Physiologically Based Pharmacokinetic Modeling of Dextromethorphan to Investigate Interindividual Variability Within CYP2D6 Activity Score Groups

Supplement S1 - Model Information and Evaluation

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Disclosures
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S1 Methods (Addendum)

S1.1 Cocktail Studies

Table S1.1.1: Phenotyping cocktails and respective drug doses

Study	Caffeine	Dextromethorphan	Digoxin	Mephenytoin	Midazolam	Omeprazole	Tolbutamide	Warfarin
Population studies								
Armani 2017 [1]	100 mg	30 mg	-	-	2 mg	20 mg	-	-
Dumond 2010 [8]	200 mg	30 mg	0.25 mg (po + iv)[a]	-	5 mg (po)[c] + 2 mg (iv)[c]	20 mg	-	10 mg[b]
Ermer 2015 [10]	200 mg	30 mg	-	-	0.025 mg/kg (iv)	40 mg	-	-
Kakuda 2014 [18]	15 mg	30 mg	0.5 mg (po)	-	1.5 mg (po)	40 mg	-	10 mg[b]
Khalilieh 2018 [21]	20 mg	30 mg	-	-	1.5 mg (po)	40 mg	-	10 mg[b]
Nyunt 2008 [28]	-	30 mg	-	-	5 mg (po)	-	-	-
Sager 2014 [31]	100 mg	30 mg	-	-	2 mg (po)	20 mg	-	-
Stage 2018 [35]	100 mg	30 mg	-	-	2.5 mg (buccal)	20 mg	-	-
DGI studies								
Gorski 2004 [14]	200 mg	30 mg	-	-	0.05 mg/kg (iv)	-	500 mg	-
Gazzaz 2018 [13]	150 mg	30 mg	-	-	2 mg (po)	20 mg	-	-
Frank 2009 [12]								
Study A	150 mg	30 mg	-	50 mg	2 mg (po) + 1 mg (iv)[c]	-	125 mg	-
Study B[d]	150 mg	30 mg	0.5 mg	50 mg	2 mg (po) + 1 mg (iv)[c]	-	125 mg	-
Study C	150 mg	30 mg	-	50 mg	2 mg (po) + 1 mg (iv)[c]	-	125 mg	-
Study D	-	30 mg	0.5 mg	50 mg	1.5 mg (po) + 1 mg (iv)[c]	-	-	-
Study E	-	30 mg	0.5 mg	50 mg	1.5 mg (po) + 1 mg (iv)[c]	-	-	-

-: not administered, [a]: doses were administered on the study days following the administration of the phenotyping cocktail, [b]: Study subjects received 10 mg vitamin K together with the warfarin dose, [b]: iv dose administered 240 min after administration of the cocktail, [d]: study excluded from modeling due to reasons described in Section S6.1, iv: intravenous, po: oral.

S1.2 Dextromethorphan Formulations

The Weibull function was implemented according to Eq. 1 and 2 [23] to describe the dissolution process for studies where dextromethorphan was administered in a cocktail capsule

$$m = 1 - \exp\left(\frac{-(t - T_{lag})^{\beta}}{\alpha}\right) \tag{1}$$

$$\alpha = (T_d)^{\beta} \tag{2}$$

where m = fraction of dissolved drug at time t, T_{lag} = lag time before the onset of dissolution, α = scale parameter, β = shape parameter, T_d = time needed to dissolve 63% of the formulation.

The final Weibull shape parameters and Weibull time parameters (50% dissolved) for the cocktail formulation used in the dextromethorphan physiologically based pharmacokinetic (PBPK) model are given in Table S2.1.1.

S1.3 Virtual Individuals

The PBPK model was built based on data from healthy individuals, using the reported sex, ethnicity and mean values for age, weight and height from each study protocol. If no demographic information was provided, the following default values were substituted: male, European, 30 years of age, 73 kg body weight and 176 cm body height (characteristics from the PK-Sim® population database [27, 38, 41]. Cytochrome P450 2D6 (CYP2D6) was implemented in accordance with literature, using the PK-Sim® expression database to define their relative expression in the different organs of the body [29]. Details on the implementation of CYP2D6 are summarized in Section **??**.

S1.4 Virtual Populations

For population simulations, virtual populations of 1000 individuals were created based on the population characteristics stated in the respective publication. If no information was provided in the publication, populations based on European male individuals aged 20–50 years were assumed. Metrics were generated (depending on ethnicity) from one of the following databases; American: Third National Health and Nutrition Examination Survey (NHANES) [27] database, Asian: Tanaka model [38], European: International Commission on Radiological Protection (ICRP) database [41]. In the generated virtual populations, system-dependent parameters such as weight, height, organ volumes, blood flow rates, tissue compositions, etc. were varied by the implemented algorithm in PK-Sim® within the limits of the databases listed above [27, 38, 41]. Since study populations were grouped by their CYP2D6 activity score or phenotype, no variability in CYP2D6 reference concentrations was assumed for population simulations. Reference concentrations of implemented proteins as well as the relative expression are provided in Section **??**.

S1.5 Lysosomal Trapping in the Intestinal Mucosa

Although dextromethorphan is rapidly absorbed from the intestine, time to reach peak plasma concentration C_{max} (t_{max}) often occurs as late as 4h after oral administration [4]. This phenomenon likely occurs due to lysosomal trapping of dextromethorphan in the intestinal mucosa [4, 20]. However, other processes, such as renal excretion may also be affected by lysosomal trapping in the respective tissue. In short, lipophilic amines (logP > 1, acid dissociation constant (pKa) > 6) accumulate in lysosomes due to rapid diffusion across the lysosomal membrane in unionized form. Subsequently, due to the acidic environment in lysosomes (pH 4–5), the amine is then ionized and thus unable to permeate back into the cytosol [20]. The information necessary to physiologically implement lysosomal trapping (i.e. relative abundances of lysosomes in relevant tissues and diffusion constants for permeation across lysosomal membranes) are not yet available in the literature. Hence, intestinal lysosomal trapping was implemented as follows: First, a surrogate protein binding partner was expressed in high abundances (500 µmol/L) in the relevant tissues (duodenum, upper jejunum, lower jejunum, upper ileum and lower ileum, each 100% of relative expression). Second, a corresponding protein binding process was implemented for dextromethorphan. Finally, the relevant parameters for the binding process - dissociation rate constant (k_{off}) and dissociation constant (K_D) - were informed by parameter optimization. For a comprehensive explanation on the process of lysosomal trapping under physiological circumstances, please refer to [20].

S1.6 PBPK Model Sensitivity Analysis

Sensitivity of the final models to single parameter changes (local sensitivity analysis) was calculated as relative change of the area under the plasma concentration-time curve $(AUC)_{0-24\,h}$. Sensitivity analysis was carried out using a relative perturbation of 1000% (variation range 10.0, maximum number of 9 steps). Parameters were included into the analysis if they have been optimized, if they are associated with optimized parameters or if they might have a strong impact due to calculation methods used in the model. Sensitivity to a parameter was calculated as the ratio of the relative change of the simulated $AUC_{0-24\,h}$ to the relative variation of the parameter according to Eq. 3:

$$S = \frac{\Delta AUC_{0-24\ h}}{\Delta p} \times \frac{p}{AUC_{0-24\ h}} \tag{3}$$

where S = sensitivity of the $AUC_{0-24\ h}$ to the examined model parameter, $\Delta AUC_{0-24\ h}$ = change of the $AUC_{0-24\,h}$, $AUC_{0-24\ h}$ = simulated $AUC_{0-24\,h}$ with the original parameter value, Δp = change of the examined parameter value, p = original parameter value.

A sensitivity of +0.5 signifies that a 100% increase of the examined parameter value causes a 50% increase of the simulated $AUC_{0-24\,h}$. The results of the sensitivity analysis are provided in Section S3.6.

S2 PBPK Base Model Building

S2.1 Drug-Dependent Parameters

Table S2.1.1: Dextromethorphan and dextrorphan drug-dependent parameters drug-dependent parameters

Parameter	Unit	Value	Source	Literature	Reference	Value	Source	Literature	Reference	Description
		Dextromethorphan				**Dextrorphan**				
MW	g/mol	271.41	Lit.	271.41	[2]	257.37	Lit.	257.37	[16, 43]	Molecular weight
pKa (strongest basic)	-	9.10	Lit.	9.10	[34]	9.10	Lit.	9.10	[34]	Acid dissociation constant
pKa (strongest acidic)	-	-	Lit.	-	-	10.10	Lit.	10.10	[34]	Acid dissociation constant
Solubility (base)	g/L	-	-	-	-	0.17	Lit.	0.17	[43]	Solubility at pH 7
Solubility (hydrobromide)	g/L	15.00	Lit.	15.00	[2]	-	-	-	-	Solubility at pH 7
logP	-	4.10	Lit.	4.10	[34]	2.90	Lit.	2.90	[22]	Lipophilicity
f_u	%	35.00	Lit.	35.00	[25]	42.00	Lit.	42.00	[42]	Fraction unbound
CYP2D6 K_M → dxt	µmol/L	4.65	Lit.	4.65^a	[5]	-	-	-	-	Michaelis-Menten constant
CYP2D6 k_{cat} → dxt (EM)	1/min	90.89	Optim.	6.60	[5]	-	-	-	-	Catalytic rate constant
CYP2D6 k_{cat} → dxt (PM)	1/min	0.00	-	-	-	-	-	-	-	Catalytic rate constant
CYP3A4 K_M	µmol/L	176.80	Lit.	176.80^a	[25]	910.00	Lit.	910.00^a	[25]	Michaelis-Menten constant
CYP3A4 k_{cat}	1/min	7.94	Lit.	5.65	[25]	7.41	Lit.	7.41	[25]	Catalytic rate constant
UGT2B15 K_M → dxt-glu	µmol/L	-	-	-	-	184.80	Lit.	184.80^a	[25]	Michaelis-Menten constant
UGT2B15 k_{cat} → dxt-glu	1/min	-	-	-	-	1137.98	Optim.	37.04	[25]	Catalytic rate constant
Lysosomal trapping K_D	µmol/L	74.21	-	-	-	-	-	-	-	Dissociation constant
Lysosomal trapping k_{off}	1/min	$7.10 \cdot 10^5$	-	-	-	-	-	-	-	Dissociation rate constant
GFR fraction	-	1.00	Asm.	-	-	1.00	Asm.	-	-	Filtered drug in the urine
EHC continuous fraction	-	1.00	Asm.	-	-	1.00	Asm.	-	-	Bile fraction cont. released
Intestinal perm.	cm/min	$2.48 \cdot 10^{-6}$	Optim.	$1.12 \cdot 10^{-3}$	Calc. [40]	$1.80 \cdot 10^{-5}$	Calc.	$1.80 \cdot 10^{-5}$	Calc. [40]	Transcellular intestinal perm.
Cellular permeability	cm/min	0.91	Calc.	PK-Sim	[19]	0.08	Calc.	PK-Sim	[19]	Perm. into the cellular space
Partition coefficients	-	Diverse	Calc.	Ber	[3]	Diverse	Calc.	Ber	[3]	Cell to plasma partitioning
Weibull time parameter	min	46.05	Optim.	[12]	-	-	-	-	-	Dissolution time (50%)
Weibull shape parameter	-	1.05	Optim.	[12]	-	-	-	-	-	Dissolution shape

-: not available, ^{a}: in vitro values corrected for binding in the assay (fu_{mic}) as given in the respective publications, asm.: assumed, Ber: Berezhkovskiy calculation method, calc.: calculated, cont.: continuously, CYP2D6: Cytochrome P450 2D6, CYP3A4: cytochrome P450 3A4, dxt: dextrorphan, dxt-glu: dextrorphan *O*-glucuronide, EHC: enterohepatic circulation, GFR: glomerular filtration rate, intest.: intestinal, lit: literature, EM: extensive metabolizer, optim.: optimized, perm.: permeability, PM: poor metabolizer, PK-Sim: PK-Sim standard calculation method, uridine 5'-diphospho-glucuronosyltransferase family 2 member B15 (UGT2B15): uridine 5'-diphospho-glucuronosyltransferase family 2 member B15.

Table S2.1.2: Dextrorphan *O*-glucuronide drug-dependent parameters

Parameter	Unit	Value	Source	Literature	Reference	Description
MW	g/mol	433.50	Lit.	433.50	[17, 43]	Molecular weight
pKa (strongest basic)	-	9.82	Lit.	9.82	[17, 43]	Acid dissociation constant
pKa (strongest acidic)	-	2.85	Lit.	2.85	[17, 43]	Acid dissociation constant
Solubility	g/L	1.20	Lit.	1.20	[17, 43]	Solubility
logP	-	0.29	Optim.	1.38	[17, 43]	Lipophilicity
f_u	%	37.00	Calc.	37.00	[42]	Fraction unbound
GFR fraction	-	4.92	Optim.	-	-	Filtered drug in the urine
EHC continuous fraction	-	1.00	Asm.	-	-	Bile fraction cont. released
Intestinal permeability	cm/min	$4.26 \cdot 10^{-6}$	Calc.	$4.26 \cdot 10^{-6}$	Calc. [40]	Transcellular intestinal perm.
Cellular permeability	cm/min	$8.51 \cdot 10^{-6}$	Calc.	CdS	[33]	Perm. into the cellular space
Partition coefficients	-	Diverse	Calc.	Ber	[3]	Cell to plasma partitioning

-: not available, asm: assumed, Ber: Berezhkovskiy calculation method, calc.: calculated, CdS: Charge dependent Schmitt, cont.: continuously, EHC: enterohepatic circulation, GFR: glomerular filtration rate, intest.: intestinal, lit.: literature, optim: optimized, perm.: permeability.

S2.2 Clinical Study Data

Table S2.2.3: Dextromethorphan study table

Route	Dose [mg]	n	Females [%]	Age [years]	Weight [kg]	Height [cm]	Metabolite measured	CYP2D6 P. Phenotype	Dataset	References
iv (inf, 30 min, sd)	0.5/kg	24	0	27 (21-35)	79 (55-110)	-	-	EM	training	Duedahl 2005 [7]
po (cap, sd)	80	36	0	26	73	-	dtt	EM	training	Tennezé 1999 [39]
po (-, sd)	60	17	41	67 (49-74)	80 (49-107)	173 (150-187)	dtt	EM	test	Feld 2013 [11]
po (cap, bid, 8 days)	60	10	0	-	-	-	dtt	EM	test	Antecip Bioventures [24]
po (cap, sd)	30	20	50	(27-42)	73	-	-	EM	test[a]	Armani 2017 [1]
po (cap, sd)	30	23	30	27	76	174	-	EM	test[a]	Dumond 2010 [8]
po (cap, sd)	30	48	35	33	76	171	-	EM	test	Edwards 2017 [9]
po (cap, sd)	30	30	40	(18-45)	78	172	dxt	EM	test[a]	Ermer 2015 [10]
po (-, sd)	30	14	0	(21-49)	-	-	-	EM	test[a]	Kakuda 2014 [18]
po (-, sd)	30	20	35	40 (22-63)	-	-	-	EM	test[a]	Khalilieh 2018 [21]
po (tab, sd)	50	24	0	25 (20-33)	64 (50-76)	-	dxt	EM	test	Nakashima 2007 [26]
po (-, sd)	30	12	25	40 (22-53)	-	-	-	EM	test[a]	Nyunt 2008 [28]
po (cap, sd)	30	10	50	20	72	172	dxt	EM	test[a]	Sager 2014 [31]
po (cap, sd)	30	5	80	26 (22-31)	-	-	dxt, dxt-glu	EM	training	Schadel 1995 [32]
po (cap, sd)	30	4	50	33 (22-46)	-	-	-	PM	training	Schadel 1995 [32]
po (cap, sd)	30	12	0	(21-29)	-	-	-	EM	test[a]	Stage 2018 [35]

Values for age, weight and height are given as mean (range), -: not given, [a]: cocktail study, AS: CYP2D6 activity score, bid: twice daily, cap: capsule, CYP2D6: Cytochrome P450 2D6, DGI: drug-gene interaction, dxt: dextrorphan, dxt-glu: dextrorphan *O*-glucuronide, dtt: total dextrorphan, EM: extensive metabolizer, inf: infusion, iv: intravenous, p.: projected, PM: poor metabolizer, po: oral, sd: single dose, sol: oral solution.

S2.3 Dextromethorphan model pathways

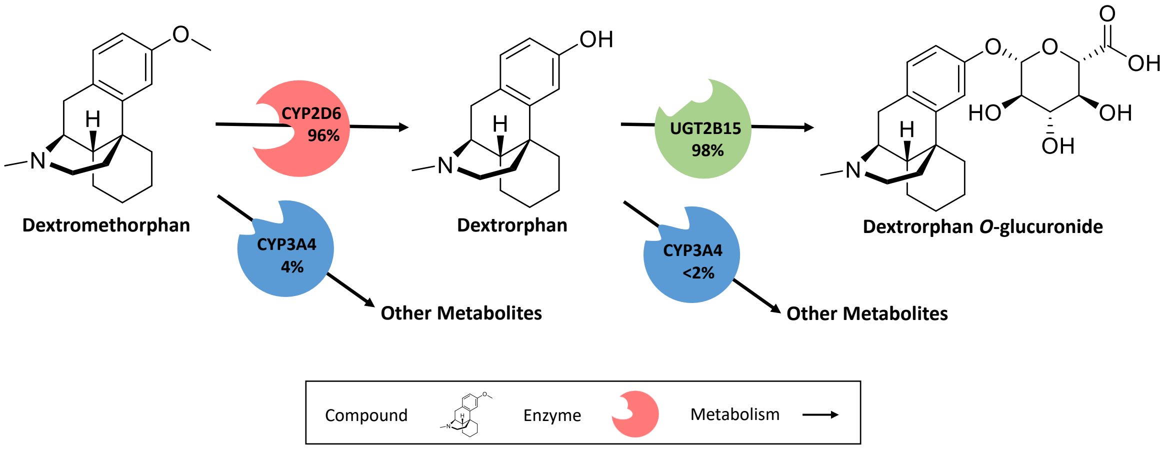


Figure S2.3.1: Implemented dextromethorphan metabolic pathways. Dextromethorphan is *O*-demethylated by CYP2D6 and *N*-demethylated by CYP3A4. The metabolite dextrorphan is further metabolized via CYP3A4 (*N*-demethylation) and UGT2B15 (*O*-glucuronidation). Dextrorphan *O*-glucuronide is excreted in the urine. Percentages shown refer to the fraction metabolized by the respective enzyme, calculated for extensive metabolizers of CYP2D6. CYP2D6: cytochrome P450 2D6, CYP3A4: cytochrome P450 3A4, UGT2B15: Uridine 5'-diphospho-glucuronosyltransferase 2B15.

S3 PBPK Base Model Evaluation

S3.1 Plasma Concentration-Time Profiles

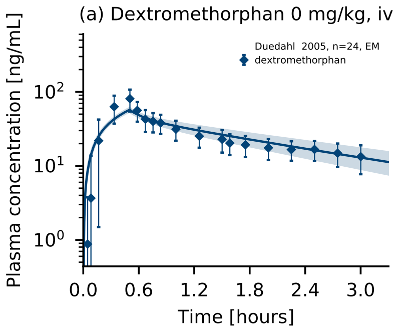


Figure S3.1.1: Dextromethorphan plasma concentration-time profile after intravenous administration of dextromethorphan (semilogarithmic representation). Population predictions (n=1000) are shown as lines with ribbons (arithmetic mean ± standard deviation (SD)), symbols represent the corresponding observed data ± SD. EM: extensive metabolizer, iv: intravenous.

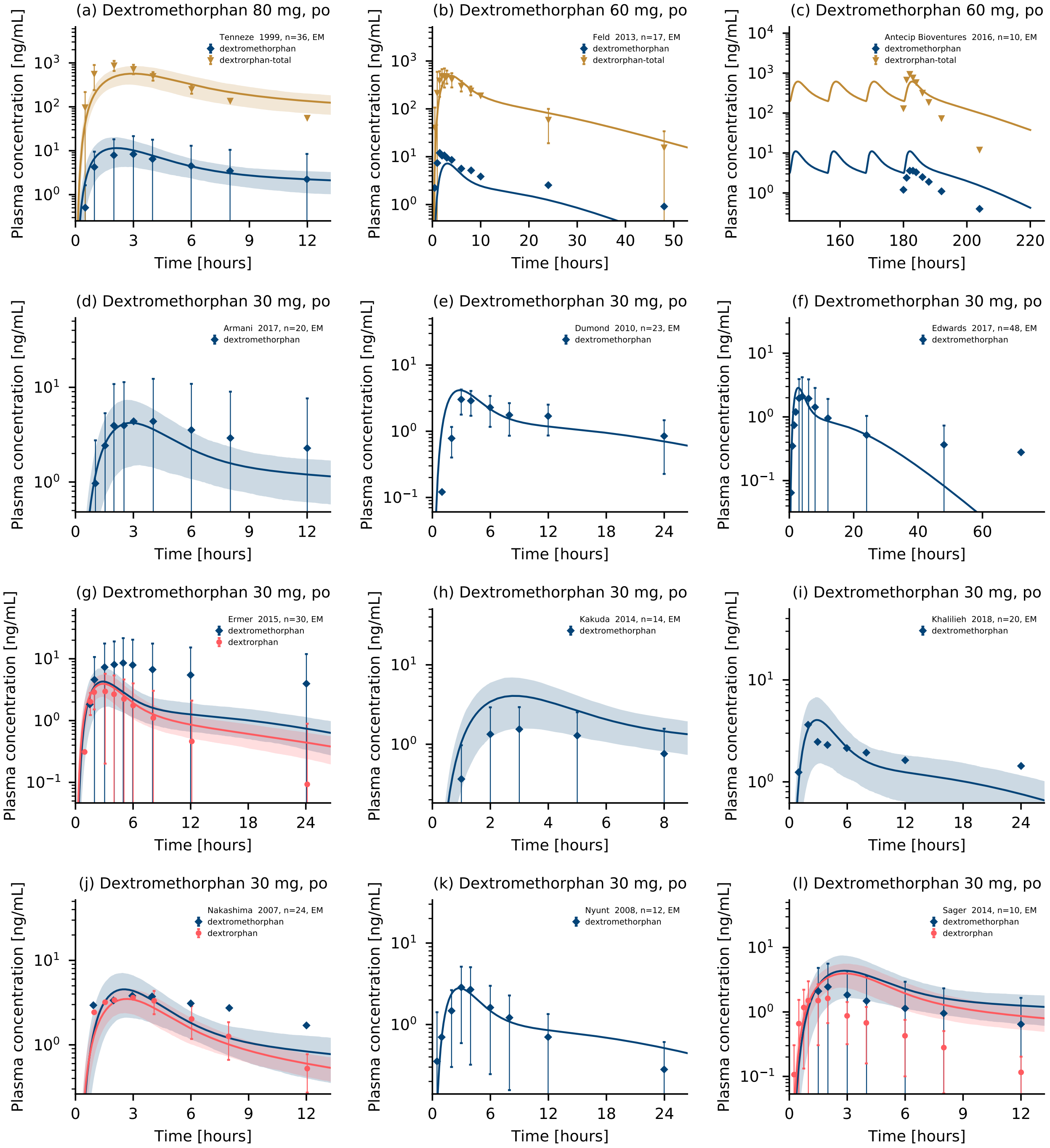


Figure S3.1.2: Dextromethorphan, dextrorphan and total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) plasma concentration-time profiles after oral administration of dextromethorphan (semilogarithmic representation). Population predictions (n=1000) are shown as lines with ribbons (arithmetic mean ± standard deviation (SD)), symbols represent the corresponding observed data ± SD. EM: extensive metabolizer, po: oral.

