombardo 2018 confirms tiers. Tacrolimus and cyclosporine are saturable.

> **Excluded from RBCs** (~ 0.55) — Drugs that don't penetrate erythrocyte membrane (often weak acids, anionic)

> Warfarin (B/P=0.58); Ibuprofen (B/P=0.57); Naproxen (B/P=0.55); Atorvastatin (B/P=0.61)

> **Equilibrate (plasma ≈ RBC)** (0.9 – 1.1) — Drug distributes equally between plasma and erythrocyte water
> Caffeine (B/P=1.04); Antipyrine (B/P=1); Atenolol (B/P=1.12); Acetaminophen (B/P=1.08)

> **Concentrate in RBCs** (1.2 – 5) — Active uptake or RBC-component binding (e.g., carbonic anhydrase, hemoglobin)
> Cyclosporine (B/P=1.4) – Concentration- and hematocrit-dependent saturable binding; range 1.4–2.0

> **Extreme RBC partitioning** (> 5) — Very high affinity for RBC components; whole blood is the assay matrix clinically
> Tacrolimus (B/P=25) – Range 13-114 in transplant patients; saturable, hematocrit-dependent; Sirolimus (B/P=36) – 95% in RBCs; Chloroquine (B/P=7) – Range 5-10; Hydroxychloroquine (B/P=7.2); Acetazolamide (B/P=5.5) – Binds carbonic anhydrase in RBCs

4. Allometric scaling

Standard exponents ($Y = a \cdot \mathrm{BW}^b$)

CL `canonical b = 0.75, alt = 0.67 (empirical 0.74 ± 0.16)`

Hu & Hayton 2001 analysed allometric b-values for 115 xenobiotic datasets (each ≥ 4 species) compiled from the literature; mean 0.74, 99% CI 0.71-0.76 — explicitly excluding 0.67. ~81% of individual b-values were statistically indistinguishable from either 0.67 or 0.75. Subset trends: renal-cleared compounds ~0.65, metabolism-dominated ~0.75.

Theory: 0.75: West/Brown/Enquist 1997 fractal vascular network theory (dominant). 0.67: Boxenbaum surface-area theory (relevant for transport-limited compounds).

Source: Hu TM 2001

Vd `canonical b = 1 (empirical 0.8 - 1.1)`

Tissue composition (water, lipid, protein) is roughly mass-proportional across mammals; V_d of free drug ($V_{d,u}$) often scales tighter to $\mathrm{BW}^{1.0}$ than total V_d.

Theory: Linear scaling with body mass; tissue partitioning per unit mass is approximately species-invariant.

Source: Mahmood I 2007

t1/2 `canonical b = 0.25 (empirical derived)`

$t_{1/2} \propto V_d/CL \propto \mathrm{BW}^{1.0}/\mathrm{BW}^{0.75} = \mathrm{BW}^{0.25}$. Empirically scales less cleanly than CL or V_d because variance compounds. Same quarter-power as gestation length, $\mathrm{heart\ rate}^{-1}$, and lifespan ("physiological time").

Theory: Mathematical derivation from Vd and CL exponents; reflects allometric "physiological time" (Boxenbaum).

Source: Boxenbaum H 1982

Mahmood Rule of Exponents (CL)

Animal CL exponent (b)	Method	Rationale
`0.55 - 0.70`	**Simple allometry (no correction)**	Animal CL exponent in this range indicates standard mass-scaling; corrections do not improve prediction.
`0.71 - 1.00`	**CL × Maximum Life-span Potential (MLP)**	Higher exponents in animal data indicate the drug is metabolised faster than mass-scaling predicts; the MLP correction "stretches" predictions toward the human-appropriate scale. Mahmood & Balian 1996 specifies b = 0.71-1.0 (inclusive); exponents > 1.0 use BrW.
`> 1.00`	**CL × Brain Weight (BRW)**	Animal CL scaling > 1 indicates extreme species variation in metabolic rate. Brain weight (inversely correlated with CYP-mediated oxidation rates) provides a stronger correction. Mahmood & Balian 1996 gives no upper cap, but ROE accuracy degrades sharply above ~1.3 — prefer IVIVE for transporter- or protein-binding-driven drugs at very high exponents.

Empirical accuracy: ~2-fold for 50-70% of small molecules with ROE applied. ~30-50% of compounds still miss observed CL by >2-fold even with ROE — particularly transporter-mediated and protein-binding-disparate drugs (see Famous Failures).