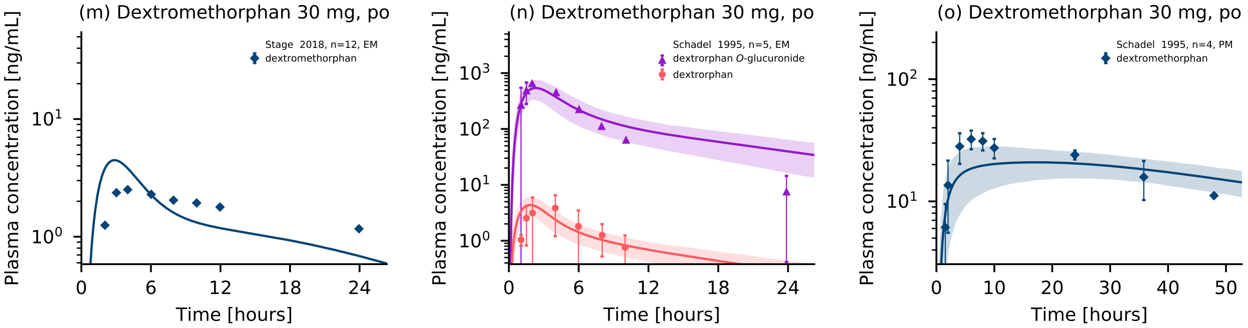


Figure S3.1.3: Dextromethorphan, dextrorphan, dextrorphan *O*-glucuronide and total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) plasma concentration-time profiles after oral administration of dextromethorphan (semilogarithmic representation). Population predictions (n=1000) are shown as lines with ribbons (arithmetic mean ± standard deviation (SD)), symbols represent the corresponding observed data ± SD. EM: extensive metabolizer, PM: poor metabolizer, po: oral.

S3.2 Goodness-of-Fit Plots: Plasma Concentrations

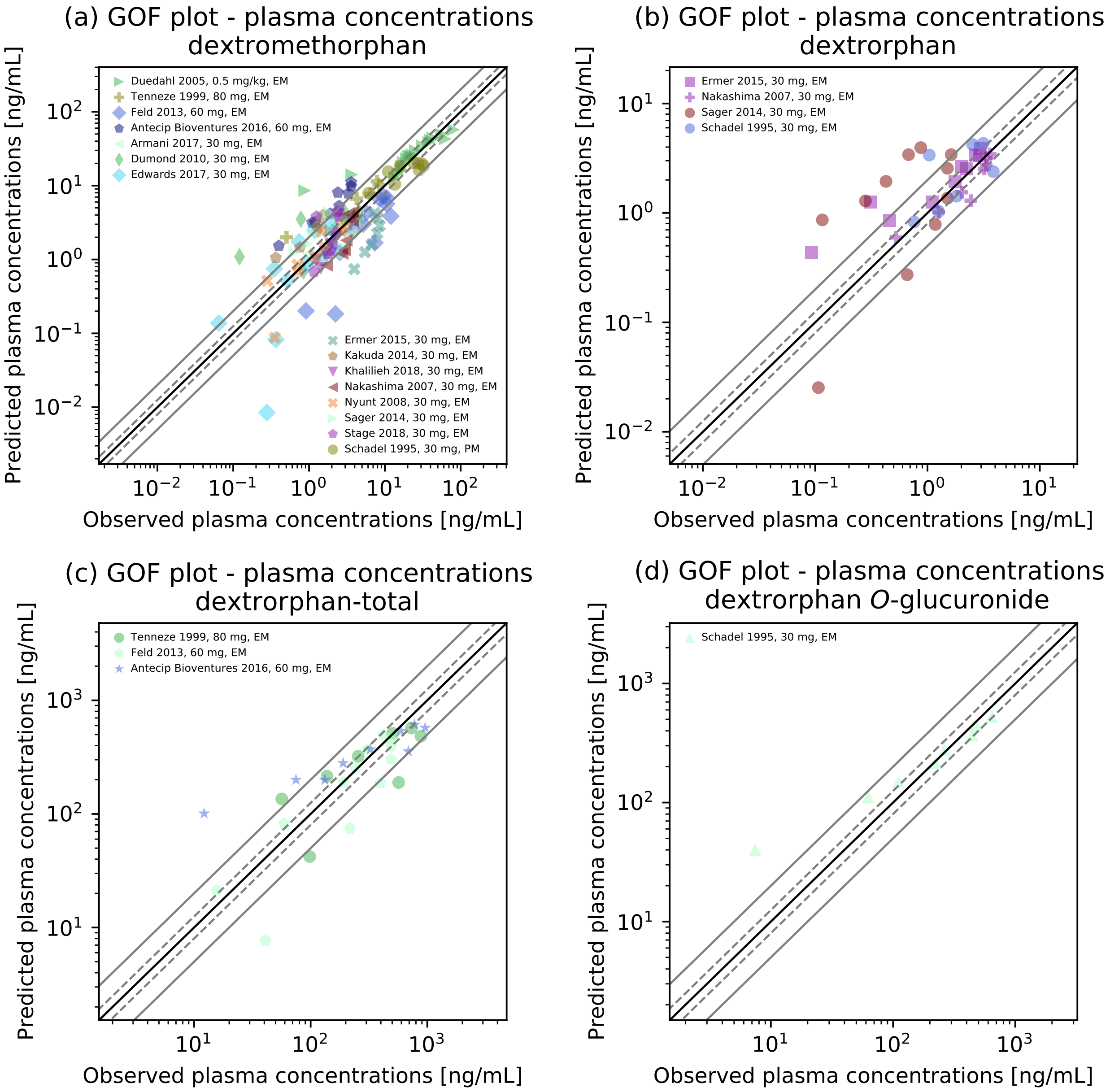


Figure S3.2.4: Goodness-of-fit plots. Predicted versus observed plasma concentration values for (a) dextromethorphan, (b) dextrorphan, (c) total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) and (d) dextrorphan *O*-glucuronide for all studies of the PBPK model building dataset. The solid black line marks the line of identity, the dashed gray lines mark the 0.8- to 1.25-fold range, the solid gray lines indicate the 0.5- to 2-fold range. Colored symbols represent the study population given in the legend. EM: extensive metabolizer, PM: poor metabolizer.

S3.3 MRD of Plasma Concentration Predictions

Table S3.3.1: Mean relative deviation of plasma concentration predictions

Dosing	Molecule	CYP2D6 status	MRD	Reference
iv, inf, 0.5 mg	dextromethorphan	EM	1.87	Duedahl et al. 2005 [7]
po, cap, 80 mg	dextromethorphan	EM	1.85	Tenneze et al. 1999 [39]
po, -, 60 mg	dextromethorphan	EM	3.19	Feld et al. 2013 [11]
po, tab, 60 mg	dextromethorphan	EM	2.73	Antecip Bioventures [24]
po, cap, 30 mg	dextromethorphan	EM	1.42	Armani et al. 2017 [1]
po, cap, 30 mg	dextromethorphan	EM	2.60	Dumond et al. 2010 [8]
po, cap, 30 mg	dextromethorphan	EM	3.32	Edwards et al. 2017 [9]
po, -, 30 mg	dextromethorphan	EM	2.96	Ermer et al. 2015 [10]
po, cap, 30 mg	dextromethorphan	EM	2.63	Kakuda et al. 2014 [18]
po, -, 30 mg	dextromethorphan	EM	1.46	Khalilieh et al. 2018 [21]
po, tab, 30 mg	dextromethorphan	EM	1.70	Nakashima et al. 2007 [26]
po, cap, 30 mg	dextromethorphan	EM	1.94	Nyunt et al. 2008 [28]
po, cap, 30 mg	dextromethorphan	EM	1.97	Sager et al. 2014 [31]
po, cap, 30 mg	dextromethorphan	PM	1.44	Schadel et al. 1995 [32]
po, cap, 30 mg	dextromethorphan	EM	1.74	Stage et al. 2018 [35]
MRD (dextromethorphan)			2.19 (1.42–3.32) 9/15 with MRD ≤ 2	
po, -, 30 mg	dextrorphan	EM	2.05	Ermer et al. 2015 [10]
po, tab, 30 mg	dextrorphan	EM	1.35	Nakashima et al. 2007 [26]
po, cap, 30 mg	dextrorphan	EM	3.56	Sager et al. 2014 [31]
po, cap, 30 mg	dextrorphan	EM	1.73	Schadel et al. 1995 [32]
MRD (dextrorphan)			2.17 (1.35–3.56) 2/4 with MRD ≤ 2	
po, cap, 30 mg	dextrorphan *O*-glucuronide	EM	2.01	Schadel et al. 1995 [32]
MRD (dextrorphan *O*-glucuronide)			2.01 0/1 with MRD ≤ 2	
po, cap, 80 mg	dextrorphan-total	EM	1.88	Tenneze et al. 1999 [39]
po, -, 60 mg	dextrorphan-total	EM	2.04	Feld et al. 2013 [11]
po, tab, 60 mg	dextrorphan-total	EM	3.40	Antecip Bioventures [24]
MRD (dextrorphan-total)			2.44 (1.88–3.40) 1/3 with MRD ≤ 2	
Overall MRD			2.21 (1.35–3.56) 12/23 with MRD ≤ 2	

-: not given, cap: capsule, CYP2D6: Cytochrome P450 2D6, EM: extensive metabolizer, inf: infusion, iv: intravenous, PM: poor metabolizer, po: oral.

S3.4 AUC$_{last}$ and C$_{max}$ Goodness-of-Fit Plots

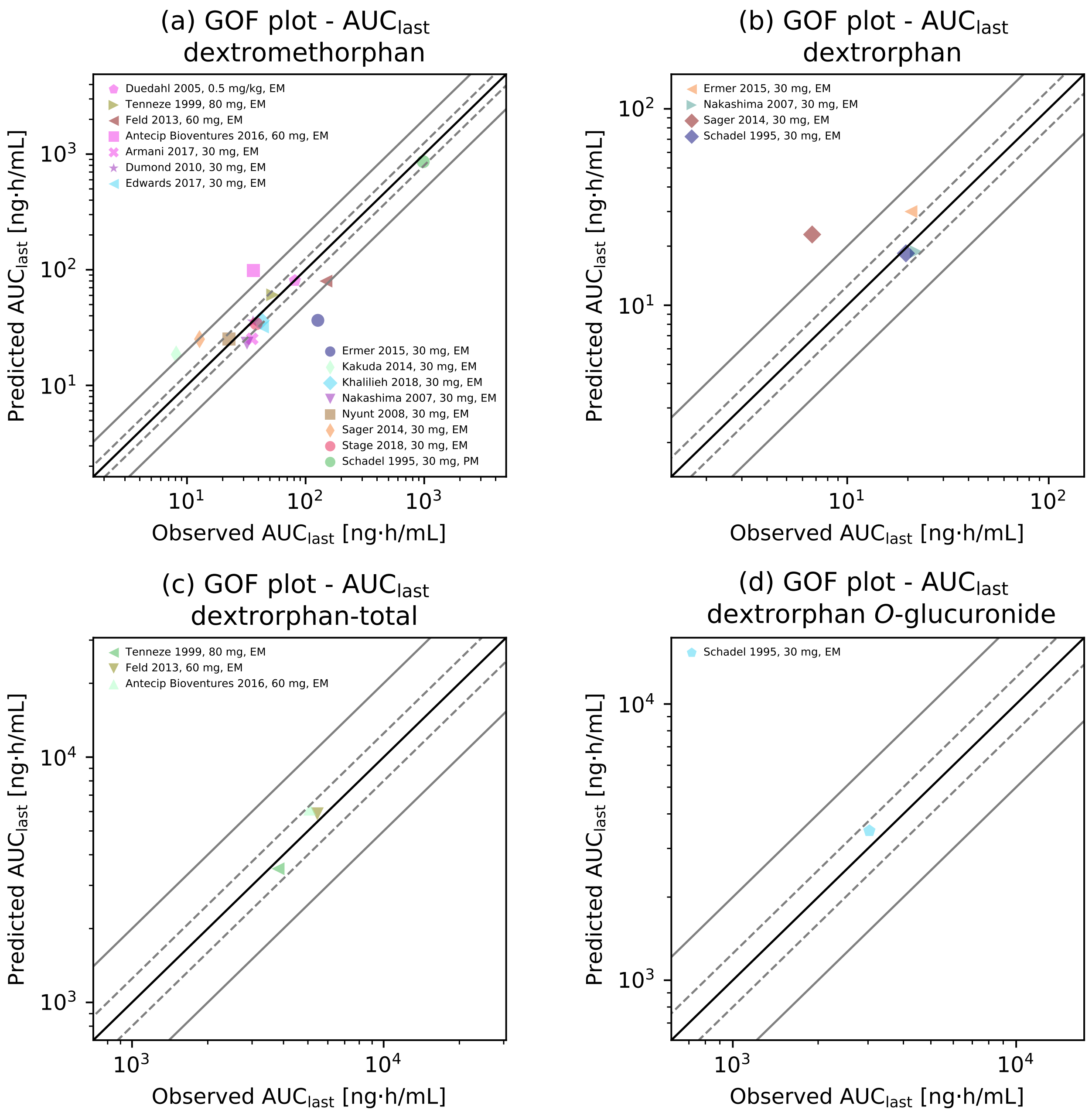
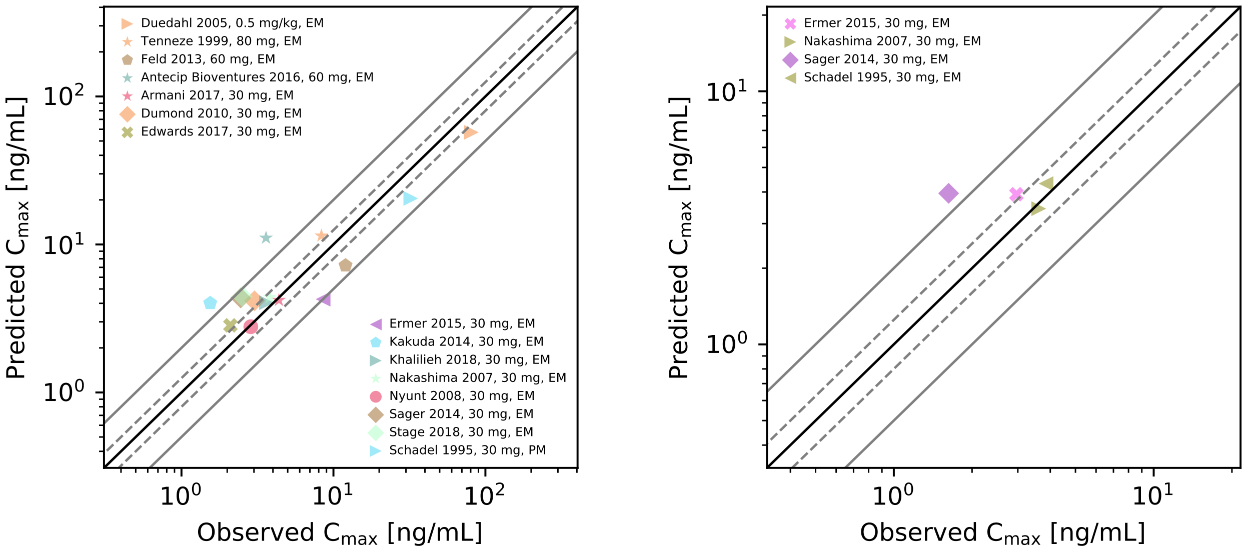
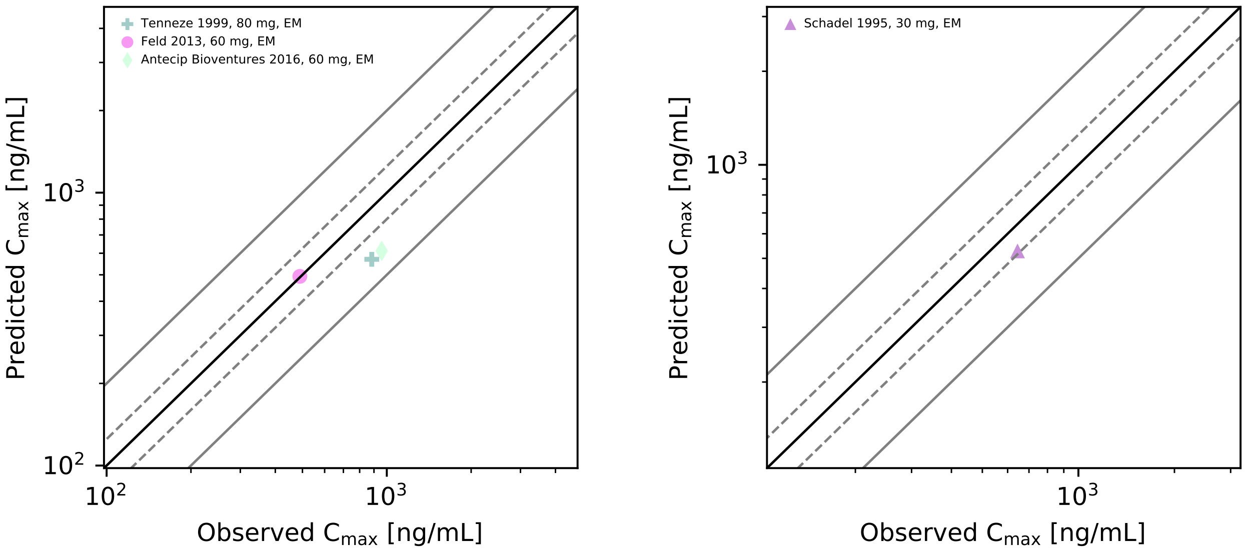


Figure S3.4.5: AUC from the time of the first concentration measurement to the last time point of concentration measurement (AUC$_{last}$) correlation plots. Predicted versus observed AUC$_{last}$ for (a) dextromethorphan, (b) dextrorphan, (c) total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) and (d) dextrorphan *O*-glucuronide for all studies of the PBPK model building dataset. The solid black line marks the line of identity, the dashed gray lines mark the 0.8- to 1.25-fold range, the solid gray lines indicate the 0.5- to 2-fold range. Colored symbols represent the study population given in the legend. AUC$_{last}$: AUC from the time of the first concentration measurement to the last time point of concentration measurement, EM: extensive metabolizer, PM: poor metabolizer.



(a) GOF plot - C_{max} dextromethorphan

(b) GOF plot - C_{max} dextrorphan



(c) GOF plot - C_{max} dextrorphan-total

(d) GOF plot - C_{max} dextrorphan *O*-glucuronide

Figure S3.4.6: C_{max} correlation plots. Predicted versus observed C_{max} for (a) dextromethorphan, (b) dextrorphan, (c) total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) and (d) dextrorphan *O*-glucuronide for all studies of the PBPK model building dataset. The solid black line marks the line of identity, the dashed gray lines mark the 0.8- to 1.25-fold range, the solid gray lines indicate the 0.5- to 2-fold range. Colored symbols represent the study population given in the legend. C_{max}: peak plasma concentration, EM: extensive metabolizer, PM: poor metabolizer.

S3.5 GMFE of Predicted $\mathrm{AUC}_{\mathrm{last}}$ and $\mathrm{C}_{\mathrm{max}}$ Values

Table S3.5.2: Predicted and observed $\mathrm{AUC}_{\mathrm{last}}$ and $\mathrm{C}_{\mathrm{max}}$ values and geometric mean fold errors

		CYP2D6	$\mathrm{AUC}_{\mathrm{last}}$ [ng·h/mL]			$\mathrm{C}_{\mathrm{max}}$ [ng/mL]			
Dosing	Molecule	status	Pred	Obs	Pred/Obs	Pred	Obs	Pred/Obs	Reference
iv, inf, 0.5 mg/kg	dextromethorphan	EM	80.25	81.20	0.99	-	-	-	Duedahl et al. 2005 [7]
po, cap, 80 mg	dextromethorphan	EM	65.59	52.78	1.24	12.94	8.33	1.55	Tenneze et al. 1999 [39]
po, -, 60 mg	dextromethorphan	EM	83.31	148.40	0.56	6.73	12.01	0.56	Feld et al. 2013 [11]
po, tab, 60 mg	dextromethorphan	EM	95.57	36.14	2.64	10.69	3.60	2.97	Antecip Bioventures 2016 [24]
po, cap, 30 mg	dextromethorphan	EM	25.66	35.47	0.72	4.33	4.38	0.99	Armani et al. 2017 [1]
po, cap, 30 mg	dextromethorphan	EM	36.25	36.01	1.01	4.22	3.02	1.39	Dumond et al. 2010 [8]
po, cap, 30 mg	dextromethorphan	EM	31.61	43.32	0.73	2.95	2.10	1.41	Edwards et al. 2017 [9]
po, -, 30 mg	dextromethorphan	EM	36.87	126.85	0.29	3.85	8.55	0.45	Ermer et al. 2015 [10]
po, cap, 30 mg	dextromethorphan	EM	19.51	8.11	2.40	4.35	1.55	2.82	Kakuda et al. 2014 [18]
po, -, 30 mg	dextromethorphan	EM	36.97	41.89	0.88	4.27	3.63	1.18	Khalilieh et al. 2018 [21]
po, tab, 30 mg	dextromethorphan	EM	23.03	32.08	0.72	4.26	3.81	1.12	Nakashima et al. 2007 [26]
po, cap, 30 mg	dextromethorphan	EM	23.77	22.53	1.05	2.45	2.86	0.86	Nyunt et al. 2008 [28]
po, cap, 30 mg	dextromethorphan	EM	25.79	12.76	2.02	4.42	2.45	1.80	Sager et al. 2014 [31]
po, cap, 30 mg	dextromethorphan	PM	848.57	981.20	0.86	20.65	32.30	0.64	Schadel et al. 1995 [32]
po, cap, 30 mg	dextromethorphan	EM	34.17	38.36	0.89	4.48	2.51	1.78	Stage et al. 2018 [35]
GMFE (dextromethorphan)					1.61 (1.01–3.45) 10/14 with GMFE ≤ 2			1.70 (1.01–2.97) 10/14 with GMFE ≤ 2	
po, -, 30 mg	dextrorphan	EM	29.47	20.71	1.42	3.76	2.96	1.27	Ermer et al. 2015 [10]
po, tab, 30 mg	dextrorphan	EM	18.53	22.02	0.84	3.35	3.61	0.93	Nakashima et al. 2007 [26]
po, cap, 30 mg	dextrorphan	EM	23.10	6.70	3.45	3.94	1.63	2.42	Sager et al. 2014 [31]
po, cap, 30 mg	dextrorphan	EM	18.40	19.56	0.94	4.34	3.85	1.13	Schadel et al. 1995 [32]
GMFE (dextrorphan)					1.78 (1.06–3.45) 3/4 with GMFE ≤ 2			1.47 (1.08–2.42) 3/4 with GMFE ≤ 2	
po, cap, 30 mg	dextrorphan *O*-glucuronide	EM	3634.81	3033.65	1.20	536.57	644.52	0.83	Schadel et al. 1995 [32]
GMFE (dextrorphan *O*-glucuronide)					1.20			1.20	

-: not given, $\mathrm{AUC}_{\mathrm{last}}$: AUC from the time of the first concentration measurement to the last time point of concentration measurement, cap: capsule, $\mathrm{C}_{\mathrm{max}}$: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, EM: extensive metabolizer, inf: infusion, iv: intravenous, obs.: observed, PM: poor metabolizer, po: oral, pred: predicted.

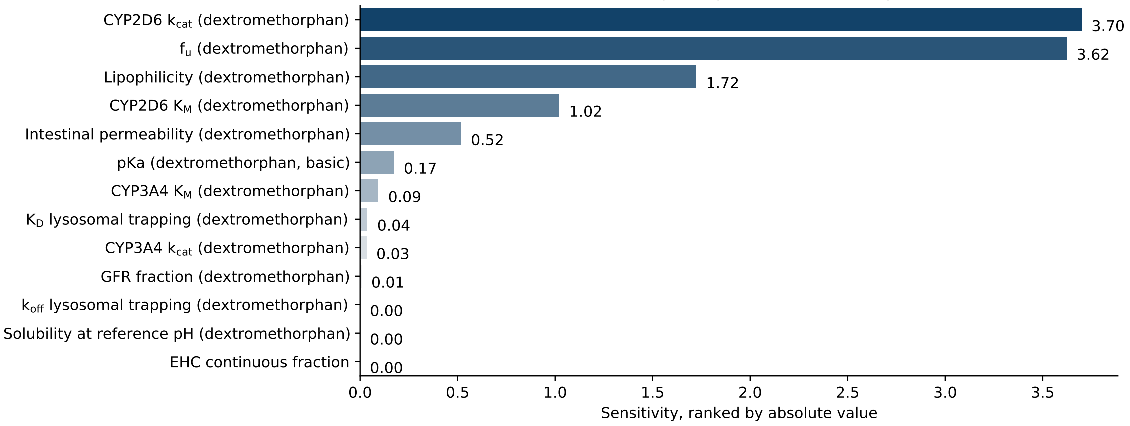
Table S3.5.2: Predicted and observed $\mathrm{AUC}_{\mathrm{last}}$ and C_{max} values and geometric mean fold errors (continued)

		CYP2D6	$\mathrm{AUC}_{\mathrm{last}}$ [ng·h/mL]			C_{max} [ng/mL]			
Dosing	Molecule	status	Pred	Obs	Pred/Obs	Pred	Obs	Pred/Obs	Reference
					1/1 with GMFE $\leq$ 2			1/1 with GMFE $\leq$ 2	
po, tab, 60 mg	dextrorphan-total	EM	8053.06	5085.21	1.58	465.71	959.10	0.49	Antecip Bioventures 2016 [24]
po, -, 60 mg	dextrorphan-total	EM	5902.53	5449.79	1.08	474.19	489.35	0.97	Feld et al. 2013 [11]
po, cap, 80 mg	dextrorphan-total	EM	3658.56	3805.82	0.96	595.96	883.78	0.67	Tenneze et al. 1999 [39]
GMFE (dextrorphan-total)					1.23 (1.04–1.58) 3/3 with GMFE $\leq$ 2			1.52 (1.03–2.04) 2/3 with GMFE $\leq$ 2	
Overall GMFE					1.57 (1.01–3.45) 18/23 with GMFE $\leq$ 2			1.61 (1.01–2.97) 17/22 with GMFE $\leq$ 2	

-: not given, $\mathrm{AUC}_{\mathrm{last}}$: AUC from the time of the first concentration measurement to the last time point of concentration measurement, cap: capsule, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, EM: extensive metabolizer, inf: infusion, iv: intravenous, obs.: observed, PM: poor metabolizer, po: oral, pred: predicted.

S3.6 Sensitivity Analysis

(a) Sensitivity analysis: dextromethorphan



(b) Sensitivity analysis: dextrorphan

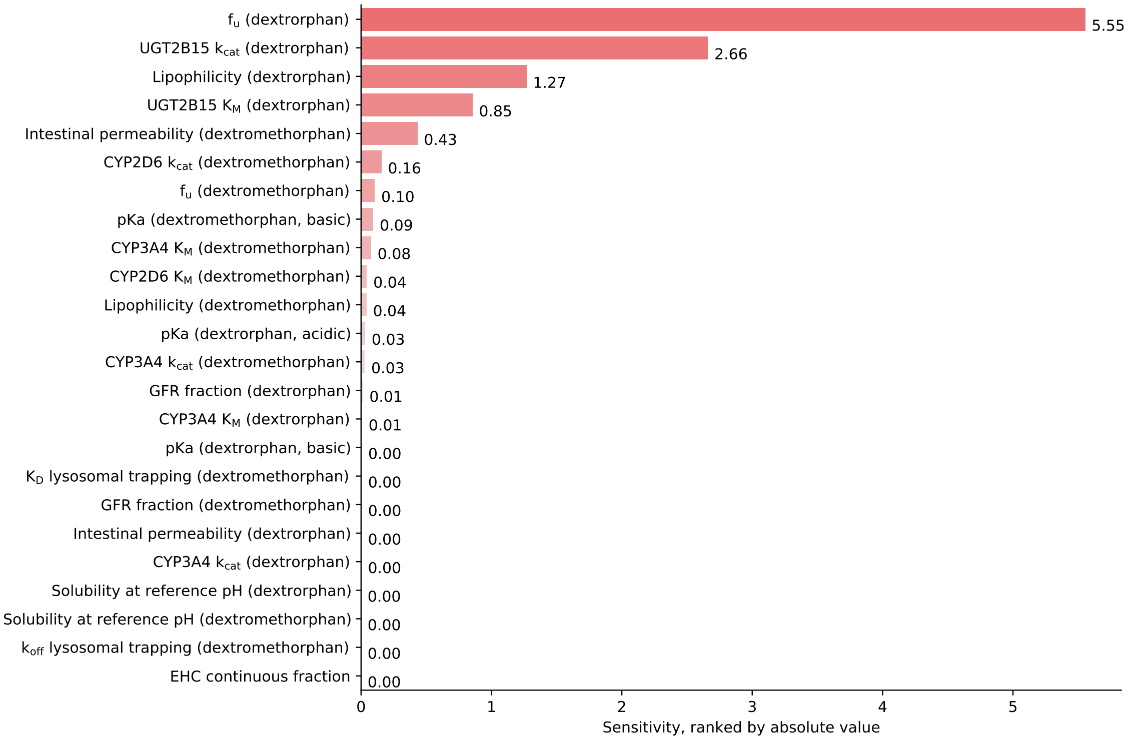


Figure S3.6.7: Sensitivity analysis of the dextromethorphan model. A sensitivity of +1.0 signifies that a 10% increase of the examined parameter value causes a 10% increase of the simulated AUC$_{0\text{-}24\,h}$. CYP2D6: Cytochrome P450 2D6, CYP3A4: cytochrome P450 3A4, f_u: fraction unbound, GFR: glomerular filtration rate, intest.: intestinal, k_{cat}: catalytic rate constant, K_D: dissociation constant, Michaelis-Menten constant (K_M): Michaelis-Menten constant, k_{off}: dissociation rate constant, pKa: acid dissociation constant.

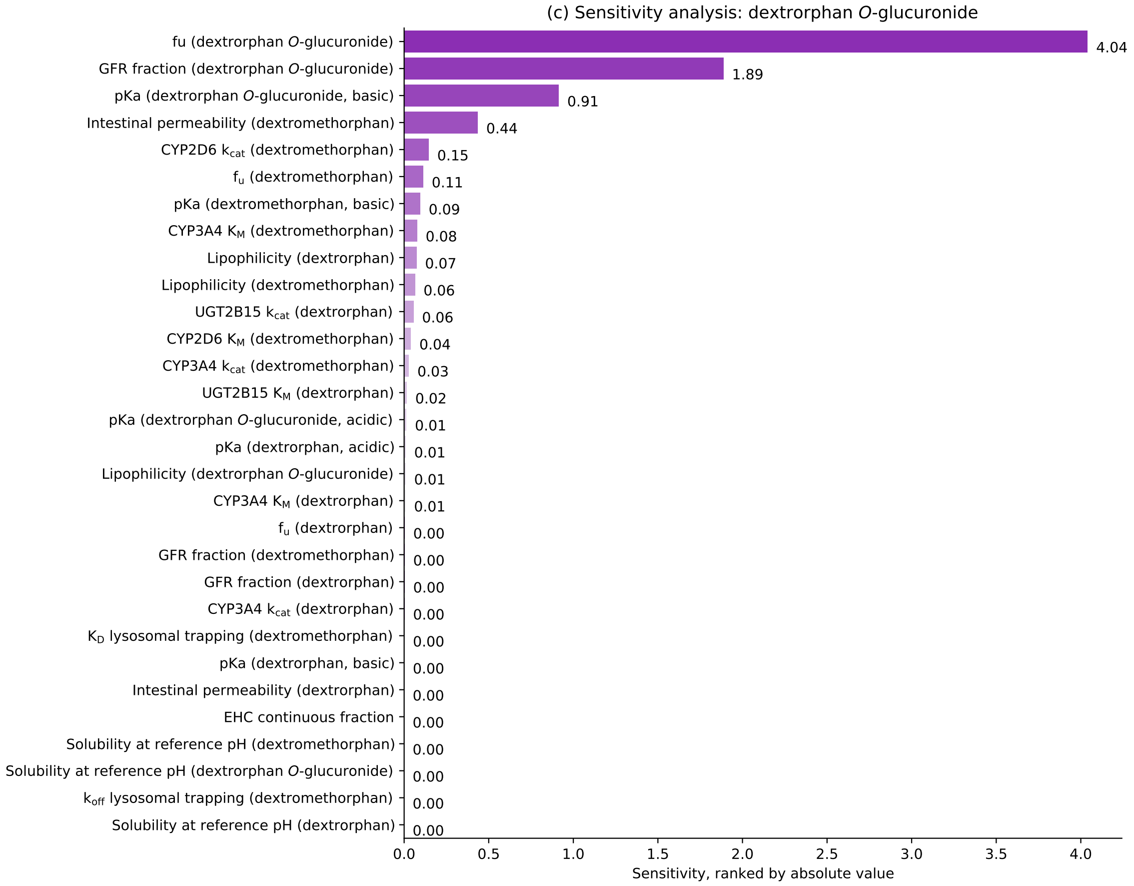


Figure S3.6.8: Sensitivity analysis of the dextromethorphan model. A sensitivity of +1.0 signifies that a 10% increase of the examined parameter value causes a 10% increase of the simulated $AUC_{0\text{-}24\,h}$. CYP2D6: Cytochrome P450 2D6, CYP3A4: cytochrome P450 3A4, f_u: fraction unbound, GFR: glomerular filtration rate, intest.: intestinal, k_{cat}: catalytic rate constant, K_D: dissociation constant, K_M: Michaelis-Menten constant, k_{off}: dissociation rate constant, pKa: acid dissociation constant.

S4 DGI Model Building

S4.1 Population k_{cat} Values

Table S4.1.1: Dextromethorphan population CYP2D6 k_{cat} values for CYP2D6 activity scores (ASs)

Activity Score	Projected Phenotype	$k_{cat} \rightarrow$ dxt [1/min]	k_{cat} Percentage of Reference (AS = 2) [%]
0	PM	0.0	0
0.25	IM	5.3	2
0.5		32.9	14
1		96.6	40
1.25	NM	115.2	48
1.5		151.8	63
2		242.5	100
3	UM	413.2	170

AS: CYP2D6 activity score, CYP2D6: Cytochrome P450 2D6, IM: intermediate metabolizer, k_{cat}: catalytic rate constant, NM: normal metabolizer, PM: poor metabolizer, UM: ultrarapid metabolizer.

S4.2 DGI Clinical Study Data

Table S4.2.2: Dextromethorphan DGI population study table

Route	Dose [mg]	n	Females [%]	Age [years]	Weight [kg]	Height [cm]	Metabolite measured	CYP2D6			Dataset	References
								Genotype	AS	P. Phenotype		
po (cap, sd)	30	6	33	22 (20-26)	-	-	dtt	-	-	EM	test	Capon 1996 [6]
po (cap, sd)	30	6	33	22 (20-26)	-	-	dtt	-	-	PM	test	Capon 1996 [6]
po (cap, sd)	30	16	50	34	73	175	-	†	1.25	NM	test[a]	Gazzaz 2018 [13]
po (-, sd)	30	11	55	31	79	-	dtt	-	-	EM	test[a]	Gorski 2004 [14]
po (-, sd)	30	1	0	31	79	-	dtt	-	-	PM	test[a]	Gorski 2004 [14]
po (cap, sd)	30	11	0	(18-55)	-	-	-	*1/*1	2	NM	test	Yamazaki 2017 [44]
po (cap, sd)	30	12	0	(18-55)	-	-	-	*10/*10	0.5	IM	test	Yamazaki 2017 [44]
po (tab, sd)	15	6	50	24 (22-26)	60	-	-	*1/*1	2	NM	training	Qiu 2016 [30]
po (tab, sd)	15	6	50	24 (22-26)	60	-	-	*1/*10	1.25	NM	training	Qiu 2016 [30]
po (tab, sd)	15	6	50	24 (22-26)	60	-	-	*10/*10	0.5	IM	training	Qiu 2016 [30]
po (sol, sd)	5	17	53	27 (18-42)	-	-	dxt	†	2	NM	test	Storelli 2018 [36]
po (sol, sd)	5	16	75	24 (21-27)	-	-	dxt	†	1	IM	test	Storelli 2018 [36]
po (cap, sd)	3/kg	6	33	(21-34)	-	-	dxt, dtt	*1/*1	2	NM	training	Zawertailo 2010 [45]

Values for age, weight and height are given as mean (range), -: not given, †: full genotype provided in publication, [a]: cocktail study, AS: CYP2D6 activity score, bid: twice daily, cap: capsule, CYP2D6: Cytochrome P450 2D6, DGI: drug-gene interaction, dxt: dextrorphan, dxt-glu: dextrorphan *O*-glucuronide, dtt: total dextrorphan, IM: intermediate metabolizer, inf: infusion, iv: intravenous, p.: projected, PM: poor metabolizer, po: oral, sd: single dose, sol: oral solution.

S5 DGI Model Evaluation

S5.1 Plasma Concentration-Time Profiles

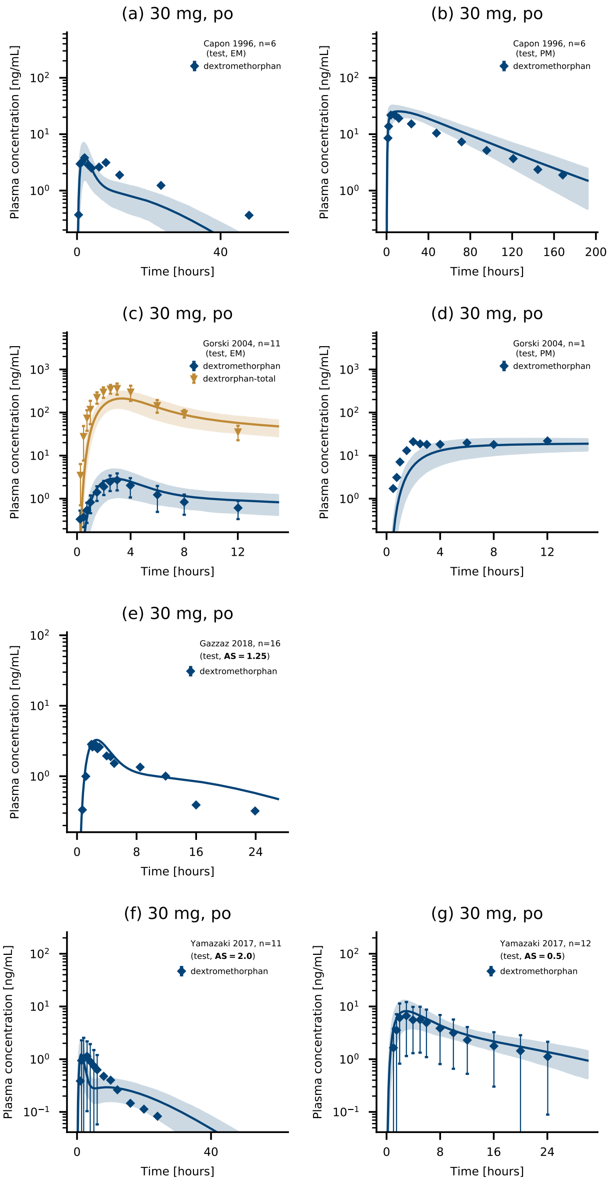


Figure S5.1.1: Dextromethorphan and total dextrorphan plasma concentrations of the modeled CYP2D6 drug-gene interaction. Predictions using the population k_{cat} of dextromethorphan and total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) plasma concentration-time profiles of the CYP2D6 drug-gene interaction (DGI) studies, compared to observed data (semilogarithmic representation). Population predictions (n=1000) are shown as lines with ribbons (arithmetic mean ± standard deviation (SD)), symbols represent the corresponding observed data ± SD. AS: activity score, EM: extensive metabolizer, PM: poor metabolizer, oral (po): oral.

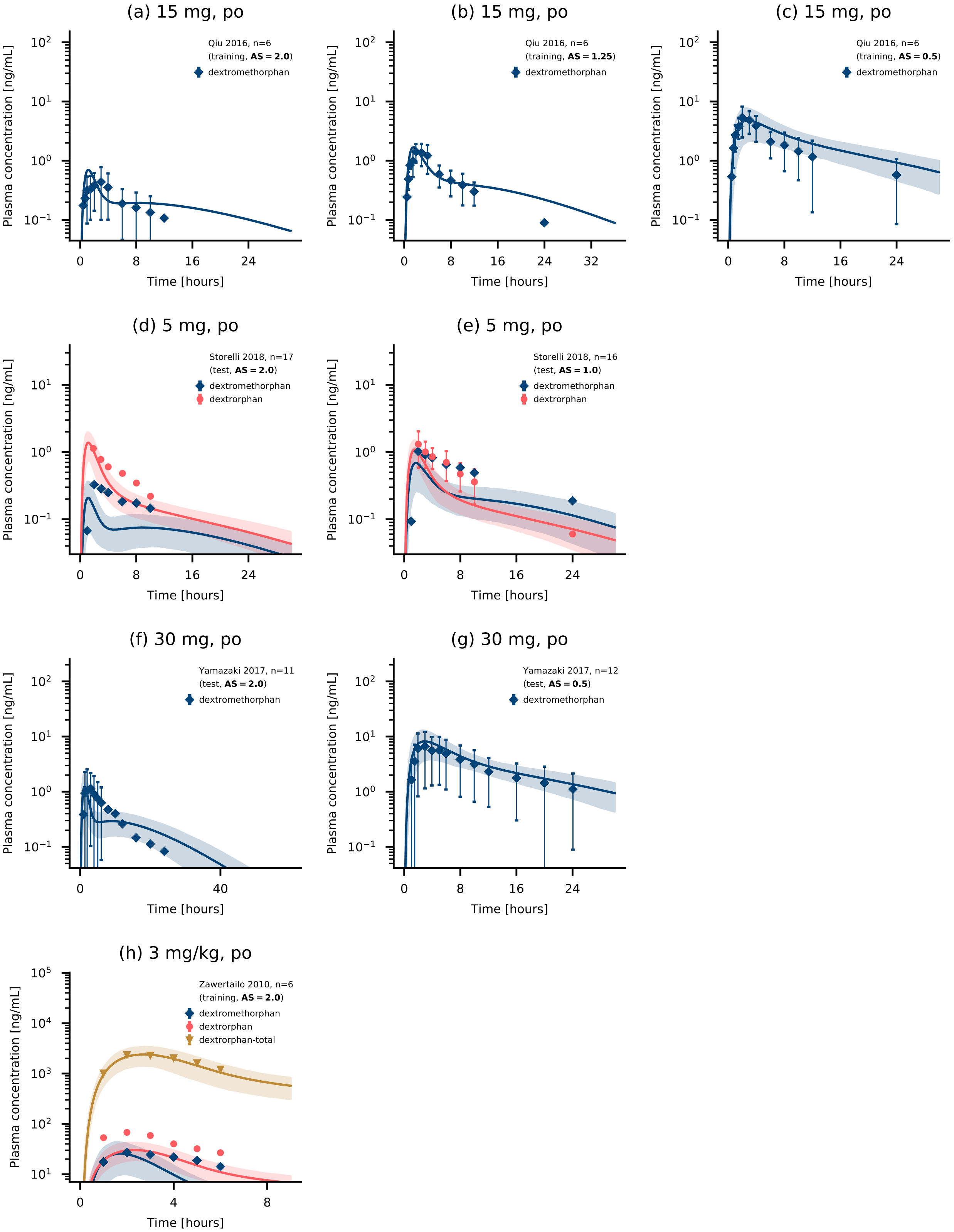


Figure S5.1.2: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations of the modeled CYP2D6 drug-gene interaction. Predictions using the population k_{cat} of dextromethorphan and total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) plasma concentration-time profiles of the CYP2D6 DGI studies, compared to observed data (semilogarithmic representation). Population predictions (n=1000) are shown as lines with ribbons (arithmetic mean $\pm$ standard deviation (SD)), symbols represent the corresponding observed data $\pm$ SD. AS: activity score, po: oral.

S5.2 Goodness-of-Fit Plots: Plasma Concentrations

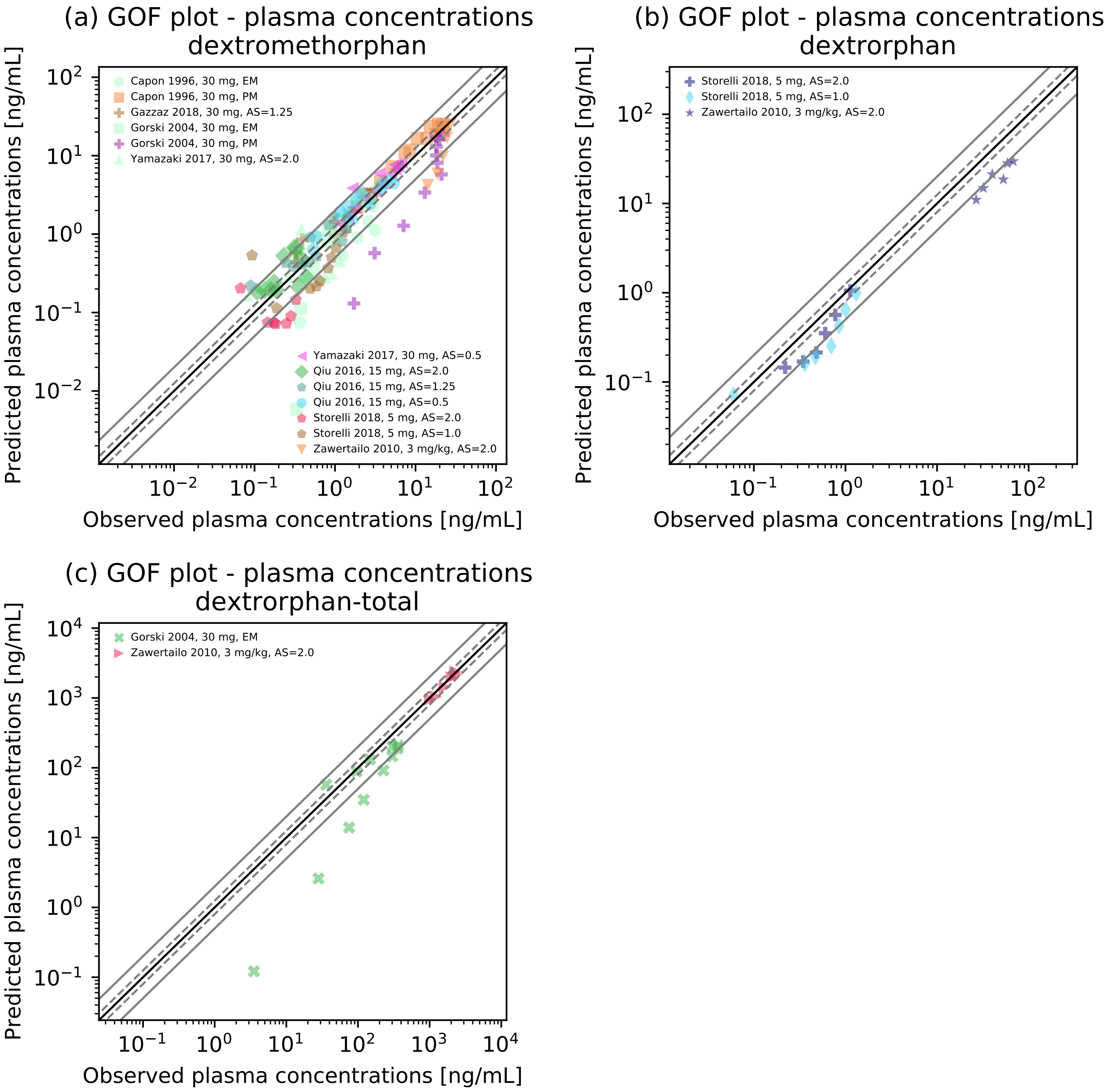


Figure S5.2.3: Goodness-of-fit plots. Predicted versus observed plasma concentration values for (a) dextromethorphan, (b) dextrorphan and (c) total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) for all studies of the DGI dataset. The solid black line marks the line of identity, the dashed gray lines mark the 0.8- to 1.25-fold range, the solid gray lines indicate the 0.5- to 2-fold range. Colored symbols represent the study population given in the legend. AS: CYP2D6 activity score, EM: extensive metabolizer, PM: poor metabolizer.