Tang & Mayersohn predictor

IF $fu(\mathrm{rat})/fu(\mathrm{human}) > 5$ → expect > 10× error in allometric prediction.

Recommendation: apply Tang & Mayersohn FCIM — $CL_h\ (\mathrm{mL/min}) = 33.35 \times (a/R_{fu})^{0.770}$, where a is the simple-allometry intercept ($CL = a \cdot \mathrm{BW}^b$ across animals) and $R_{fu} = fu(\mathrm{rat})/fu(\mathrm{human})$ — or use IVIVE / human-relevant in vitro data. The single most actionable predictor of allometric failure (Mahmood 2002, Tang & Mayersohn 2005-2006). When animal-vs-human plasma protein binding diverges by > 5×, simple allometry

typically misses observed CL by an order of magnitude. High lipophilicity ($\mathrm{cLogP} > \sim 4$) and transporter substrate status are additional risk factors but neither is a standalone failure rule.

Famous allometric scaling failures

UCN-01 (7-hydroxystaurosporine) — 5800× overprediction

Mechanism: Extreme species difference in α1-acid glycoprotein (AAG) binding. Human AAG binds UCN-01 with $K_a \approx 8 \times 10^8\ \mathrm{M}^{-1}$ (Fuse 1998); animal AAG binds weakly. Simple allometry overpredicts UCN-01 human CL by ~5800× because it ignores the AAG-binding mismatch. Tang & Mayersohn 2005 FCIM corrects for this: $CL_h\ (\mathrm{mL/min}) = 33.35 \times (a/R_{fu})^{0.770}$, where a is the simple-allometry intercept from the animal $CL = a \cdot \mathrm{BW}^b$ fit and $R_{fu} = fu(\mathrm{rat})/fu(\mathrm{human})$. With $R_{fu} \approx 87.5$, FCIM brings the prediction to within ~5-fold of observed.

Why it matters: The textbook extreme case. Demonstrates that interspecies differences in plasma protein binding can dominate allometric prediction by orders of magnitude.

Source: Fuse E 1998

Diazepam — 33× overprediction

Mechanism: Hepatic intrinsic clearance is much higher in mouse than human; CYP2C19 + CYP3A4 species differences are the dominant driver. Chimeric humanised-liver mouse work (PXB / TK-NOG models, Kakuni / Yoshizato / Tateno groups) has consistently shown that "humanising" the hepatocyte pool brings rodent CL closer to human, consistent with the species-difference mechanism. Diazepam is mostly albumin-bound, so albumin affinity differences are a secondary contributor; AAG involvement is minor. Simple allometry predicted ~860 mL/min; observed human CL ~26 mL/min.

Why it matters: The original "vertical allometry" case (Boxenbaum & Ronfeld 1983). Recognisable drug; ideal for explaining why CL scaling can fail.

Source: Tang H 2006

Valproic acid — 29× overprediction

Mechanism: Plasma protein binding ~90% in humans, lower in rodents. Hepatic glucuronidation rate also species-divergent. Free CL collapse + UGT differences compound.

Why it matters: Widely used drug, illustrates protein-binding-driven failure. Tang & Mayersohn 2006 dataset benchmark case.

Source: Tang H 2006

Tamsulosin — 16× overprediction

Mechanism: Strong AAG binding in humans (>99% bound); CYP3A4/CYP2D6 metabolism with marked species differences.

Why it matters: Marketed BPH drug; modern allometric failure exemplar.

Source: Tang H 2006

Rosuvastatin — 3× underprediction

Mechanism: Hepatic uptake rate-limited by human OATP1B1 (~77% of hepatic uptake) and OATP1B3 with marked species differences. Oatp1a/1b knockout mice show 8× higher systemic exposure. Without transporter-specific corrections, simple allometry underpredicts CL.

Why it matters: Modern, current-relevance failure case (statin class). Demonstrates that transporter-mediated uptake breaks classical allometric scaling — increasingly relevant for OATP/BCRP/P-gp substrates.

Source: Bowman CM 2019

Methotrexate — 2.5× underprediction

Mechanism: Renal OAT3-mediated tubular secretion species differences. OAT3 activity varies 3-5× per kg kidney across species. Knockout mouse data confirm OAT3 is essential for MTX clearance.

Why it matters: Renal allometric failure (most published failures are hepatic). Important for renally-cleared OAT/OCT substrates.