S5.3 MRD of Plasma Concentration Predictions

Table S5.3.1: Mean relative deviation of plasma concentration predictions

Dosing	Molecule	CYP2D6 status	MRD	Reference
po, cap, 30 mg	dextromethorphan	EM	2.00	Capon et al. 1996 [6]
po, cap, 30 mg	dextromethorphan	PM	1.34	Capon et al. 1996 [6]
po, cap, 30 mg	dextromethorphan	AS=1.25	1.40	Gazzaz et al. 2018 [13]
po, -, 30 mg	dextromethorphan	EM	3.68	Gorski et al. 2004 [14]
po, -, 30 mg	dextromethorphan	PM	3.36	Gorski et al. 2004 [14]
po, cap, 30 mg	dextromethorphan	AS=2.0	1.96	Yamazaki et al. 2017 [44]
po, cap, 30 mg	dextromethorphan	AS=0.5	1.46	Yamazaki et al. 2017 [44]
po, tab, 15 mg	dextromethorphan	AS=2.0	1.59	Qiu et al. 2016 [30]
po, tab, 15 mg	dextromethorphan	AS=1.25	1.59	Qiu et al. 2016 [30]
po, tab, 15 mg	dextromethorphan	AS=0.5	1.38	Qiu et al. 2016 [30]
po, sol, 5 mg	dextromethorphan	AS=2.0	2.68	Storelli et al. 2018 [37]
po, sol, 5 mg	dextromethorphan	AS=1.0	2.47	Storelli et al. 2018 [37]
po, cap, 3 mg/kg	dextromethorphan	AS=2.0	2.11	Zawertailo et al. 2010 [45]
MRD (dextromethorphan)			2.08 (1.34–3.68) 8/13 with MRD $\leq$ 2	
po, sol, 5 mg	dextrorphan	AS=2.0	1.69	Storelli et al. 2018 [37]
po, sol, 5 mg	dextrorphan	AS=1.0	1.98	Storelli et al. 2018 [37]
po, cap, 3 mg/kg	dextrorphan	AS=2.0	2.26	Zawertailo et al. 2010 [45]
MRD (dextrorphan)			1.98 (1.69–2.26) 2/3 with MRD $\leq$ 2	
po, -, 30 mg	dextrorphan-total	EM	4.26	Gorski et al. 2004 [14]
po, cap, 3 mg/kg	dextrorphan-total	AS=2.0	1.10	Zawertailo et al. 2010 [45]
MRD (dextrorphan-total)			2.68 (1.10–4.26) 1/2 with MRD $\leq$ 2	
Overall MRD			2.13 (1.10–4.26) 11/18 with MRD $\leq$ 2	

-: not given, AS: CYP2D6 activity score, cap: capsule, CYP2D6: Cytochrome P450 2D6, EM: extensive metabolizer, inf: infusion, iv: intravenous, PM: poor metabolizer, po: oral, sol: oral solution.

S5.4 $\mathrm{AUC}_{\mathrm{last}}$ and $\mathrm{C}_{\mathrm{max}}$ Goodness-of-Fit Plots

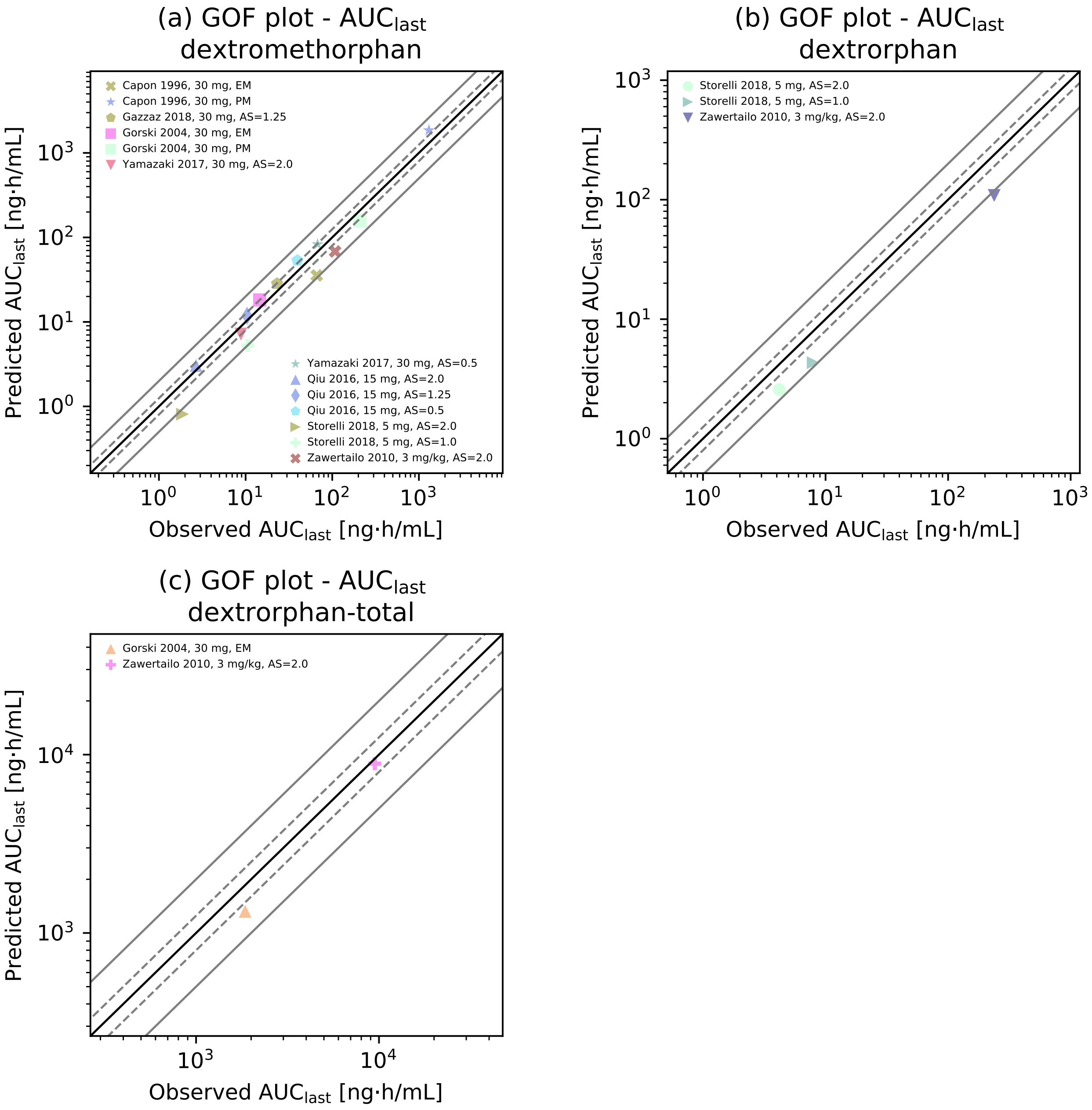
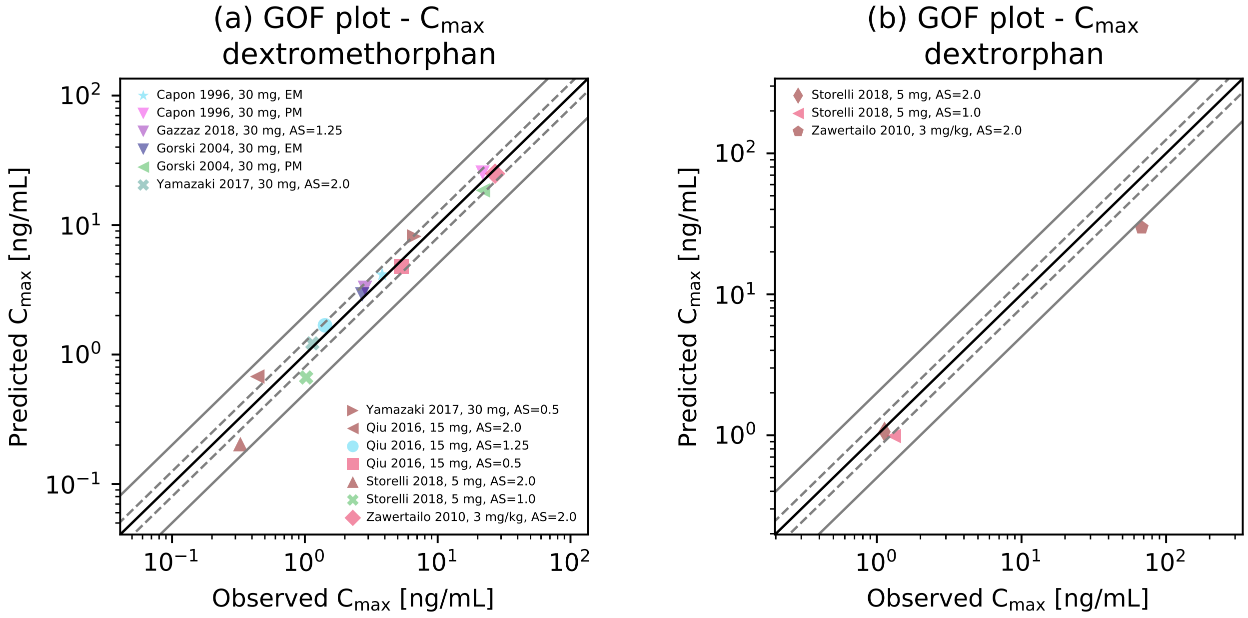


Figure S5.4.4: AUC correlation plots. Predicted versus observed $\mathrm{AUC}_{\mathrm{last}}$ for (a) dextromethorphan, (b) dextrorphan and (c) total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) for all studies of the DGI dataset. The solid black line marks the line of identity, the dashed gray lines mark the 0.8- to 1.25-fold range, the solid gray lines indicate the 0.5- to 2-fold range. Colored symbols represent the study population given in the legend. AS: CYP2D6 activity score, $\mathrm{AUC}_{\mathrm{last}}$: AUC from the time of the first concentration measurement to the last time point of concentration measurement, EM: extensive metabolizer, PM: poor metabolizer.



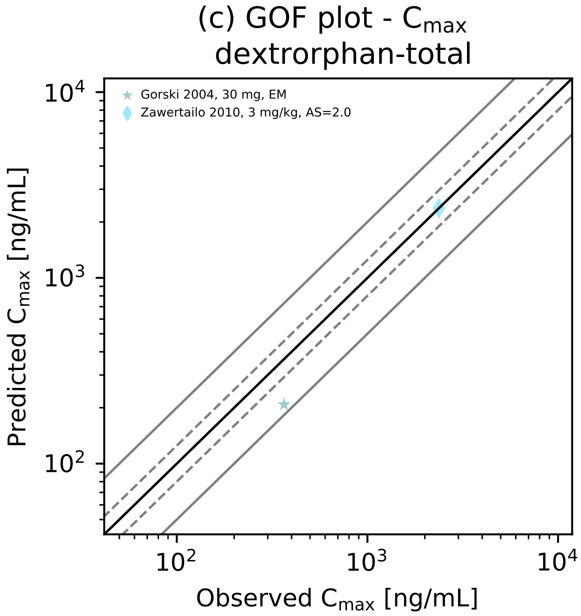


Figure S5.4.5: C_{max} correlation plots. Predicted versus observed C_{max} for (a) dextromethorphan, (b) dextrorphan and (c) total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) for all studies of the DGI dataset. The solid black line marks the line of identity, the dashed gray lines mark the 0.8- to 1.25-fold range, the solid gray lines indicate the 0.5- to 2-fold range. Colored symbols represent the study population given in the legend. AS: CYP2D6 activity score, C_{max}: peak plasma concentration, EM: extensive metabolizer, PM: poor metabolizer.

S5.5 GMFE of Predicted AUC$_{last}$ and C$_{max}$ Values

Table S5.5.2: Predicted and observed AUC$_{last}$ and C$_{max}$ values and geometric mean fold errors

		CYP2D6	AUC$_{last}$ [ng·h/ml]			C$_{max}$ [ng/ml]			
Dosing	Molecule	status	Pred	Obs	Pred/Obs	Pred	Obs	Pred/Obs	Reference
po, cap, 30 mg	dextromethorphan	EM	34.02	66.20	0.51	3.50	3.82	0.92	Capon et al. 1996 [6]
po, cap, 30 mg	dextromethorphan	PM	1840.48	1304.44	1.41	24.92	21.81	1.14	Capon et al. 1996 [6]
po, -, 30 mg	dextromethorphan	EM	17.77	14.62	1.22	2.98	2.70	1.10	Gorski et al. 2004 [14]
po, -, 30 mg	dextromethorphan	PM	171.48	208.95	0.82	20.09	21.93	0.92	Gorski et al. 2004 [14]
po, cap, 30 mg	dextromethorphan	AS=1.25	28.60	23.09	1.24	3.45	2.83	1.22	Gazzaz et al. 2018 [13]
po, cap, 30 mg	dextromethorphan	AS=2.0	7.34	8.83	0.83	1.13	1.14	0.99	Yamazaki et al. 2017 [44]
po, cap, 30 mg	dextromethorphan	AS=0.5	85.58	67.73	1.26	8.87	6.65	1.33	Yamazaki et al. 2017 [44]
po, tab, 15 mg	dextromethorphan	AS=2.0	2.91	2.68	1.08	0.62	0.44	1.41	Qiu et al. 2016 [30]
po, tab, 15 mg	dextromethorphan	AS=1.25	12.42	10.41	1.19	1.72	1.42	1.22	Qiu et al. 2016 [30]
po, tab, 15 mg	dextromethorphan	AS=0.5	54.16	39.65	1.37	5.12	5.33	0.96	Qiu et al. 2016 [30]
po, sol, 5 mg	dextromethorphan	AS=2.0	0.80	1.87	0.43	0.20	0.33	0.62	Storelli et al. 2018 [37]
po, sol, 5 mg	dextromethorphan	AS=1.0	5.42	10.59	0.51	0.65	1.02	0.63	Storelli et al. 2018 [37]
po, cap, 3 mg/kg	dextromethorphan	AS=2.0	69.64	107.81	0.65	25.94	27.04	0.96	Zawertailo et al. 2010 [45]
GMFE (dextromethorphan)					1.46 (1.08–2.33) 12/13 with GMFE ≤ 2			1.22 (1.01–1.61) 13/13 with GMFE ≤ 2	
po, sol, 5 mg	dextrorphan	AS=2.0	2.60	4.19	0.62	1.38	1.13	1.22	Storelli et al. 2018 [37]
po, sol, 5 mg	dextrorphan	AS=1.0	4.37	7.94	0.55	1.06	1.31	0.81	Storelli et al. 2018 [37]
po, cap, 3 mg/kg	dextrorphan	AS=2.0	109.82	237.65	0.46	30.63	67.77	0.45	Zawertailo et al. 2010 [45]
GMFE (dextrorphan)					1.87 (1.61–2.17) 2/3 with GMFE ≤ 2			1.52 (1.08–2.22) 2/3 with GMFE ≤ 2	
po, -, 30 mg	dextrorphan-total	EM	1307.35	1854.58	0.70	214.79	365.28	0.59	Gorski et al. 2004 [14]

-: not given, AS: CYP2D6 activity score, AUC$_{last}$: AUC from the time of the first concentration measurement to the last time point of concentration measurement, cap: capsule, C$_{max}$: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, EM: extensive metabolizer, inf: infusion, iv: intravenous, obs.: observed, PM: poor metabolizer, po: oral, pred: predicted.

Table S5.5.2: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors (continued)

		CYP2D6	AUC_{last} [ng·h/ml]			C_{max} [ng/ml]			
Dosing	Molecule	status	Pred	Obs	Pred/Obs	Pred	Obs	Pred/Obs	Reference
cap, 3 mg/kg	dextrorphan-total	AS=2.0	8998.15	9490.66	0.95	2427.95	2370.93	1.02	Zawertailo et al. 2010 [45]
GMFE (dextrorphan-total)					1.24 (1.05–1.43) 2/2 with GMFE ≤ 2			1.36 (1.02–1.69) 2/2 with GMFE ≤ 2	
Overall GMFE					1.50 (1.05–2.33) 16/18 with GMFE ≤ 2			1.28 (1.01–2.22) 17/18 with GMFE ≤ 2	

-: not given, AS: CYP2D6 activity score, AUC_{last}: AUC from the time of the first concentration measurement to the last time point of concentration measurement, cap: capsule, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, EM: extensive metabolizer, inf: infusion, iv: intravenous, obs.: observed, PM: poor metabolizer, po: oral, pred: predicted.

S5.6 DGI AUC_{last} and C_{max} Ratio Plots

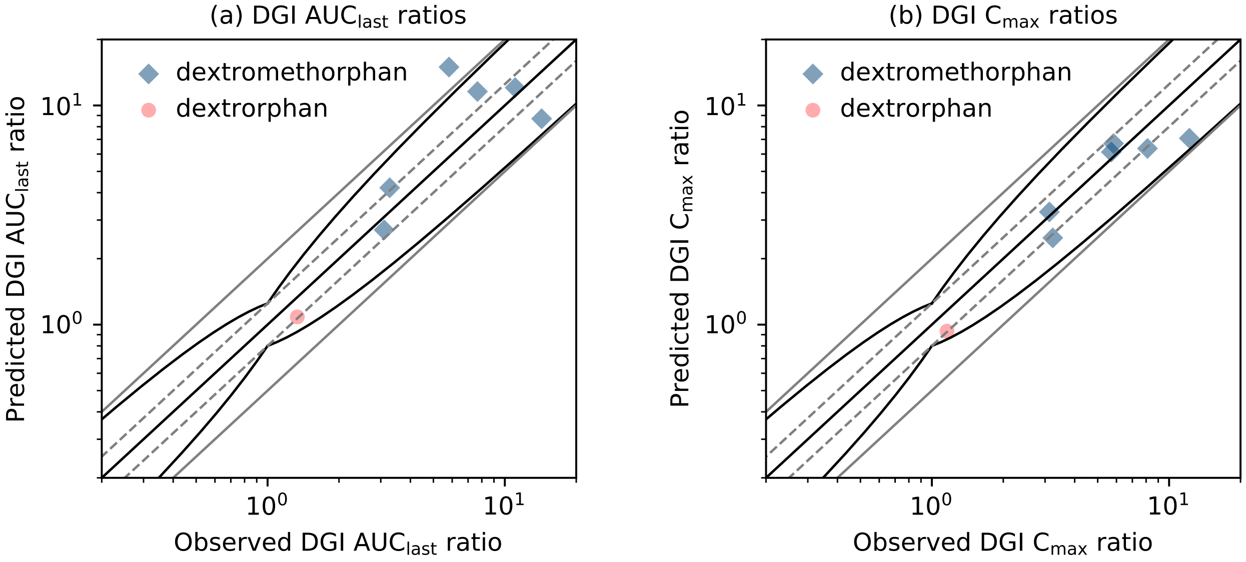


Figure S5.6.6: Predicted versus observed dextromethorphan DGI ratios. Comparison of predicted versus observed (a) AUC_{last} ratios and (b) C_{max} ratios for dextromethorphan CYP2D6 DGI-studies. The straight black line indicates the line of identity, curved black lines show prediction success limits proposed by Guest et al. including 1.25-fold variability [15]. Solid light gray lines indicate 2-fold deviation, dashed light gray lines show 1.25-fold deviation. AUC_{last}: AUC from the time of the first concentration measurement to the last time point of concentration measurement, C_{max}: peak plasma concentration, DGI: drug-gene interaction

S5.7 GMFE of Predicted DGI AUC_{last} and C_{last} Ratios

Table S5.7.3: Geometric mean fold error of predicted DGI AUC_{last} and C_{max} ratios

		CYP2D6			AUC_{last} ratio			C_{max} ratio			
Molecule	Dosing	AS	Genotype	p. Phenotype	Pred	Obs	Pred/Obs	Pred	Obs	Pred/Obs	Reference
dextromethorphan	30 mg, cap, sd	-	-	PM	16.55	5.82	2.84	7.2	5.71	1.26	Capon et al. 1996 [6]
dextromethorphan	30 mg, -, sd	-	-	PM	10.67	14.29	0.75	7.02	8.11	0.87	Gorski et al. 2004 [14]
dextromethorphan	5 mg, sol, sd	1.0	†	IM	4.37	3.27	1.34	3.2	3.13	1.02	Storelli et al. 2018 [37]
dextrorphan	5 mg, sol, sd	1.0	†	IM	1.07	1.33	0.8	0.92	1.16	0.8	Storelli et al. 2018 [37]
dextromethorphan	15 mg, tab, sd	1.25	*1/*10	NM	2.97	3.1	0.96	2.94	3.23	0.91	Qiu et al. 2016 [30]
dextromethorphan	15 mg, tab, sd	0.5	*10/*10	IM	14.01	11.06	1.27	8.94	12.17	0.73	Qiu et al. 2016 [30]
dextromethorphan	30 mg, cap, sd	0.5	*10/*10	IM	12.07	7.67	1.57	8.17	5.84	1.4	Yamazaki et al. 2017 [44]
Overall GMFE						1.45 (1.04–2.84) 6/7 with GMFE ≤ 2				1.21 (1.02–1.40) 7/7 with GMFE ≤ 2	
Ratios within the limits of *Guest et al.* [15] (including 1.25-fold deviation)						6/7				7/7	

-: not available, †: full genotype provided in publication, AS: CYP2D6 activity score, AUC_{last}: AUC from the time of the first concentration measurement to the last time point of concentration measurement, cap: capsule, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, obs: observed, IM: intermediate metabolizer, NM: normal metabolizer, p.: projected, PM: poor metabolizer, pred: predicted, sol: oral solution, sd: single dose.

S6 Interindividual Variability Within Activity Score Groups

S6.1 Exploratory Analysis of Reported Individual Plasma Concentration-Time Profiles

In the PhD thesis by Frank [12], plasma concentration-time profiles for dextromethorphan, dextrorphan and total dextrorphan were reported for five cocktail studies (A–E) for a total of 84 individuals. To assess the plausibility of the reported individual profiles, AUC_{last} and C_{max} values were calculated for all observed dextromethorphan profiles. The authors assumed that AUC_{last} and C_{max} values would generally decrease with increasing CYP2D6 activity scores. This was true for four (A, C, D and E) of the five studies, as depicted in Figure S6.1.1. As AUC_{last} and C_{max} values clearly violated this assumption, study B was excluded from the subsequent modeling steps and analyses.

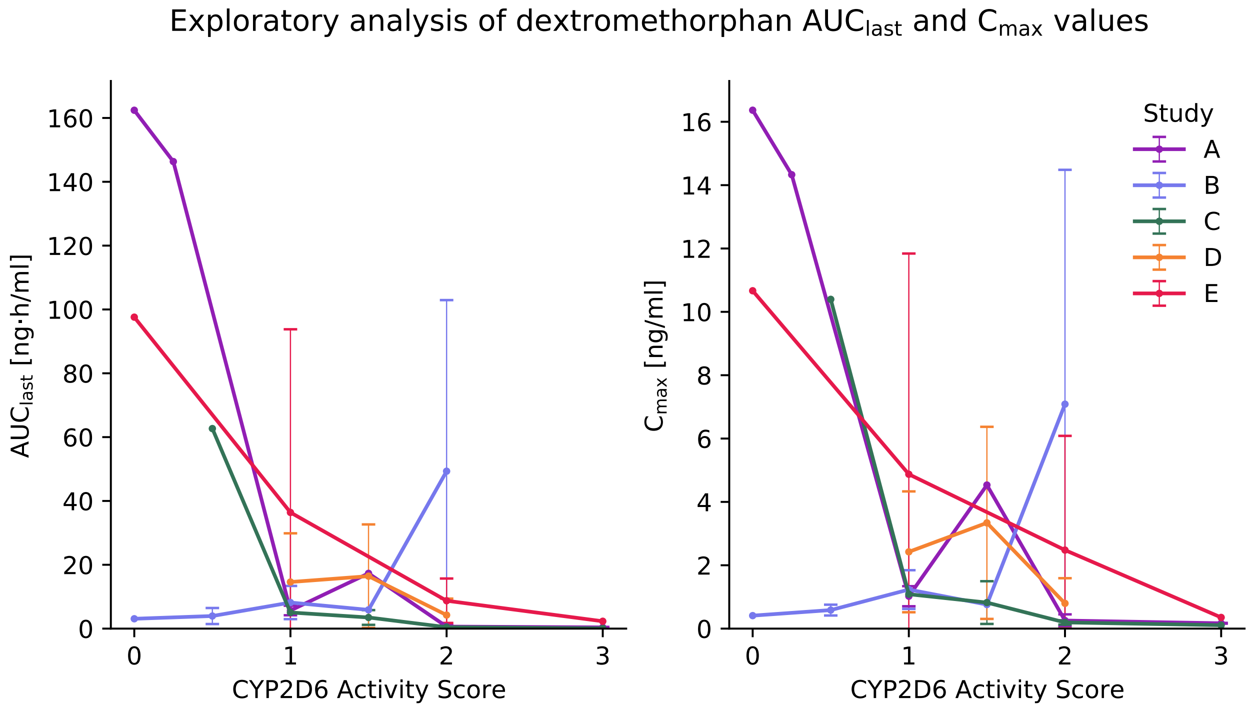


Figure S6.1.1: Exploratory analysis of dextromethorphan AUC_{last} and C_{max} values. Observed AUC_{last} (left) and C_{max} values (right panel) for dextromethorphan for individual profiles. Lines and symbols represent the observed AUC_{last} and C_{max} data points per activity score AUC_{last}: AUC from the time of the first concentration measurement to the last time point of concentration measurement, C_{max}: peak plasma concentration.

S6.2 Mean Individual k_{cat} Values

Table S6.2.1: CYP2D6 activity scores in the DGI study population with population k_{cat} values and mean individual optimized k_{cat} values.

Activity Score	Projected Phenotype	Individuals (n)	Population k_{cat} [1/min]	Mean Individual k_{cat} [1/min]
0	PM	2	0.0	-
0.25	IM	1	5.3	-
0.5		1	32.9	-
1		25	96.6	106.3 (2.5)
1.25	NM	0	115.2	-
1.5		7	151.8	168.5 (1.9)
2		26	242.5	260.0 (2.1)
3	UM	4	413.2	462 (1.3)

Individual optimized k_{cat} values are given as mean (SD), IM: intermediate metabolizer, k_{cat}: catalytic rate constant, NM: normal metabolizer, PM: poor metabolizer, n: number of individuals, UM: ultrarapid metabolizer.

S6.3 Clinical Study Data

Table S6.3.2: Dextromethorphan cocktail study table [12]

Subject ID	Sex	Age [years]	Weight [kg]	Height [cm]	Ethnicity	CYP2D6			Dataset
						genotype	AS	p. phenotype	
A01	male	42	84	188	caucasian	_*4/*10_	0.25	IM	training
A02	male	27	65	171	caucasian	_*1/*41_	1.5	NM	test
A03	male	34	77	189	caucasian	_*1/*1_	2	NM	test
A04	male	24	78	183	caucasian	_*1/*4_	1	IM	test
A05	male	27	69	176	caucasian	_*1/*4_	1	IM	test
A06	male	24	86	181	caucasian	_*1/*1_	2	NM	test
A07	male	27	74	173	caucasian	_*1/*4_	1	IM	training
A08	male	23	71	180	caucasian	_*4/*4_	0	PM	training
A09	male	27	90	190	caucasian	_*1/*2_	2	NM	training
A10	male	38	80	185	caucasian	_*2/*4_	1	IM	test
A11	male	34	101	195	caucasian	_*1/*4_	1	IM	test
A12	male	34	65	174	caucasian	_*2/*2x2_	3	UM	test
A13	male	31	83	189	caucasian	_*1/*4_	1	IM	training
A14	male	25	79	180	caucasian	_*1/*2_	2	NM	test
A15	male	23	69	175	caucasian	_*1x2/*2_	3	UM	test
A16	male	29	86	188	caucasian	_*1/*4_	1	IM	test
C01	male	25	80	178	caucasian	_*1/*1_	2	NM	test
C02	male	24	71	173	caucasian	_*1/*1_	2	NM	training
C03	male	37	66	178	caucasian	_*1/*1_	2	NM	training
C04	male	27	92	185	caucasian	_*2x2/*3_	2	NM	test
C05	male	21	79	190	caucasian	-	-	-	test
C06	male	29	76	176	caucasian	_*1/*1x2_	3	UM	training
C07	male	31	84	185	caucasian	-	-	-	test
C08	male	26	83	182	caucasian	_*4/*41_	0.5	IM	training
C09	male	25	77	184	caucasian	-	-	-	test
C10	male	26	69	184	caucasian	_*2/*9_	1.5	NM	training
C11	male	33	91	194	caucasian	_*1/*41_	1.5	NM	test
C12	male	43	71	177	caucasian	_*1/*41_	1.5	NM	test
C13	male	29	79	179	caucasian	-	-	-	test
C14	male	30	89	187	caucasian	_*1/*41_	1.5	NM	test
C15	male	22	74	176	caucasian	_*1/*4_	1	IM	training
C16	male	29	99	189	caucasian	-	-	-	test
D01	male	44	60	171	caucasian	_*1/*2_	2	NM	test
D02	male	25	75	185	caucasian	_*2/*41_	1.5	NM	training
D03	male	23	82	183	caucasian	_*1/*1_	2	NM	training
D04	male	18	74	186	caucasian	_*2/*2_	2	NM	test
D05	male	46	69	178	caucasian	-	-	-	test
D06	male	48	73	179	caucasian	_*2/*4_	1	IM	test
D07	male	30	69	173	caucasian	_*1/*2_	2	NM	test
D08	male	27	70	180	caucasian	_*2/*4_	1	IM	training
D09	male	42	74	173	caucasian	_*2/*2_	2	NM	test
D10	male	26	73	184	caucasian	_*1/*41_	1.5	NM	test

Studies A, C and D were performed in healthy subjects, whereas participants of study E were HIV-infected patients, which did not yet receive any antiretroviral treatment.
-: not given, AS: CYP2D6 activity score, CYP2D6: Cytochrome P450 2D6, IM: intermediate metabolizer, NM: normal metabolizer, p.: projected, PM: poor metabolizer, UM: ultrarapid metabolizer.

Table S6.3.2: Dextromethorphan cocktail study table [12] *(continued)*

Subject ID	Sex	Age [years]	Weight [kg]	Height [cm]	Ethnicity	CYP2D6			Dataset
						genotype	AS	p. phenotype	
D11	male	26	70	175	caucasian	_*2/*4_	1	IM	training
D12	male	27	73	190	caucasian	_*2/*4x2_	1	IM	test
E01	male	33	56	185	caucasian	_*1/*4_	1	IM	test
E02	male	51	106	170	caucasian	_*1/*4_	1	IM	test
E03	male	39	75	175	caucasian	_*1/*4_	1	IM	test
E04	male	48	73	173	caucasian	_*1/*1_	2	NM	training
E05	male	33	85	190	caucasian	_*1/*1_	2	NM	test
E06	male	35	72	175	caucasian	_*1/*3_	1	IM	test
E07	female	32	73	164	african american	_*1/*1_	2	NM	test
E08	male	43	76	172	african american	_*1/*1_	2	NM	test
E09	male	57	62	174	caucasian	_*1/*1_	2	NM	test
E10	male	30	49	171	caucasian	_*1/*5_	1	IM	training
E11	male	41	86	184	caucasian	_*1/*4_	1	IM	test
E12	male	38	69	176	caucasian	_*1/*1_	2	NM	training
E13	male	43	66	167	african american	_*1/*1_	2	NM	test
E14	male	30	75	180	caucasian	_*1/*4_	1	IM	test
E15	female	27	55	164	caucasian	_*1/*1_	2	NM	training
E16	male	59	87	183	caucasian	_*1/*4_	1	IM	training
E17	female	28	50	167	african american	_*1/2x*4_	1	IM	test
E18	female	39	63	178	caucasian	_*1/*1_	2	NM	test
E20	male	34	73	176	caucasian	_*1/*1_	2	NM	training
E21	female	36	54	156	african american	_*1/*5_	1	IM	training
E22	male	42	94	169	caucasian	_*4/*6_	0	PM	test
E23	male	60	64	178	caucasian	_*1x2/*1_	3	UM	training
E24	male	33	70	180	caucasian	_*1/*1_	2	NM	training
E25	female	60	73	180	caucasian	_*1/*1_	2	NM	training
E26	male	25	83	166	caucasian	_*1/*3_	1	IM	training
E27	male	40	70	176	caucasian	_*1/*1_	2	NM	test
E28	male	48	80	172	caucasian	_*1/*4_	1	IM	training
E30	female	38	67	173	caucasian	_*1/*4_	1	IM	test

Studies A, C and D were performed in healthy subjects, whereas participants of study E were HIV-infected patients, which did not yet receive any antiretroviral treatment.
-: not given, AS: CYP2D6 activity score, CYP2D6: Cytochrome P450 2D6, IM: intermediate metabolizer, NM: normal metabolizer, p.: projected, PM: poor metabolizer, UM: ultrarapid metabolizer.

S6.4 Plasma Concentration-Time Profiles

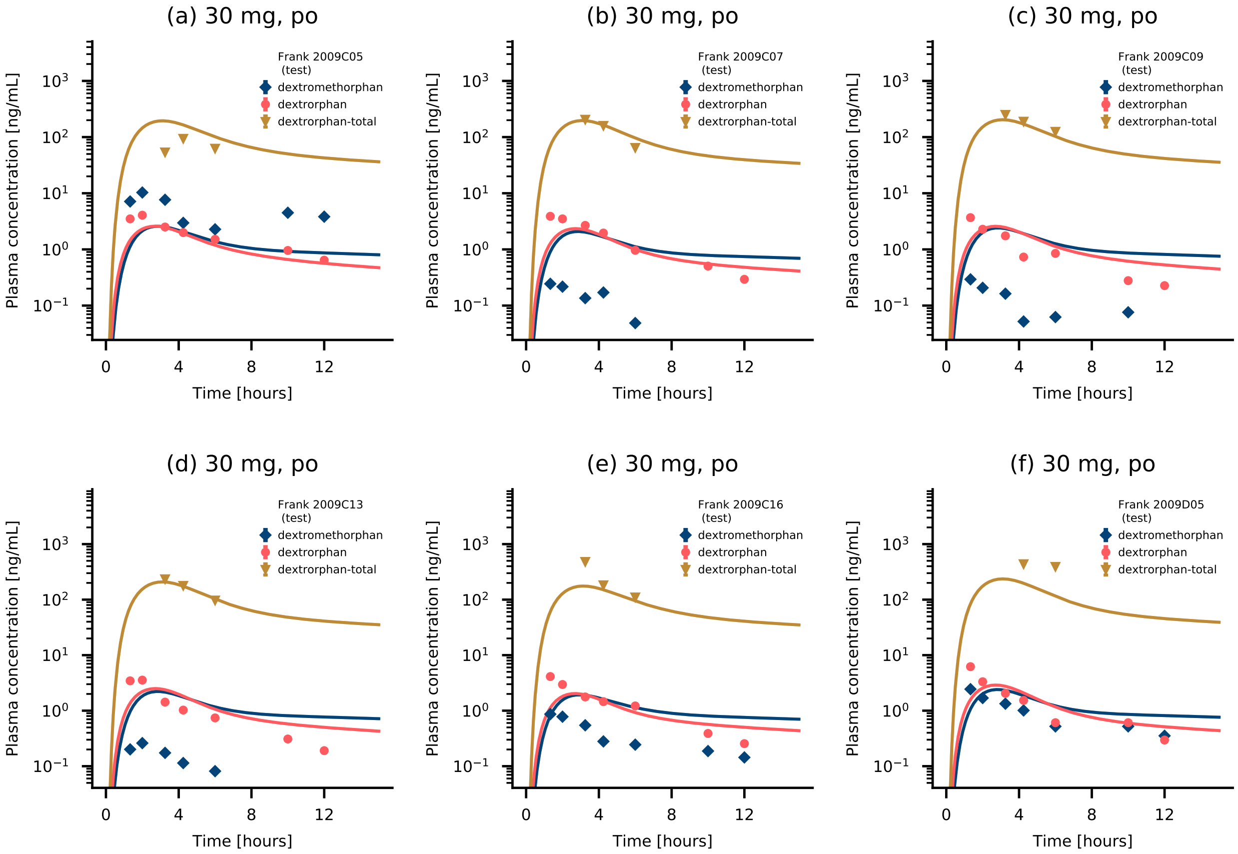


Figure S6.4.2: Dextromethorphan plasma concentrations for individuals where no genotype was provided. The simulations were performed using the model CYP2D6 k_{cat} value for normal metabolizers (see Section S2.1). Predictions of dextromethorphan and dextrorphan profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. po: oral.

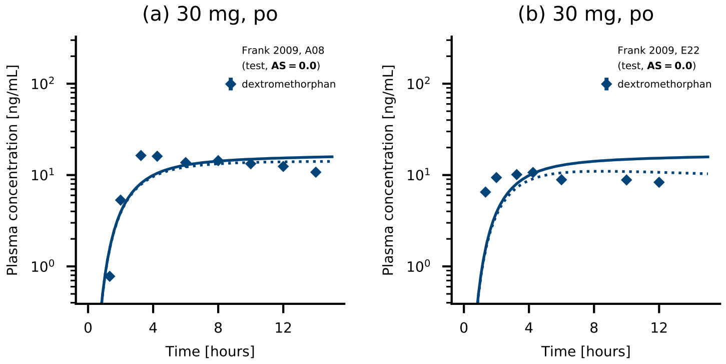


Figure S6.4.3: Dextromethorphan plasma concentrations for individuals with a CYP2D6 AS = 0 (poor metabolizer (PM)). Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.

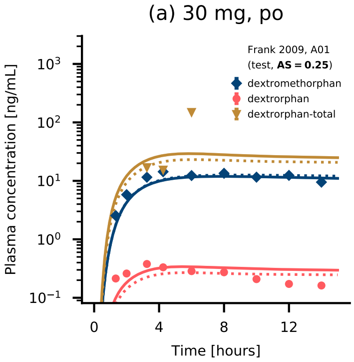


Figure S6.4.4: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations for individuals with a CYP2D6 AS = 0.25. Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.

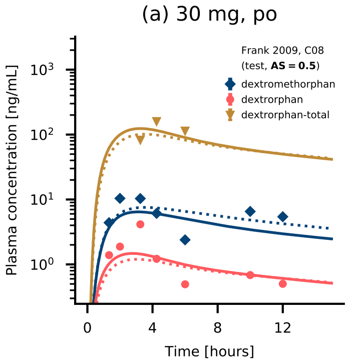


Figure S6.4.5: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations for individuals with a CYP2D6 AS = 0.5. Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.

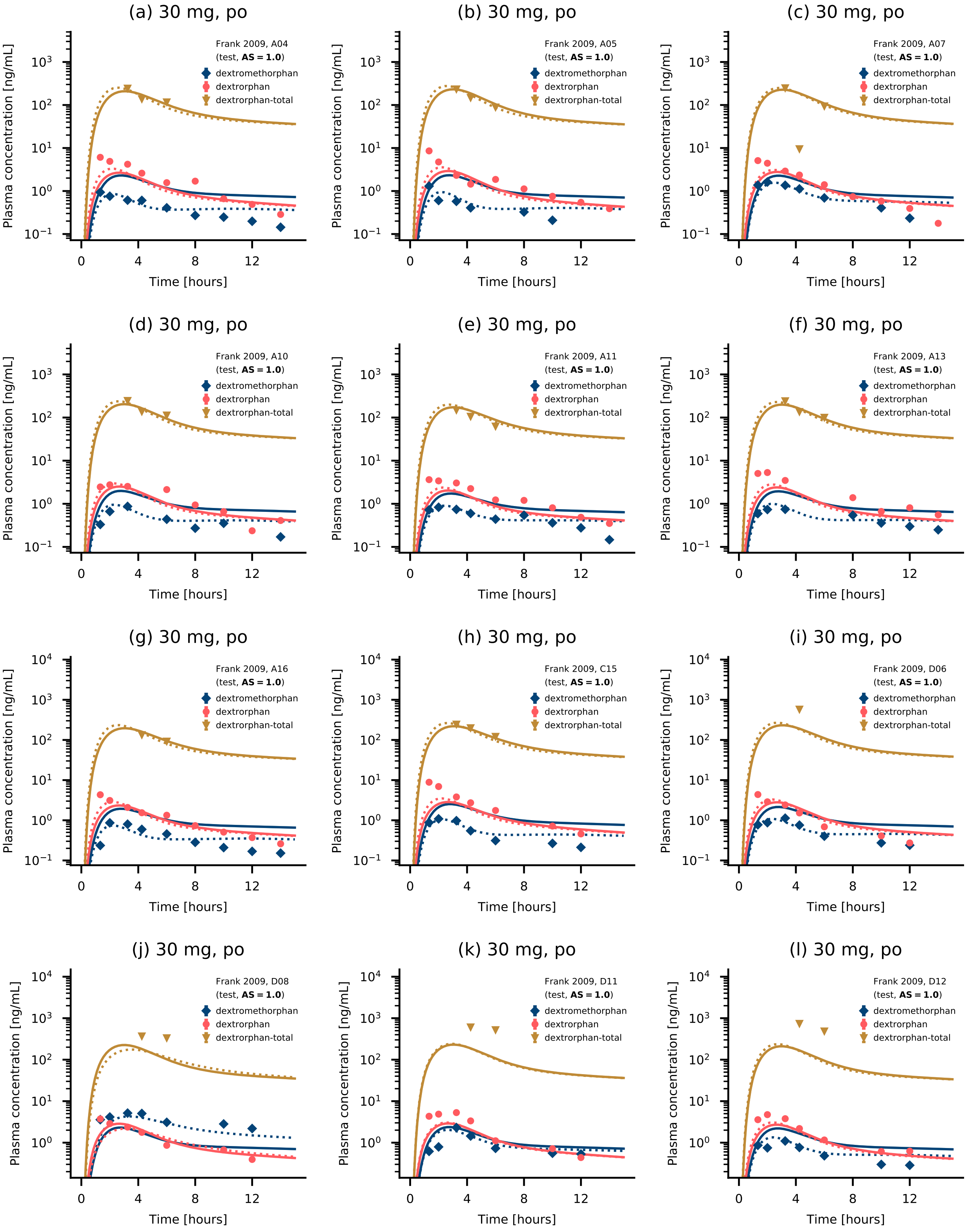
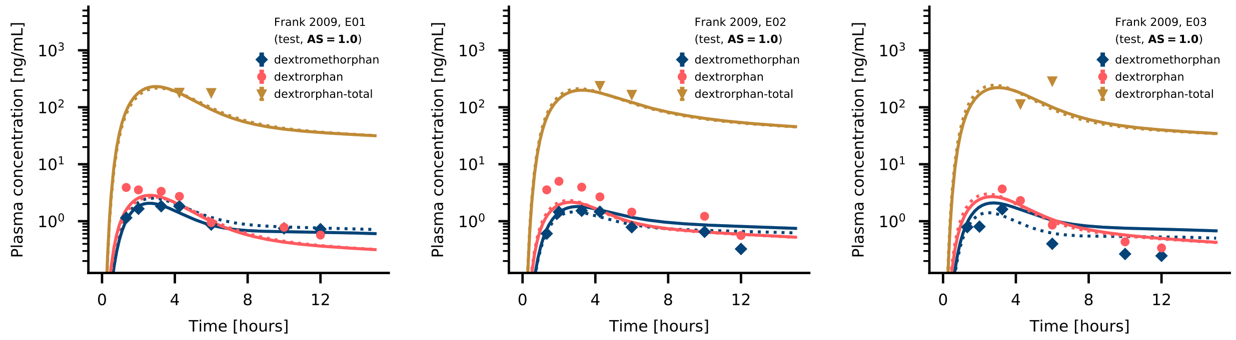
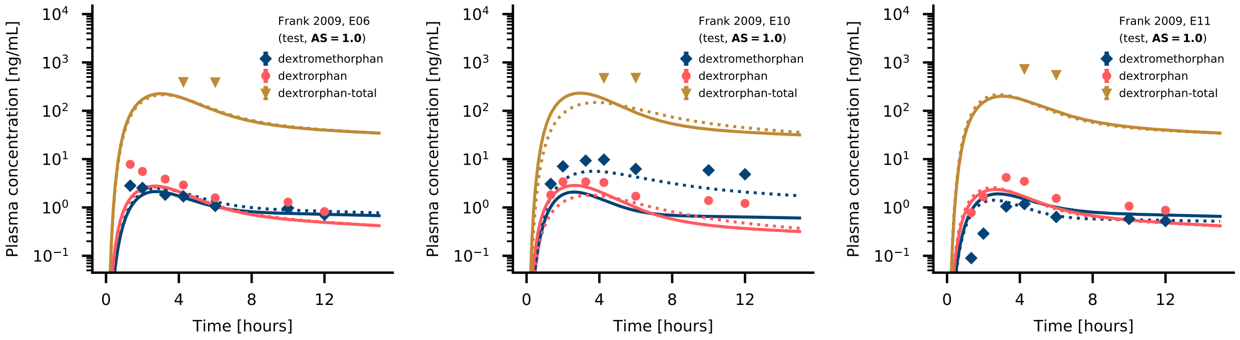
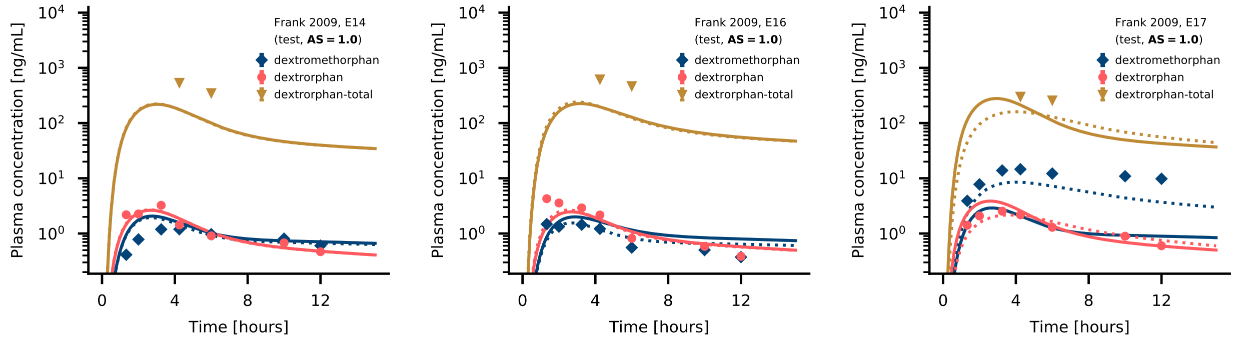


Figure S6.4.6: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations for individuals with a CYP2D6 AS = 1. Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.


(a) 30 mg, po (b) 30 mg, po (c) 30 mg, po


(d) 30 mg, po (e) 30 mg, po (f) 30 mg, po


(g) 30 mg, po (h) 30 mg, po (i) 30 mg, po

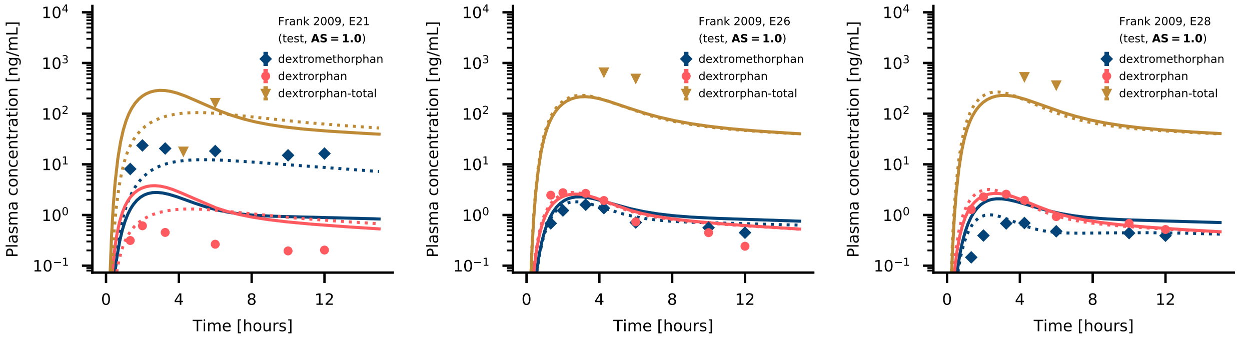

(j) 30 mg, po (k) 30 mg, po (l) 30 mg, po

Figure S6.4.7: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations for individuals with a CYP2D6 AS = 1. Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.