Source: Tang H 2006

5. Permeability

Caco-2 / MDCK / PAMPA permeability tiers

Standard cutoffs (Papp ×10^{-6} cm/s). PAMPA typically runs lower than Caco-2 for transcellular drugs (commonly 2–15×) because PAMPA lacks the paracellular pathway; the gap shrinks toward ~1× for highly lipophilic compounds where transcellular flux dominates both assays. Drug values from Kus 2023 / Teksin 2010 / Hubatsch 2007; absolute PAMPA numbers are protocol-specific (Chen 2008 Pe ≠ vendor DS-PAMPA).

LOW
< 1 × 10⁻⁶ cm/s
Poor passive permeability; bioavailability often limited; carrier-mediated absorption may rescue.

MODERATE
1 – 10 × 10⁻⁶ cm/s
Adequate for oral absorption; combined paracellular + transcellular routes typical.

HIGH
> 10 × 10⁻⁶ cm/s
Rapid transcellular permeability; absorption rarely the rate-limiting step.

Drug benchmarks

Drug	Caco-2	PAMPA	Tier	Mechanism
Mannitol	0.2	0.02	low	Paracellular integrity QC marker; Caco-2 $P_{app} > 0.5 \times 10^{-6}$ cm/s indicates a leaky monolayer (Hubatsch 2007). The ~10× drop in PAMPA vs Caco-2 reflects PAMPA's lack of paracellular pathway — the key conceptual difference between the two assays.
Ranitidine	0.4	0.7	low	BCS Class III (low fa); paracellular
Hydrochlorothiazide	0.7	0.5	low	BCS III/IV; poor passive permeability
Atenolol	0.7	0.5	low	Canonical low-permeability paracellular marker (BCS Class III, $f_a \approx 50\%$ in human). PAMPA P_e typically < 0.5 in standard assays.
Furosemide	1	0.6	moderate	BCS IV; paracellular contribution dominates. Highly subclone-dependent (range 0.1-3 across labs).
Metoprolol	40	1.5	high	High transcellular passive permeability; BCS I high-perm reference
Propranolol	50	4.3	high	Transcellular; benchmark high-permeability beta-blocker
Carbamazepine	42	27	high	Highly lipophilic; rapid transcellular
Naproxen	45	42	high	Weak acid (pK_a 4.2); value reported at apical pH 6.5 (gradient assay). Symmetric pH 7.4 lowers P_{app} ~5-10×; BSA receiver further halves it (in vivo sink).
Verapamil	33	9.4	high	High passive permeability + P-gp substrate (efflux ratio matters in vivo)

P-gp efflux probes

Efflux ratio $\mathrm{ER} = P_{app}(B \to A) / P_{app}(A \to B)$. FDA/EMA threshold for P-gp substrate classification: $\mathrm{ER} \geq 2$ with significant attenuation by P-gp inhibitor.

Digoxin — ER ≈ 17
ER ~10-20 in MDR1-MDCK, ~15-50 in Caco-2 (subclone-dependent); classical P-gp probe — net efflux requires basolateral uptake

Loperamide — ER ≈ 30
Very high ER; CNS-restricted in vivo because of P-gp efflux at the blood-brain barrier

Talinolol — ER ≈ 8
Range 3-12 across labs; standard P-gp positive control for oral absorption studies

Fexofenadine — ER ≈ 30
ER ~28-37 in Caco-2; clinically relevant P-gp + OATP substrate

Sun 2002: Caco-2 P_{app} → human jejunal P_{eff}

$$\log_{10} P_{eff,h} = 0.4926 \cdot \log_{10} P_{app,\mathrm{Caco-2}} - 0.1454, \quad R^2 = 0.51 \text{ (all-drug fit)}$$

Units: enter P_{app} in 10^{-6} cm/s (e.g. 40 for metoprolol); predicted P_{eff} is in 10^{-4} cm/s.

Coefficients from Sun 2002's all-drug fit ($R^2 = 0.51$, $n = 24$, pH 7.4). Same paper reports $R^2 \approx 0.84$ on the passively-absorbed subset alone. Units matter: enter P_{app} in 10^{-6} cm/s and the predicted P_{eff} comes out in 10^{-4} cm/s. Carrier-mediated drugs (cephalexin, valacyclovir, levodopa, gabapentin) deviate 3-35× ABOVE the line because Caco-2 underexpresses uptake transporters (PEPT1, OATP) by 2-595× vs human duodenum.

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