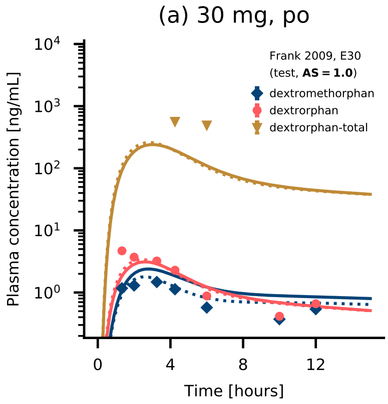
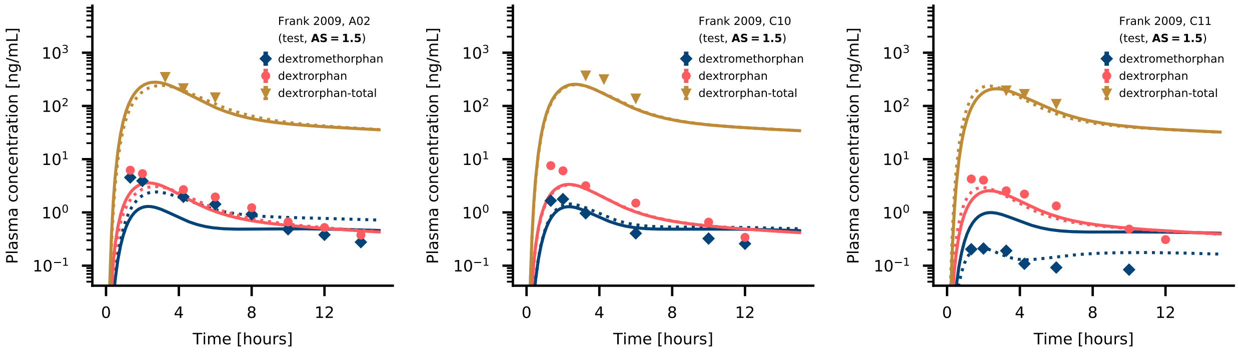
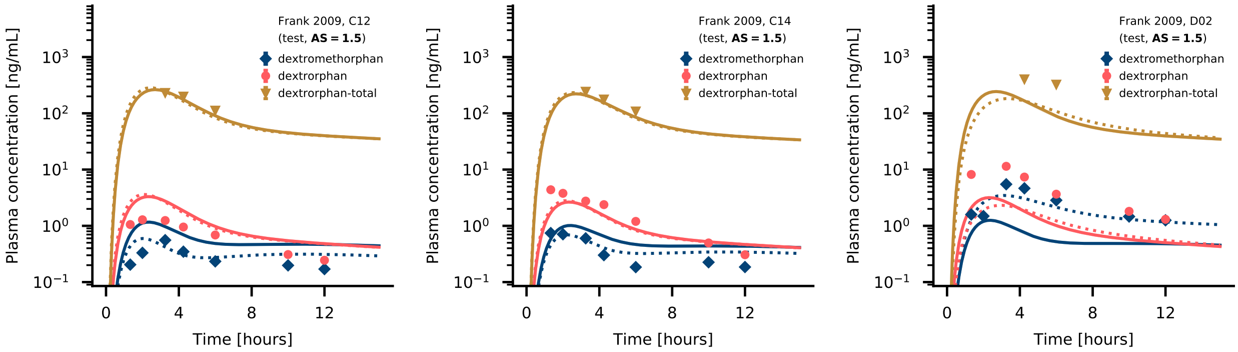


Figure S6.4.8: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations for individuals with a CYP2D6 AS = 1. Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.


(a) 30 mg, po

(b) 30 mg, po

(c) 30 mg, po


(d) 30 mg, po

(e) 30 mg, po

(f) 30 mg, po

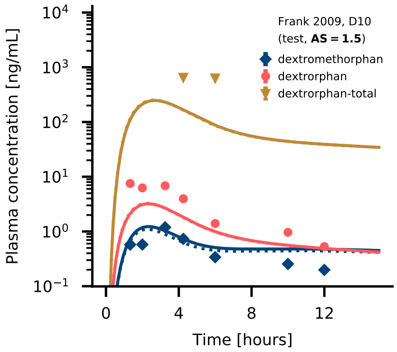

(g) 30 mg, po

Figure S6.4.9: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations for individuals with a CYP2D6 AS = 1.5. Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.

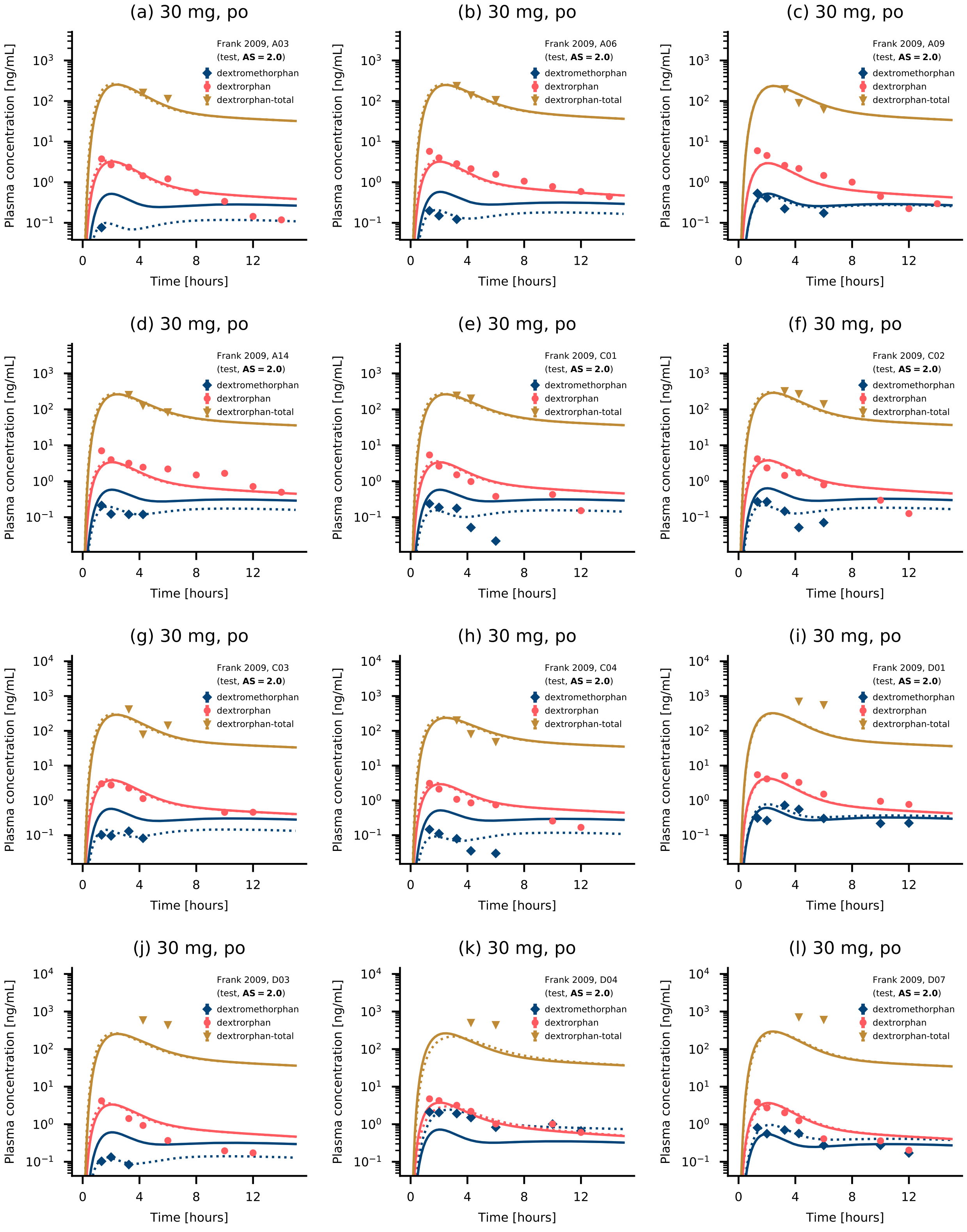


Figure S6.4.10: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations for individuals with a CYP2D6 AS = 2. Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.

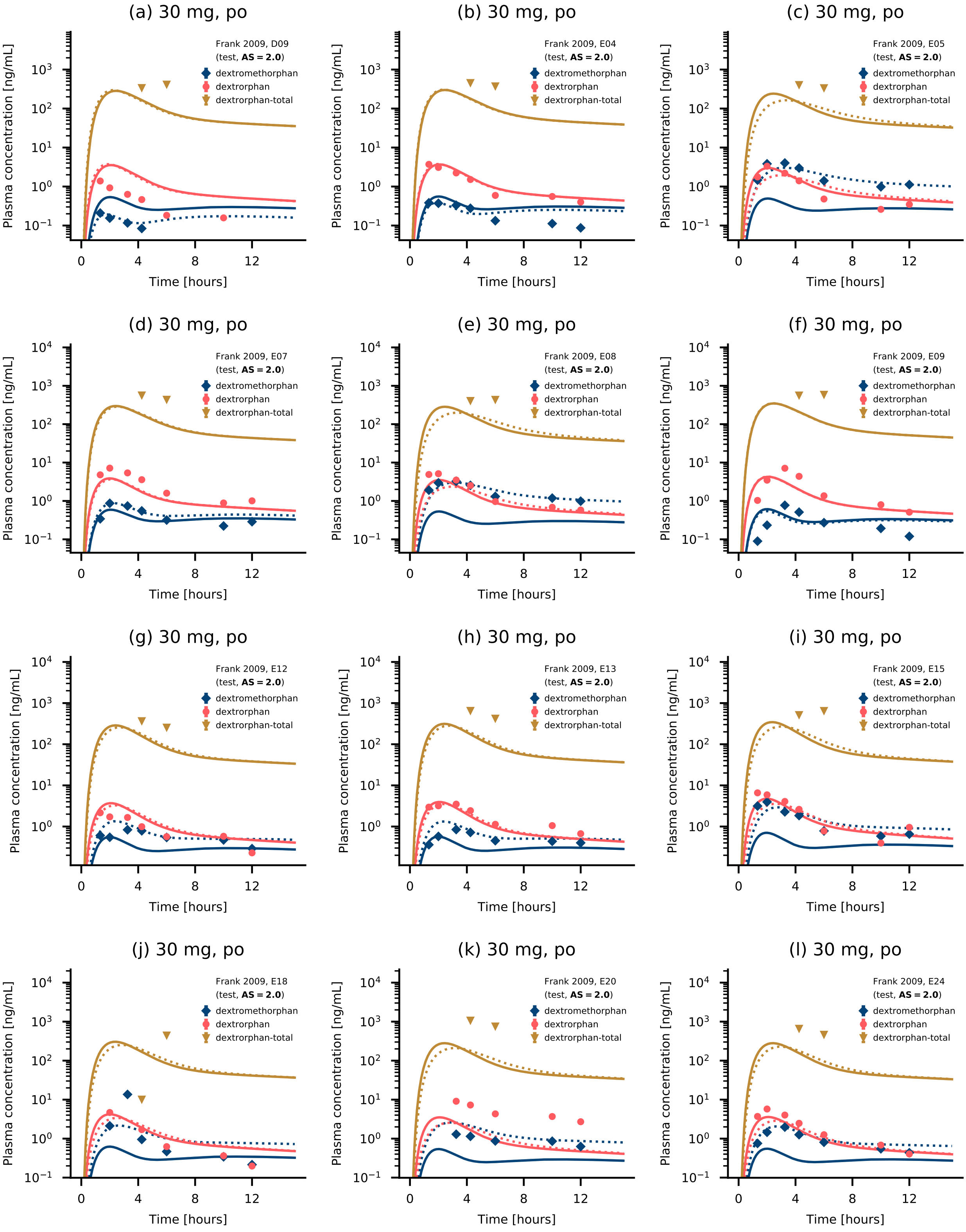


Figure S6.4.11: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations for individuals with a CYP2D6 AS = 2. Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.

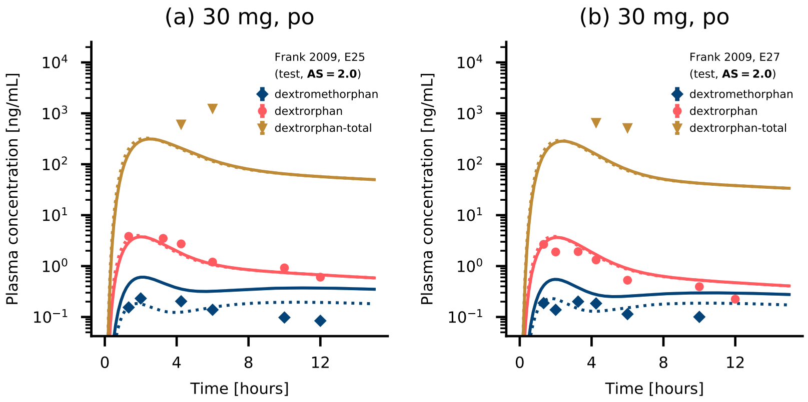


Figure S6.4.12: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations for individuals with a CYP2D6 AS = 2. Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.

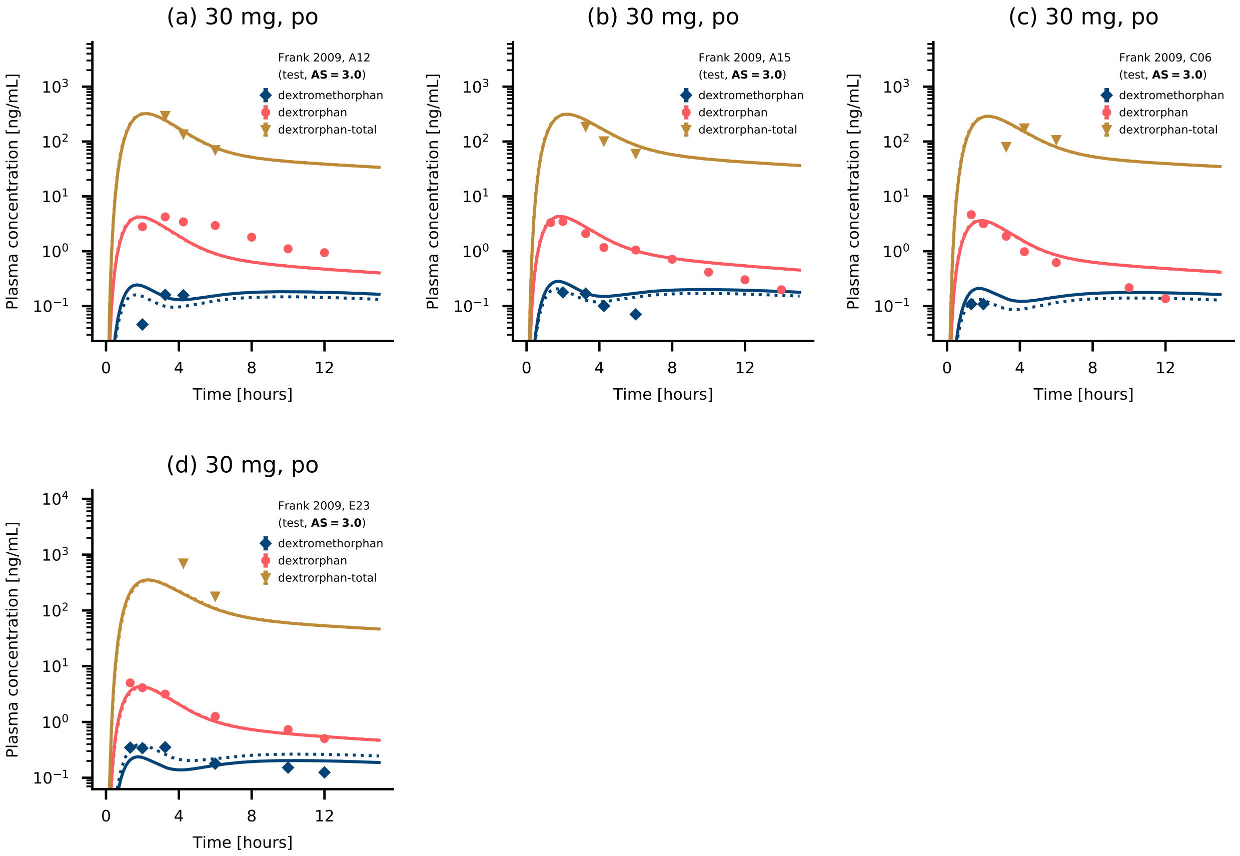


Figure S6.4.13: Dextromethorphan, dextrorphan and total dextrorphan plasma concentrations for individuals with a CYP2D6 AS = 3. Predictions of dextromethorphan plasma concentration-time profiles, compared to observed data [12] (semilogarithmic representation). Predictions using the population k_{cat} are shown as solid lines, individual predictions are shown as dotted lines. Symbols represent the corresponding observed data. AS: activity score, po: oral.

S6.5 MRD of Plasma Concentration Predictions

Table S6.5.3: Mean relative deviation of plasma concentration predictions

Dosing	Molecule	CYP2D6 status	MRD		Subject ID
			population k_{cat}	optim. ind. k_{cat}	
po, cap, 30 mg	dextromethorphan	AS=0.25	1.27	1.26	A01
po, cap, 30 mg	dextromethorphan	AS=1.5	2.59	2.06	A02
po, cap, 30 mg	dextromethorphan	AS=2.0	5.08	1.21	A03
po, cap, 30 mg	dextromethorphan	AS=1.0	3.22	1.60	A04
po, cap, 30 mg	dextromethorphan	AS=1.0	3.19	1.59	A05
po, cap, 30 mg	dextromethorphan	AS=2.0	2.70	1.20	A06
po, cap, 30 mg	dextromethorphan	AS=1.0	1.77	1.47	A07
po, cap, 30 mg	dextromethorphan	AS=0.0	1.50	1.49	A08
po, cap, 30 mg	dextromethorphan	AS=2.0	1.50	1.43	A09
po, cap, 30 mg	dextromethorphan	AS=1.0	2.68	1.55	A10
po, cap, 30 mg	dextromethorphan	AS=1.0	2.26	1.48	A11
po, cap, 30 mg	dextromethorphan	AS=3.0	2.26	1.97	A12
po, cap, 30 mg	dextromethorphan	AS=1.0	2.12	1.32	A13
po, cap, 30 mg	dextromethorphan	AS=2.0	3.19	1.29	A14
po, cap, 30 mg	dextromethorphan	AS=3.0	1.61	1.43	A15
po, cap, 30 mg	dextromethorphan	AS=1.0	3.06	1.67	A16
po, cap, 30 mg	dextromethorphan	AS=2.0	4.73	2.51	C01
po, cap, 30 mg	dextromethorphan	AS=2.0	3.43	1.76	C02
po, cap, 30 mg	dextromethorphan	AS=2.0	4.14	1.33	C03
po, cap, 30 mg	dextromethorphan	AS=2.0	5.65	1.97	C04
po, cap, 30 mg	dextromethorphan	-	3.75	3.75	C05
po, cap, 30 mg	dextromethorphan	AS=3.0	1.79	1.15	C06
po, cap, 30 mg	dextromethorphan	-	10.79	10.79	C07
po, cap, 30 mg	dextromethorphan	AS=0.5	1.70	1.61	C08
po, cap, 30 mg	dextromethorphan	-	14.00	14.00	C09
po, cap, 30 mg	dextromethorphan	AS=1.5	1.61	1.65	C10
po, cap, 30 mg	dextromethorphan	AS=1.5	4.60	1.46	C11
po, cap, 30 mg	dextromethorphan	AS=1.5	2.53	1.62	C12
po, cap, 30 mg	dextromethorphan	-	10.29	10.29	C13
po, cap, 30 mg	dextromethorphan	AS=1.5	1.91	1.51	C14
po, cap, 30 mg	dextromethorphan	AS=1.0	2.96	1.46	C15
po, cap, 30 mg	dextromethorphan	-	3.78	3.78	C16
po, cap, 30 mg	dextromethorphan	AS=2.0	1.68	1.77	D01
po, cap, 30 mg	dextromethorphan	AS=1.5	3.64	1.42	D02
po, cap, 30 mg	dextromethorphan	AS=2.0	4.70	1.10	D03
po, cap, 30 mg	dextromethorphan	AS=2.0	3.13	1.35	D04
po, cap, 30 mg	dextromethorphan	-	1.94	1.94	D05
po, cap, 30 mg	dextromethorphan	AS=1.0	2.31	1.41	D06
po, cap, 30 mg	dextromethorphan	AS=2.0	1.63	1.56	D07
po, cap, 30 mg	dextromethorphan	AS=1.0	2.86	1.57	D08
po, cap, 30 mg	dextromethorphan	AS=2.0	2.97	1.24	D09
po, cap, 30 mg	dextromethorphan	AS=1.5	1.69	1.60	D10
po, cap, 30 mg	dextromethorphan	AS=1.0	1.64	1.49	D11
po, cap, 30 mg	dextromethorphan	AS=1.0	2.20	1.44	D12
po, cap, 30 mg	dextromethorphan	AS=1.0	1.15	1.20	E01
po, cap, 30 mg	dextromethorphan	AS=1.0	1.49	1.34	E02
po, cap, 30 mg	dextromethorphan	AS=1.0	2.23	1.67	E03
po, cap, 30 mg	dextromethorphan	AS=2.0	1.98	1.75	E04

-: not given, AS: CYP2D6 activity score, cap: capsule, CYP2D6: Cytochrome P450 2D6, ind.: individual, optim.: optimized, po: oral.

Table S6.5.3: Mean relative deviation of plasma concentration predictions (continued)

Dosing	Molecule	CYP2D6 status	MRD		Subject ID
			population k_{cat}	optim. ind. k_{cat}	
po, cap, 30 mg	dextromethorphan	AS=2.0	6.49	1.35	E05
po, cap, 30 mg	dextromethorphan	AS=1.0	1.54	1.51	E06
po, cap, 30 mg	dextromethorphan	AS=2.0	1.46	1.45	E07
po, cap, 30 mg	dextromethorphan	AS=2.0	5.64	1.30	E08
po, cap, 30 mg	dextromethorphan	AS=2.0	2.44	2.37	E09
po, cap, 30 mg	dextromethorphan	AS=1.0	5.90	1.94	E10
po, cap, 30 mg	dextromethorphan	AS=1.0	3.07	2.65	E11
po, cap, 30 mg	dextromethorphan	AS=2.0	1.84	1.51	E12
po, cap, 30 mg	dextromethorphan	AS=2.0	1.71	1.56	E13
po, cap, 30 mg	dextromethorphan	AS=1.0	1.64	1.58	E14
po, cap, 30 mg	dextromethorphan	AS=2.0	3.91	1.63	E15
po, cap, 30 mg	dextromethorphan	AS=1.0	1.68	1.45	E16
po, cap, 30 mg	dextromethorphan	AS=1.0	6.78	1.95	E17
po, cap, 30 mg	dextromethorphan	AS=2.0	4.89	2.89	E18
po, cap, 30 mg	dextromethorphan	AS=2.0	3.23	1.63	E20
po, cap, 30 mg	dextromethorphan	AS=1.0	11.61	2.48	E21
po, cap, 30 mg	dextromethorphan	AS=0.0	2.06	2.00	E22
po, cap, 30 mg	dextromethorphan	AS=3.0	1.63	1.51	E23
po, cap, 30 mg	dextromethorphan	AS=2.0	2.96	1.29	E24
po, cap, 30 mg	dextromethorphan	AS=2.0	2.94	1.65	E25
po, cap, 30 mg	dextromethorphan	AS=1.0	1.56	1.27	E26
po, cap, 30 mg	dextromethorphan	AS=2.0	2.31	1.45	E27
po, cap, 30 mg	dextromethorphan	AS=1.0	3.12	1.90	E28
po, cap, 30 mg	dextromethorphan	AS=1.0	1.75	1.36	E30
MRD (dextromethorphan)			3.29 (1.15–14.00) 26/72	2.09 (1.10–14.00) 61/72 with MRD $\leq$ 2	
po, cap, 30 mg	dextrorphan	AS=0.25	1.54	1.62	A01
po, cap, 30 mg	dextrorphan	AS=1.5	1.65	1.78	A02
po, cap, 30 mg	dextrorphan	AS=2.0	1.83	1.81	A03
po, cap, 30 mg	dextrorphan	AS=1.0	1.91	1.73	A04
po, cap, 30 mg	dextrorphan	AS=1.0	1.90	1.70	A05
po, cap, 30 mg	dextrorphan	AS=2.0	1.48	1.44	A06
po, cap, 30 mg	dextrorphan	AS=1.0	1.76	1.66	A07
po, cap, 30 mg	dextrorphan	AS=2.0	1.73	1.72	A09
po, cap, 30 mg	dextrorphan	AS=1.0	1.55	1.54	A10
po, cap, 30 mg	dextrorphan	AS=1.0	1.76	1.64	A11
po, cap, 30 mg	dextrorphan	AS=3.0	2.09	2.10	A12
po, cap, 30 mg	dextrorphan	AS=1.0	2.07	1.88	A13
po, cap, 30 mg	dextrorphan	AS=2.0	1.91	1.88	A14
po, cap, 30 mg	dextrorphan	AS=3.0	1.52	1.52	A15
po, cap, 30 mg	dextrorphan	AS=1.0	1.61	1.43	A16
po, cap, 30 mg	dextrorphan	AS=2.0	2.05	1.97	C01
po, cap, 30 mg	dextrorphan	AS=2.0	2.02	1.99	C02
po, cap, 30 mg	dextrorphan	AS=2.0	1.28	1.26	C03
po, cap, 30 mg	dextrorphan	AS=2.0	1.90	1.85	C04
po, cap, 30 mg	dextrorphan	-	1.54	1.54	C05
po, cap, 30 mg	dextrorphan	AS=3.0	1.92	1.90	C06

-: not given, AS: CYP2D6 activity score, cap: capsule, CYP2D6: Cytochrome P450 2D6, ind.: individual, optim.: optimized, po: oral.

Table S6.5.3: Mean relative deviation of plasma concentration predictions (continued)

Dosing	Molecule	CYP2D6 status	MRD population k_{cat}	MRD optim. ind. k_{cat}	Subject ID
po, cap, 30 mg	dextrorphan	-	1.66	1.66	C07
po, cap, 30 mg	dextrorphan	AS=0.5	1.67	1.84	C08
po, cap, 30 mg	dextrorphan	-	2.00	2.00	C09
po, cap, 30 mg	dextrorphan	AS=1.5	1.84	1.87	C10
po, cap, 30 mg	dextrorphan	AS=1.5	1.63	1.51	C11
po, cap, 30 mg	dextrorphan	AS=1.5	1.99	2.06	C12
po, cap, 30 mg	dextrorphan	-	1.95	1.95	C13
po, cap, 30 mg	dextrorphan	AS=1.5	1.61	1.55	C14
po, cap, 30 mg	dextrorphan	AS=1.0	2.18	1.86	C15
po, cap, 30 mg	dextrorphan	-	1.84	1.84	C16
po, cap, 30 mg	dextrorphan	AS=2.0	1.59	1.59	D01
po, cap, 30 mg	dextrorphan	AS=1.5	3.60	3.91	D02
po, cap, 30 mg	dextrorphan	AS=2.0	2.37	2.27	D03
po, cap, 30 mg	dextrorphan	AS=2.0	1.31	1.55	D04
po, cap, 30 mg	dextrorphan	-	1.89	1.89	D05
po, cap, 30 mg	dextrorphan	AS=1.0	1.68	1.49	D06
po, cap, 30 mg	dextrorphan	AS=2.0	1.66	1.72	D07
po, cap, 30 mg	dextrorphan	AS=1.0	1.43	1.76	D08
po, cap, 30 mg	dextrorphan	AS=2.0	3.27	3.26	D09
po, cap, 30 mg	dextrorphan	AS=1.5	2.14	2.11	D10
po, cap, 30 mg	dextrorphan	AS=1.0	1.72	1.66	D11
po, cap, 30 mg	dextrorphan	AS=1.0	1.57	1.43	D12
po, cap, 30 mg	dextrorphan	AS=1.0	1.63	1.69	E01
po, cap, 30 mg	dextrorphan	AS=1.0	2.00	1.91	E02
po, cap, 30 mg	dextrorphan	AS=1.0	1.35	1.32	E03
po, cap, 30 mg	dextrorphan	AS=2.0	1.27	1.25	E04
po, cap, 30 mg	dextrorphan	AS=2.0	1.41	1.79	E05
po, cap, 30 mg	dextrorphan	AS=1.0	2.27	2.35	E06
po, cap, 30 mg	dextrorphan	AS=2.0	1.73	1.74	E07
po, cap, 30 mg	dextrorphan	AS=2.0	1.43	1.97	E08
po, cap, 30 mg	dextrorphan	AS=2.0	1.88	1.90	E09
po, cap, 30 mg	dextrorphan	AS=1.0	2.03	2.19	E10
po, cap, 30 mg	dextrorphan	AS=1.0	1.77	1.85	E11
po, cap, 30 mg	dextrorphan	AS=2.0	1.68	1.69	E12
po, cap, 30 mg	dextrorphan	AS=2.0	1.38	1.35	E13
po, cap, 30 mg	dextrorphan	AS=1.0	1.26	1.24	E14
po, cap, 30 mg	dextrorphan	AS=2.0	1.49	1.83	E15
po, cap, 30 mg	dextrorphan	AS=1.0	1.67	1.57	E16
po, cap, 30 mg	dextrorphan	AS=1.0	1.38	1.27	E17
po, cap, 30 mg	dextrorphan	AS=2.0	1.76	1.92	E18
po, cap, 30 mg	dextrorphan	AS=2.0	5.10	4.55	E20
po, cap, 30 mg	dextrorphan	AS=1.0	5.33	3.11	E21
po, cap, 30 mg	dextrorphan	AS=3.0	1.20	1.22	E23
po, cap, 30 mg	dextrorphan	AS=2.0	1.43	1.62	E24
po, cap, 30 mg	dextrorphan	AS=2.0	1.29	1.30	E25
po, cap, 30 mg	dextrorphan	AS=1.0	1.61	1.56	E26
po, cap, 30 mg	dextrorphan	AS=2.0	1.59	1.59	E27
po, cap, 30 mg	dextrorphan	AS=1.0	1.10	1.27	E28
po, cap, 30 mg	dextrorphan	AS=1.0	1.55	1.45	E30

-: not given, AS: CYP2D6 activity score, cap: capsule, CYP2D6: Cytochrome P450 2D6, ind.: individual, optim.: optimized, po: oral.

Table S6.5.3: Mean relative deviation of plasma concentration predictions (continued)

Dosing	Molecule	CYP2D6 status	MRD population k_{cat}	MRD optim. ind. k_{cat}	Subject ID
MRD (dextrorphan)			1.85 (1.10–5.33) 57/72	1.82 (1.22–4.55) 60/70 with MRD $\leq$ 2	
po, cap, 30 mg	dextrorphan-total	AS=0.25	2.75	2.99	A01
po, cap, 30 mg	dextrorphan-total	AS=1.5	1.40	1.35	A02
po, cap, 30 mg	dextrorphan-total	AS=2.0	1.41	1.50	A03
po, cap, 30 mg	dextrorphan-total	AS=1.0	1.20	1.22	A04
po, cap, 30 mg	dextrorphan-total	AS=1.0	1.17	1.09	A05
po, cap, 30 mg	dextrorphan-total	AS=2.0	1.17	1.20	A06
po, cap, 30 mg	dextrorphan-total	AS=1.0	5.56	5.48	A07
po, cap, 30 mg	dextrorphan-total	AS=2.0	1.33	1.33	A09
po, cap, 30 mg	dextrorphan-total	AS=1.0	1.21	1.25	A10
po, cap, 30 mg	dextrorphan-total	AS=1.0	1.30	1.27	A11
po, cap, 30 mg	dextrorphan-total	AS=3.0	1.15	1.15	A12
po, cap, 30 mg	dextrorphan-total	AS=1.0	1.18	1.17	A13
po, cap, 30 mg	dextrorphan-total	AS=2.0	1.14	1.14	A14
po, cap, 30 mg	dextrorphan-total	AS=3.0	1.44	1.42	A15
po, cap, 30 mg	dextrorphan-total	AS=1.0	1.13	1.14	A16
po, cap, 30 mg	dextrorphan-total	AS=2.0	1.17	1.23	C01
po, cap, 30 mg	dextrorphan-total	AS=2.0	1.54	1.63	C02
po, cap, 30 mg	dextrorphan-total	AS=2.0	1.88	1.90	C03
po, cap, 30 mg	dextrorphan-total	AS=2.0	1.56	1.48	C04
po, cap, 30 mg	dextrorphan-total	-	2.33	2.33	C05
po, cap, 30 mg	dextrorphan-total	AS=3.0	1.88	1.87	C06
po, cap, 30 mg	dextrorphan-total	-	1.25	1.25	C07
po, cap, 30 mg	dextrorphan-total	AS=0.5	1.39	1.43	C08
po, cap, 30 mg	dextrorphan-total	-	1.21	1.21	C09
po, cap, 30 mg	dextrorphan-total	AS=1.5	1.72	1.70	C10
po, cap, 30 mg	dextrorphan-total	AS=1.5	1.24	1.36	C11
po, cap, 30 mg	dextrorphan-total	AS=1.5	1.17	1.25	C12
po, cap, 30 mg	dextrorphan-total	-	1.08	1.08	C13
po, cap, 30 mg	dextrorphan-total	AS=1.5	1.22	1.25	C14
po, cap, 30 mg	dextrorphan-total	AS=1.0	1.11	1.19	C15
po, cap, 30 mg	dextrorphan-total	-	1.84	1.84	C16
po, cap, 30 mg	dextrorphan-total	AS=2.0	5.36	5.22	D01
po, cap, 30 mg	dextrorphan-total	AS=1.5	3.08	2.76	D02
po, cap, 30 mg	dextrorphan-total	AS=2.0	4.53	4.83	D03
po, cap, 30 mg	dextrorphan-total	AS=2.0	4.14	3.61	D04
po, cap, 30 mg	dextrorphan-total	-	2.85	2.85	D05
po, cap, 30 mg	dextrorphan-total	AS=1.0	3.06	3.21	D06
po, cap, 30 mg	dextrorphan-total	AS=2.0	5.92	5.56	D07
po, cap, 30 mg	dextrorphan-total	AS=1.0	2.70	2.60	D08
po, cap, 30 mg	dextrorphan-total	AS=2.0	3.52	3.70	D09
po, cap, 30 mg	dextrorphan-total	AS=1.5	5.51	5.60	D10
po, cap, 30 mg	dextrorphan-total	AS=1.0	4.09	4.19	D11
po, cap, 30 mg	dextrorphan-total	AS=1.0	4.84	5.20	D12
po, cap, 30 mg	dextrorphan-total	AS=1.0	1.62	1.55	E01
po, cap, 30 mg	dextrorphan-total	AS=1.0	1.38	1.38	E02
po, cap, 30 mg	dextrorphan-total	AS=1.0	2.26	2.38	E03

-: not given, AS: CYP2D6 activity score, cap: capsule, CYP2D6: Cytochrome P450 2D6, ind.: individual, optim.: optimized, po: oral.

Table S6.5.3: Mean relative deviation of plasma concentration predictions (continued)

Dosing	Molecule	CYP2D6 status	MRD		Subject ID
			population k_{cat}	optim. ind. k_{cat}	
po, cap, 30 mg	dextrorphan-total	AS=2.0	3.32	3.40	E04
po, cap, 30 mg	dextrorphan-total	AS=2.0	3.73	3.12	E05
po, cap, 30 mg	dextrorphan-total	AS=1.0	3.07	3.00	E06
po, cap, 30 mg	dextrorphan-total	AS=2.0	4.03	3.88	E07
po, cap, 30 mg	dextrorphan-total	AS=2.0	3.75	3.04	E08
po, cap, 30 mg	dextrorphan-total	AS=2.0	4.07	4.11	E09
po, cap, 30 mg	dextrorphan-total	AS=1.0	4.00	3.89	E10
po, cap, 30 mg	dextrorphan-total	AS=1.0	5.17	5.36	E11
po, cap, 30 mg	dextrorphan-total	AS=2.0	2.84	2.54	E12
po, cap, 30 mg	dextrorphan-total	AS=2.0	4.36	3.92	E13
po, cap, 30 mg	dextrorphan-total	AS=1.0	3.34	3.37	E14
po, cap, 30 mg	dextrorphan-total	AS=2.0	4.95	3.96	E15
po, cap, 30 mg	dextrorphan-total	AS=1.0	3.48	3.53	E16
po, cap, 30 mg	dextrorphan-total	AS=1.0	1.95	1.97	E17
po, cap, 30 mg	dextrorphan-total	AS=2.0	9.98	10.14	E18
po, cap, 30 mg	dextrorphan-total	AS=2.0	8.25	6.70	E20
po, cap, 30 mg	dextrorphan-total	AS=1.0	6.08	3.55	E21
po, cap, 30 mg	dextrorphan-total	AS=3.0	2.67	2.61	E23
po, cap, 30 mg	dextrorphan-total	AS=2.0	5.23	4.36	E24
po, cap, 30 mg	dextrorphan-total	AS=2.0	6.30	6.58	E25
po, cap, 30 mg	dextrorphan-total	AS=1.0	3.94	4.02	E26
po, cap, 30 mg	dextrorphan-total	AS=2.0	5.41	5.70	E27
po, cap, 30 mg	dextrorphan-total	AS=1.0	2.98	3.24	E28
po, cap, 30 mg	dextrorphan-total	AS=1.0	3.71	3.88	E30
MRD (dextrorphan-total)			2.99 (1.08–9.98) 31/70	2.90 (1.08–10.14) 31/70 with MRD ≤ 2	
Overall MRD			2.72 (1.08–14.00) 114/212	2.27 (1.08–14.00) 152/212 with MRD ≤ 2	

-: not given, AS: CYP2D6 activity score, cap: capsule, CYP2D6: Cytochrome P450 2D6, ind.: individual, optim.: optimized, po: oral.

S6.6 Goodness-of-Fit Plots

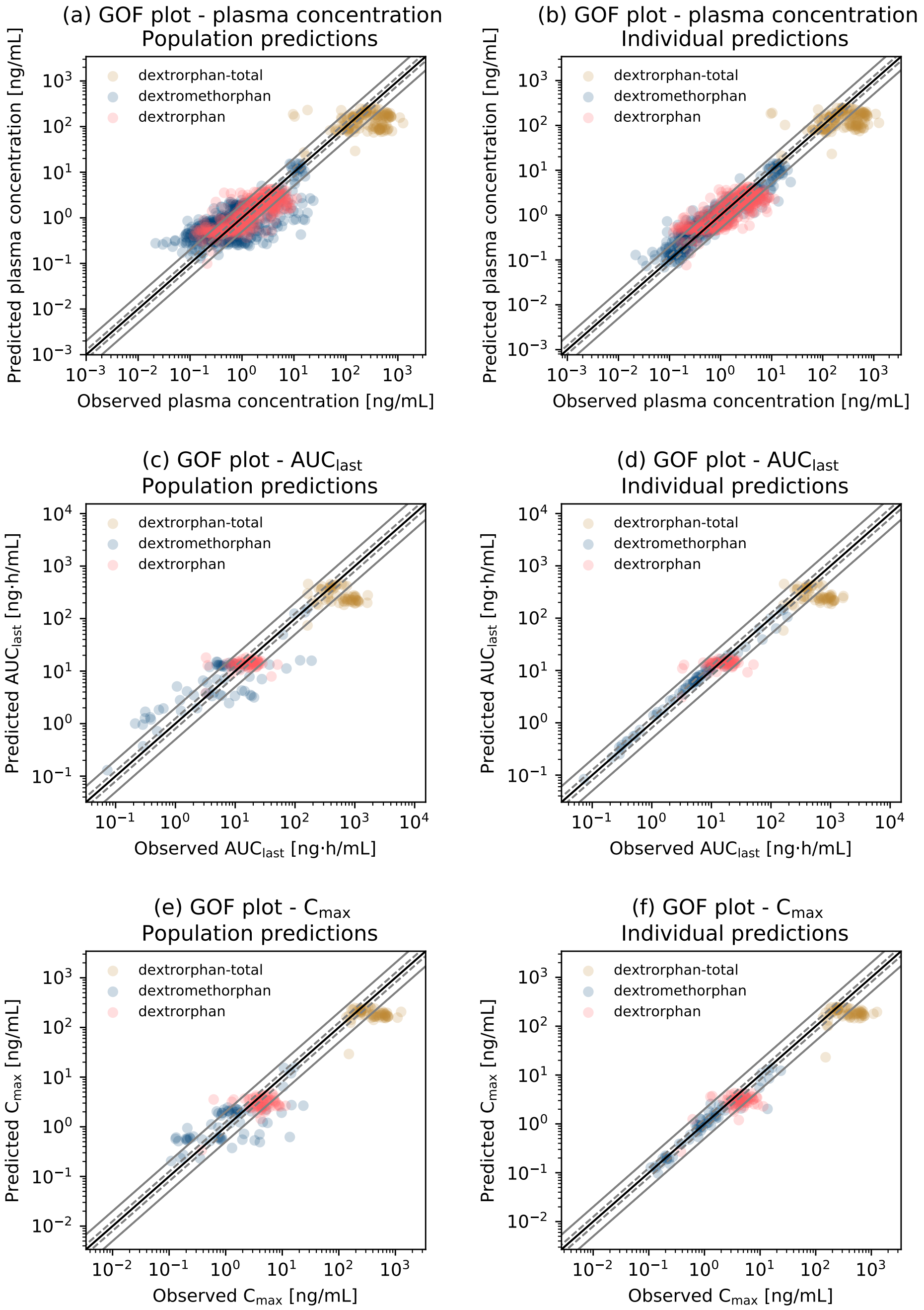


Figure S6.6.14: Goodness-of-fit plots for plasma concentrations, AUC_{last} and C_{max} values comparing predictions using the population k_{cat} (left column) to individual predictions (right column). Predicted versus observed (a, b) plasma concentrations, (c, d) AUC_{last} and (e, f) C_{max} values for dextromethorphan, dextrorphan and total dextrorphan (dextrorphan + dextrorphan *O*-glucuronide) for all individuals. The solid black line marks the line of identity, the dashed gray lines mark the 0.8- to 1.25-fold range, the solid gray lines indicate the 0.5- to 2-fold range. Colored symbols show the predicted compared to observed values for an individual study participant. AUC_{last}: AUC from the time of the first concentration measurement to the last time point of concentration measurement, C_{max}: peak plasma concentration.

S6.7 GMFE of Predicted AUC_{last} and C_{max} Values

Table S6.7.4: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors

Molecule	CYP2D6 status	AUC_{last} [ng·h/mL]					C_{max} [ng/mL]					Subject ID
		Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs		
		population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	
dextromethorphan	AS=0.25	131.51	138.87	146.34	0.90	0.95	11.92	12.59	14.33	0.83	0.88	A01
dextromethorphan	AS=1.5	7.84	14.67	17.31	0.45	0.85	1.30	2.07	4.53	0.29	0.46	A02
dextromethorphan	AS=2.0	*	*	*	*	*	0.52	0.09	0.08	6.80	1.21	A03
dextromethorphan	AS=1.0	15.04	5.75	4.87	3.09	1.18	2.30	0.85	0.94	2.46	0.90	A04
dextromethorphan	AS=1.0	11.94	4.62	3.72	3.21	1.24	2.33	0.93	1.30	1.79	0.72	A05
dextromethorphan	AS=2.0	1.33	0.34	0.28	4.67	1.20	0.58	0.20	0.20	2.92	1.03	A06
dextromethorphan	AS=1.0	13.19	8.83	6.68	1.97	1.05	2.28	1.43	1.62	1.41	0.89	A07
dextromethorphan	AS=0.0	156.79	146.08	162.42	0.97	0.90	15.85	14.08	16.37	0.97	0.86	A08
dextromethorphan	AS=2.0	1.75	1.60	1.24	1.41	1.29	0.52	0.48	0.53	0.98	0.90	A09
dextromethorphan	AS=1.0	13.16	6.41	5.34	2.46	1.20	1.99	0.92	0.87	2.29	1.06	A10
dextromethorphan	AS=1.0	12.28	6.40	5.99	2.05	1.07	1.73	0.85	0.83	2.08	1.03	A11
dextromethorphan	AS=3.0	0.52	0.25	0.30	1.72	0.88	0.24	0.15	0.16	1.52	0.94	A12
dextromethorphan	AS=1.0	13.27	7.01	6.49	2.04	1.08	1.95	0.96	0.74	2.62	1.29	A13
dextromethorphan	AS=2.0	1.32	0.45	0.38	3.47	1.18	0.58	0.19	0.21	2.75	0.91	A14
dextromethorphan	AS=3.0	0.89	0.56	0.56	1.61	1.12	0.28	0.20	0.18	1.59	1.10	A15
dextromethorphan	AS=1.0	13.05	5.18	4.92	2.65	1.05	1.94	0.73	0.86	2.24	0.84	A16
dextromethorphan	AS=2.0	1.83	0.56	0.53	3.45	1.06	0.58	0.15	0.24	2.45	0.64	C01
dextromethorphan	AS=2.0	1.95	0.73	0.63	3.09	1.16	0.64	0.21	0.27	2.36	0.78	C02
dextromethorphan	AS=2.0	1.26	0.32	0.31	4.07	1.03	0.57	0.13	0.13	4.41	1.04	C03
dextromethorphan	AS=2.0	1.68	0.38	0.31	5.37	1.20	0.52	0.10	0.15	3.54	0.66	C04
dextromethorphan	-	15.57	15.57	48.37	0.32	0.32	2.58	2.58	10.31	0.25	0.25	C05
dextromethorphan	AS=3.0	0.13	0.08	0.07	1.79	1.15	0.21	0.13	0.11	1.93	1.18	C06
dextromethorphan	-	7.47	7.47	0.69	10.74	10.74	2.08	2.08	0.24	8.53	8.53	C07
dextromethorphan	AS=0.5	49.56	63.17	62.68	0.79	1.01	6.45	7.53	10.39	0.62	0.72	C08
dextromethorphan	-	12.79	12.79	0.87	14.70	14.70	2.41	2.41	0.29	8.23	8.23	C09
dextromethorphan	AS=1.5	7.15	8.02	6.61	1.08	1.21	1.28	1.36	1.78	0.72	0.77	C10
dextromethorphan	AS=1.5	5.10	1.38	1.06	4.80	1.30	0.99	0.21	0.21	4.74	1.02	C11
dextromethorphan	AS=1.5	6.59	3.64	2.91	2.27	1.25	1.16	0.59	0.56	2.09	1.07	C12
dextromethorphan	-	7.90	7.90	0.73	10.77	10.77	2.22	2.22	0.26	8.51	8.51	C13
dextromethorphan	AS=1.5	6.07	4.27	3.38	1.79	1.26	1.01	0.68	0.74	1.36	0.92	C14
dextromethorphan	AS=1.0	14.86	6.01	5.05	2.94	1.19	2.53	1.03	1.09	2.33	0.95	C15
dextromethorphan	-	12.49	12.49	3.41	3.66	3.66	1.93	1.93	0.87	2.23	2.23	C16

*: no AUC_{last} calculated due to insufficient amount of observed data points, -: not available, †: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 2 for studies D and E) and should be interpreted with caution, AS: CYP2D6 activity score, AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

Table S6.7.4: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors (continued)

Molecule	CYP2D6 status	AUC_{last} [ng·h/mL]					C_{max} [ng/mL]					Subject ID
		Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs		
		population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	
dextromethorphan	AS=2.0	3.66	4.46	3.63	1.01	1.23	0.61	0.77	0.72	0.84	1.07	D01
dextromethorphan	AS=1.5	7.04	22.06	27.89	0.25	0.79	1.25	3.46	5.48	0.23	0.63	D02
dextromethorphan	AS=2.0	1.00	0.22	0.21	4.73	1.02	0.61	0.13	0.13	4.58	0.95	D03
dextromethorphan	AS=2.0	4.27	14.10	12.89	0.33	1.09	0.72	2.31	2.11	0.34	1.09	D04
dextromethorphan	-	14.27	14.27	8.66	1.65	1.65	2.40	2.40	2.44	0.98	0.98	D05
dextromethorphan	AS=1.0	12.76	6.27	5.56	2.30	1.13	2.15	1.05	1.13	1.90	0.93	D06
dextromethorphan	AS=2.0	3.36	5.41	4.11	0.82	1.32	0.55	0.94	0.80	0.68	1.17	D07
dextromethorphan	AS=1.0	13.28	28.47	37.31	0.36	0.76	2.31	4.29	5.16	0.45	0.83	D08
dextromethorphan	AS=2.0	1.20	0.43	0.39	3.09	1.12	0.54	0.19	0.21	2.56	0.90	D09
dextromethorphan	AS=1.5	6.90	6.15	4.96	1.39	1.24	1.23	1.06	1.19	1.03	0.89	D10
dextromethorphan	AS=1.0	13.70	11.47	9.73	1.41	1.18	2.38	1.89	2.31	1.03	0.82	D11
dextromethorphan	AS=1.0	12.84	7.53	5.80	2.21	1.30	2.21	1.27	1.10	2.01	1.16	D12
dextromethorphan	AS=1.0	11.15	14.17	11.92	0.94	1.19	2.07	2.44	1.83	1.13	1.33	E01
dextromethorphan	AS=1.0	12.49	9.83	9.76	1.28	1.01	1.81	1.42	1.53	1.19	0.93	E02
dextromethorphan	AS=1.0	12.37	8.14	6.28	1.97	1.30	2.09	1.30	1.62	1.29	0.80	E03
dextromethorphan	AS=2.0	3.48	2.66	2.03	1.72	1.31	0.55	0.39	0.38	1.45	1.01	E04
dextromethorphan	AS=2.0	3.16	20.19	20.65	0.15	0.98	0.49	3.04	4.02	0.12	0.76	E05
dextromethorphan	AS=1.0	12.47	14.99	14.40	0.87	1.04	2.14	2.45	2.82	0.76	0.87	E06
dextromethorphan	AS=2.0	3.90	5.44	4.37	0.89	1.25	0.59	0.86	0.87	0.68	0.99	E07
dextromethorphan	AS=2.0	3.38	19.53	18.81	0.18	1.04	0.53	3.04	3.26	0.16	0.93	E08
dextromethorphan	AS=2.0	3.80	3.46	3.25	1.17	1.06	0.61	0.54	0.77	0.79	0.70	E09
dextromethorphan	AS=1.0	11.23	39.11	71.91	0.16	0.54	2.09	5.50	9.74	0.21	0.56	E10
dextromethorphan	AS=1.0	11.70	8.43	7.14	1.64	1.18	1.91	1.30	1.18	1.63	1.11	E11
dextromethorphan	AS=2.0	3.40	7.48	5.98	0.57	1.25	0.56	1.27	0.83	0.67	1.53	E12
dextromethorphan	AS=2.0	3.48	7.37	5.61	0.62	1.31	0.57	1.26	0.84	0.68	1.49	E13
dextromethorphan	AS=1.0	12.15	11.29	9.66	1.26	1.17	2.07	1.83	1.19	1.73	1.54	E14
dextromethorphan	AS=2.0	4.16	16.56	14.35	0.29	1.15	0.70	2.80	3.96	0.18	0.71	E15
dextromethorphan	AS=1.0	12.90	9.78	8.47	1.52	1.15	2.00	1.47	1.48	1.35	1.00	E16
dextromethorphan	AS=1.0	16.05	63.43	121.81	0.13	0.52	2.91	8.47	14.57	0.20	0.58	E17
dextromethorphan	AS=2.0	3.51	11.55	17.93	0.20	0.64	0.62	2.02	13.60	0.05	0.15	E18
dextromethorphan	AS=2.0	2.45	11.75	7.90	0.31	1.49	0.54	2.56	1.29	0.42	1.98	E20
dextromethorphan	AS=1.0	15.78	105.27	189.37	0.08	0.56	2.79	12.25	23.61	0.12	0.52	E21
dextromethorphan	AS=0.0	124.38	98.69	97.59	1.27	1.01	15.80	10.94	10.67	1.48	1.03	E22
dextromethorphan	AS=3.0	1.97	2.79	2.30	0.85	1.21	0.24	0.39	0.35	0.67	1.10	E23
dextromethorphan	AS=2.0	3.36	11.76	9.91	0.34	1.19	0.55	1.93	1.97	0.28	0.98	E24

*: no AUC_{last} calculated due to insufficient amount of observed data points, -: not available, †: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 2 for studies D and E) and should be interpreted with caution, AS: CYP2D6 activity score, AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

Table S6.7.4: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors (continued)

Molecule	CYP2D6 status	AUC_{last} [ng·h/mL]					C_{max} [ng/mL]					Subject ID
		Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs		
		population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	
dextromethorphan	AS=2.0	4.11	1.78	1.56	2.63	1.14	0.61	0.19	0.23	2.62	0.84	E25
dextromethorphan	AS=1.0	14.14	11.00	9.18	1.54	1.20	2.29	1.74	1.60	1.43	1.09	E26
dextromethorphan	AS=2.0	3.38	1.44	1.20	2.82	1.20	0.55	0.22	0.20	2.73	1.12	E27
dextromethorphan	AS=1.0	12.84	6.00	5.22	2.46	1.15	2.09	0.97	0.69	3.01	1.39	E28
dextromethorphan	AS=1.0	14.37	10.44	8.06	1.78	1.30	2.39	1.63	1.48	1.62	1.11	E30
GMFE (dextromethorphan)		population k_{cat}			3.14 (1.01–14.70) 31/71 with GMFE $\leq$ 2					3.04 (1.02–20.00) 33/72 with GMFE $\leq$ 2		
		ind. optim. k_{cat}				1.75 (1.01–14.70) 66/71 with GMFE $\leq$ 2					1.67 (1.00–8.53) 65/72 with GMFE $\leq$ 2	
dextrorphan	AS=0.25	3.80	3.05	3.20	1.19	0.95	0.34	0.27	0.38	0.90	0.71	A01
dextrorphan	AS=1.5	15.45	15.23	23.58	0.66	0.65	3.59	2.73	6.20	0.58	0.44	A02
dextrorphan	AS=2.0	13.63	13.54	12.74	1.07	1.06	3.24	3.42	3.76	0.86	0.91	A03
dextrorphan	AS=1.0	14.70	15.01	23.58	0.62	0.64	2.67	3.27	6.07	0.44	0.54	A04
dextrorphan	AS=1.0	15.18	15.39	20.28	0.75	0.76	2.92	3.50	8.57	0.34	0.41	A05
dextrorphan	AS=2.0	14.62	14.61	19.99	0.73	0.73	3.22	3.39	5.77	0.56	0.59	A06
dextrorphan	AS=1.0	14.91	15.08	18.44	0.81	0.82	2.79	2.91	5.10	0.55	0.57	A07
dextrorphan	AS=2.0	13.28	13.28	18.38	0.72	0.72	2.95	2.97	5.97	0.49	0.50	A09
dextrorphan	AS=1.0	13.31	13.66	17.41	0.76	0.78	2.51	2.89	2.75	0.91	1.05	A10
dextrorphan	AS=1.0	11.58	11.85	18.45	0.63	0.64	2.03	2.30	3.63	0.56	0.63	A11
dextrorphan	AS=3.0	14.86	12.17	24.21	0.61	0.52	4.21	4.20	4.22	1.00	1.00	A12
dextrorphan	AS=1.0	13.19	13.71	24.45	0.54	0.56	2.40	2.71	5.30	0.45	0.51	A13
dextrorphan	AS=2.0	14.82	14.78	25.10	0.59	0.59	3.39	3.56	7.03	0.48	0.51	A14
dextrorphan	AS=3.0	16.86	16.83	13.25	1.27	1.27	4.30	4.27	3.47	1.24	1.23	A15
dextrorphan	AS=1.0	12.84	13.11	14.73	0.87	0.89	2.34	2.83	4.32	0.54	0.65	A16
dextrorphan	AS=2.0	13.95	13.88	9.57	1.46	1.45	3.37	3.56	5.38	0.63	0.66	C01
dextrorphan	AS=2.0	15.21	15.12	10.55	1.44	1.43	3.81	4.00	4.20	0.91	0.95	C02
dextrorphan	AS=2.0	15.28	15.08	11.83	1.29	1.28	3.80	4.00	3.01	1.26	1.33	C03
dextrorphan	AS=2.0	12.47	12.42	8.22	1.52	1.51	2.93	3.11	3.09	0.95	1.01	C04
dextrorphan	-	13.91	13.91	18.28	0.76	0.76	2.59	2.59	4.07	0.64	0.64	C05
dextrorphan	AS=3.0	13.53	13.49	10.29	1.31	1.31	3.61	3.61	4.63	0.78	0.78	C06
dextrorphan	-	12.14	12.41	14.67	0.83	0.83	2.34	2.34	3.89	0.60	0.60	C07

*: no AUC_{last} calculated due to insufficient amount of observed data points, -: not available, †: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 2 for studies D and E) and should be interpreted with caution, AS: CYP2D6 activity score, AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

Table S6.7.4: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors (continued)

		AUC_{last} [ng·h/mL]					C_{max} [ng/mL]					
Molecule	CYP2D6 status	Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs		Subject ID
		population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	
dextrorphan	AS=0.5	10.52	9.41	12.19	0.86	0.77	1.48	1.20	4.14	0.36	0.29	C08
dextrorphan	-	13.49	13.49	9.56	1.41	1.41	2.58	2.58	3.68	0.70	0.70	C09
dextrorphan	AS=1.5	14.54	14.50	21.27	0.68	0.68	3.36	3.15	7.57	0.44	0.42	C10
dextrorphan	AS=1.5	11.63	11.67	16.35	0.71	0.71	2.55	2.93	4.25	0.60	0.69	C11
dextrorphan	AS=1.5	14.11	14.13	7.32	1.93	1.93	3.30	3.59	1.28	2.58	2.80	C12
dextrorphan	-	12.88	12.88	10.47	1.23	1.23	2.50	2.50	3.55	0.70	0.70	C13
dextrorphan	AS=1.5	11.98	12.03	16.33	0.73	0.74	2.65	2.76	4.38	0.60	0.63	C14
dextrorphan	AS=1.0	14.89	15.25	24.67	0.60	0.62	2.85	3.44	8.85	0.32	0.39	C15
dextrorphan	-	11.09	11.09	12.72	0.87	0.87	2.03	2.03	4.12	0.49	0.49	C16
dextrorphan	AS=2.0	15.91	15.93	23.63	0.67	0.67	4.28	4.15	5.46	0.78	0.76	D01
dextrorphan	AS=1.5	13.31	12.96	50.92	0.26	0.25	3.17	2.29	11.43	0.28	0.20	D02
dextrorphan	AS=2.0	13.33	13.40	8.58	1.55	1.56	3.35	3.17	4.20	0.80	0.76	D03
dextrorphan	AS=2.0	15.79	15.44	18.62	0.85	0.83	3.77	2.78	4.74	0.80	0.59	D04
dextrorphan	-	14.40	14.40	13.21	1.09	1.09	2.89	2.89	6.20	0.47	0.47	D05
dextrorphan	AS=1.0	13.87	14.10	12.29	1.13	1.15	2.81	3.19	4.38	0.64	0.73	D06
dextrorphan	AS=2.0	14.10	14.11	10.13	1.39	1.39	3.67	3.36	3.86	0.95	0.87	D07
dextrorphan	AS=1.0	14.11	13.25	13.82	1.02	0.96	2.86	2.19	3.73	0.77	0.59	D08
dextrorphan	AS=2.0	13.91	12.80	3.47	4.00	3.68	3.55	3.72	1.39	2.56	2.68	D09
dextrorphan	AS=1.5	14.03	14.04	28.51	0.49	0.49	3.21	3.19	7.54	0.43	0.42	D10
dextrorphan	AS=1.0	14.49	14.59	21.95	0.66	0.66	2.91	2.80	5.30	0.55	0.53	D11
dextrorphan	AS=1.0	13.43	13.63	18.50	0.73	0.74	2.71	2.94	4.74	0.57	0.62	D12
dextrorphan	AS=1.0	12.86	12.76	17.56	0.73	0.73	2.85	2.57	3.91	0.73	0.66	E01
dextrorphan	AS=1.0	11.89	12.08	22.24	0.53	0.54	2.16	2.15	5.02	0.43	0.43	E02
dextrorphan	AS=1.0	9.00	8.60	8.75	1.03	0.98	2.70	2.63	3.68	0.73	0.71	E03
dextrorphan	AS=2.0	14.42	14.40	12.37	1.17	1.16	3.69	3.78	3.71	0.99	1.02	E04
dextrorphan	AS=2.0	12.22	11.43	10.42	1.17	1.10	2.99	1.93	3.32	0.90	0.58	E05
dextrorphan	AS=1.0	13.61	13.49	25.24	0.54	0.53	2.77	2.53	7.80	0.36	0.32	E06
dextrorphan	AS=2.0	15.58	15.56	27.20	0.57	0.57	3.87	3.66	7.16	0.54	0.51	E07
dextrorphan	AS=2.0	13.86	13.23	19.02	0.73	0.70	3.51	2.33	5.12	0.69	0.45	E08
dextrorphan	AS=2.0	16.43	16.42	23.77	0.69	0.69	4.26	4.29	7.10	0.60	0.60	E09
dextrorphan	AS=1.0	12.90	11.48	22.31	0.58	0.51	2.86	1.79	3.40	0.84	0.53	E10
dextrorphan	AS=1.0	12.05	12.20	19.52	0.62	0.63	2.35	2.39	4.17	0.56	0.57	E11
dextrorphan	AS=2.0	14.21	14.20	9.07	1.57	1.56	3.70	3.12	2.16	1.71	1.44	E12
dextrorphan	AS=2.0	15.01	15.01	18.21	0.82	0.82	3.96	3.36	3.50	1.13	0.96	E13
dextrorphan	AS=1.0	13.05	13.09	13.44	0.97	0.97	2.64	2.51	3.24	0.81	0.77	E14

*: no AUC_{last} calculated due to insufficient amount of observed data points, -: not available, †: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 2 for studies D and E) and should be interpreted with caution, AS: CYP2D6 activity score, AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

Table S6.7.4: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors (continued)

Molecule	CYP2D6 status	AUC_{last} [ng·h/mL]					C_{max} [ng/mL]					Subject ID
		Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs		
		population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	
dextrorphan	AS=2.0	17.65	17.41	19.88	0.89	0.88	4.75	3.33	6.59	0.72	0.51	E15
dextrorphan	AS=1.0	13.17	13.35	15.34	0.86	0.87	2.47	2.47	4.27	0.58	0.58	E16
dextrorphan	AS=1.0	18.06	15.15	15.19	1.19	1.00	3.87	2.14	2.54	1.52	0.84	E17
dextrorphan	AS=2.0	13.33	13.67	10.96	1.22	1.25	4.21	3.15	4.68	0.90	0.67	E18
dextrorphan	AS=2.0	7.91	9.23	40.37	0.20	0.23	3.51	2.48	9.09	0.39	0.27	E20
dextrorphan	AS=1.0	18.07	10.95	3.25	5.56	3.37	3.79	1.24	0.61	6.19	2.03	E21
dextrorphan	AS=3.0	16.36	16.40	18.37	0.89	0.89	4.32	4.24	5.02	0.86	0.84	E23
dextrorphan	AS=2.0	13.86	13.71	20.35	0.68	0.67	3.59	2.66	5.74	0.63	0.46	E24
dextrorphan	AS=2.0	15.06	15.15	19.11	0.79	0.79	3.76	3.51	3.83	0.98	0.91	E25
dextrorphan	AS=1.0	13.99	14.16	12.58	1.11	1.13	2.59	2.58	2.75	0.94	0.94	E26
dextrorphan	AS=2.0	14.10	14.03	9.45	1.49	1.48	3.65	3.81	2.67	1.37	1.43	E27
dextrorphan	AS=1.0	13.59	13.87	13.29	1.02	1.04	2.67	3.10	2.57	1.04	1.20	E28
dextrorphan	AS=1.0	15.52	15.70	15.96	0.97	0.98	3.11	3.21	4.68	0.66	0.69	E30
GMFE (dextrorphan)		population k_{cat}			1.56 (1.02–5.56) 65/71 with GMFE ≤ 2					1.74 (1.02–6.19) 52/70 with GMFE ≤ 2		
		ind. optim. k_{cat}				1.52 (1.00–4.35) 65/71 with GMFE ≤ 2					1.77 (1.00–5.00) 53/70 with GMFE ≤ 2	
dextrorphan-total†	AS=0.25	74.20	58.21	161.67	0.46	0.36	29.23	23.13	150.57	0.19	0.15	A01
dextrorphan-total†	AS=1.5	454.99	475.88	601.15	0.76	0.79	279.59	240.73	357.76	0.78	0.67	A02
dextrorphan-total†	AS=2.0	183.04	169.66	244.59	0.75	0.69	254.27	131.90	165.50	1.54	0.80	A03
dextrorphan-total†	AS=1.0	424.62	402.80	412.90	1.03	0.98	209.12	227.79	246.57	0.85	0.92	A04
dextrorphan-total†	AS=1.0	454.50	424.97	394.40	1.15	1.08	231.55	248.29	236.53	0.98	1.05	A05
dextrorphan-total†	AS=2.0	392.52	374.71	408.72	0.96	0.92	249.29	213.58	243.48	1.02	0.88	A06
dextrorphan-total†	AS=1.0	456.59	450.25	165.81	2.75	2.72	226.94	240.80	251.20	0.90	0.96	A07
dextrorphan-total†	AS=2.0	364.60	362.66	275.97	1.32	1.31	235.26	205.83	203.07	1.16	1.01	A09
dextrorphan-total†	AS=1.0	402.03	385.18	409.90	0.98	0.94	204.39	218.86	248.89	0.82	0.88	A10
dextrorphan-total†	AS=1.0	355.67	351.09	273.45	1.30	1.28	173.18	188.07	150.82	1.15	1.25	A11
dextrorphan-total†	AS=3.0	391.50	385.54	384.82	1.02	1.00	322.96	241.70	298.56	1.08	0.81	A12
dextrorphan-total†	AS=1.0	394.78	382.08	393.84	1.00	0.97	199.11	213.38	245.03	0.81	0.87	A13
dextrorphan-total†	AS=2.0	396.92	376.71	373.92	1.06	1.01	262.34	220.25	259.95	1.01	0.85	A14

*: no AUC_{last} calculated due to insufficient amount of observed data points, -: not available, †: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 2 for studies D and E) and should be interpreted with caution, AS: CYP2D6 activity score, AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

Table S6.7.4: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors (continued)

Molecule	CYP2D6 status	AUC_{last} [ng·h/mL]					C_{max} [ng/mL]					Subject ID
		Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs		
		population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	
dextrorphan-total†	AS=3.0	412.59	408.01	282.20	1.46	1.45	314.56	244.64	189.69	1.66	1.29	A15
dextrorphan-total†	AS=1.0	217.90	196.43	197.95	1.10	0.99	195.69	150.81	135.38	1.45	1.11	A16
dextrorphan-total†	AS=2.0	401.27	182.30	227.89	1.76	0.80	262.48	220.11	249.92	1.05	0.88	C01
dextrorphan-total†	AS=2.0	424.15	400.81	658.17	0.64	0.61	288.64	238.43	332.02	0.87	0.72	C02
dextrorphan-total†	AS=2.0	390.84	363.31	409.76	0.95	0.89	289.88	227.44	429.82	0.67	0.53	C03
dextrorphan-total†	AS=2.0	373.50	351.28	249.66	1.50	1.41	236.62	200.55	207.19	1.14	0.97	C04
dextrorphan-total†	-	407.26	407.26	211.28	1.93	1.93	195.02	195.02	94.97	2.05	2.05	C05
dextrorphan-total†	AS=3.0	381.95	376.42	374.65	1.02	1.00	288.07	225.95	177.33	1.62	1.27	C06
dextrorphan-total†	-	401.92	401.92	369.49	1.09	1.09	196.93	196.93	207.71	0.95	0.95	C07
dextrorphan-total†	AS=0.5	298.66	257.64	361.64	0.83	0.71	123.96	100.89	161.12	0.77	0.63	C08
dextrorphan-total†	-	419.51	419.51	495.73	0.85	0.85	203.83	203.83	253.26	0.80	0.80	C09
dextrorphan-total†	AS=1.5	417.32	421.64	736.42	0.57	0.57	255.36	235.39	380.92	0.67	0.62	C10
dextrorphan-total†	AS=1.5	362.15	331.47	429.22	0.84	0.77	210.39	193.95	199.73	1.05	0.97	C11
dextrorphan-total†	AS=1.5	432.92	408.08	486.83	0.89	0.84	263.30	243.68	234.47	1.12	1.04	C12
dextrorphan-total†	-	427.02	427.02	444.12	0.96	0.96	208.64	208.64	237.05	0.88	0.88	C13
dextrorphan-total†	AS=1.5	384.85	374.74	459.39	0.84	0.82	221.79	210.97	246.57	0.90	0.86	C14
dextrorphan-total†	AS=1.0	453.27	434.50	501.42	0.90	0.87	220.11	241.79	247.34	0.89	0.98	C15
dextrorphan-total†	-	373.44	373.44	565.76	0.66	0.66	175.74	175.74	486.45	0.36	0.36	C16
dextrorphan-total†	AS=2.0	216.72	222.34	1118.88	0.19	0.20	322.59	178.02	715.52	0.45	0.25	D01
dextrorphan-total†	AS=1.5	215.92	235.93	643.82	0.34	0.37	243.57	166.09	409.23	0.60	0.41	D02
dextrorphan-total†	AS=2.0	206.22	192.90	916.72	0.22	0.21	253.66	145.40	604.84	0.42	0.24	D03
dextrorphan-total†	AS=2.0	210.91	239.27	843.28	0.25	0.28	263.27	175.27	514.76	0.51	0.34	D04
dextrorphan-total†	-	266.16	266.16	733.43	0.36	0.36	236.55	236.55	442.69	0.53	0.53	D05
dextrorphan-total†	AS=1.0	*	*	*	*	*	232.19	182.19	584.25	0.40	0.31	D06
dextrorphan-total†	AS=2.0	206.70	220.21	1175.42	0.18	0.19	294.37	174.40	725.81	0.41	0.24	D07
dextrorphan-total†	AS=1.0	240.53	242.27	621.04	0.39	0.39	225.72	166.26	373.20	0.60	0.45	D08
dextrorphan-total†	AS=2.0	209.00	197.10	671.12	0.31	0.29	284.35	153.37	422.10	0.67	0.36	D09
dextrorphan-total†	AS=1.5	215.12	211.81	1132.72	0.19	0.19	247.51	164.62	656.32	0.38	0.25	D10
dextrorphan-total†	AS=1.0	250.64	245.81	997.96	0.25	0.25	230.56	186.75	615.14	0.37	0.30	D11
dextrorphan-total†	AS=1.0	222.69	208.61	1069.74	0.21	0.20	210.41	161.69	748.98	0.28	0.22	D12
dextrorphan-total†	AS=1.0	226.73	233.80	319.11	0.71	0.73	231.23	178.23	183.51	1.26	0.97	E01
dextrorphan-total†	AS=1.0	258.72	257.99	355.20	0.73	0.73	199.71	181.42	241.42	0.83	0.75	E02
dextrorphan-total†	AS=1.0	237.66	225.35	355.60	0.67	0.63	221.17	174.50	290.84	0.76	0.60	E03
dextrorphan-total†	AS=2.0	230.12	224.43	736.33	0.31	0.30	299.18	173.57	463.28	0.65	0.37	E04

*: no AUC_{last} calculated due to insufficient amount of observed data points, -: not available, †: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 2 for studies D and E) and should be interpreted with caution, AS: CYP2D6 activity score, AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

Table S6.7.4: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors (continued)

Molecule	CYP2D6 status	AUC_{last} [ng·h/mL]					C_{max} [ng/mL]					Subject ID
		Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs		
		population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	
dextrorphan-total†	AS=2.0	183.00	213.64	657.99	0.28	0.32	241.17	149.52	411.81	0.59	0.36	E05
dextrorphan-total†	AS=1.0	239.50	243.56	698.13	0.34	0.35	225.90	181.06	401.51	0.56	0.45	E06
dextrorphan-total†	AS=2.0	226.27	235.11	889.13	0.25	0.26	297.46	180.96	576.53	0.52	0.31	E07
dextrorphan-total†	AS=2.0	213.98	256.04	749.94	0.29	0.34	284.10	181.68	442.69	0.64	0.41	E08
dextrorphan-total†	AS=2.0	267.65	265.21	1026.95	0.26	0.26	346.78	205.39	599.70	0.58	0.34	E09
dextrorphan-total†	AS=1.0	227.56	222.95	858.04	0.27	0.26	232.09	146.24	491.60	0.47	0.30	E10
dextrorphan-total†	AS=1.0	223.13	216.46	1138.83	0.20	0.19	200.12	163.28	746.40	0.27	0.22	E11
dextrorphan-total†	AS=2.0	198.39	221.73	548.05	0.36	0.40	287.50	174.66	373.20	0.77	0.47	E12
dextrorphan-total†	AS=2.0	220.02	244.75	942.32	0.23	0.26	312.94	192.70	664.04	0.47	0.29	E13
dextrorphan-total†	AS=1.0	234.15	232.37	776.34	0.30	0.30	218.61	175.89	545.65	0.40	0.32	E14
dextrorphan-total†	AS=2.0	228.09	282.61	1038.21	0.22	0.27	344.89	215.69	661.47	0.52	0.33	E15
dextrorphan-total†	AS=1.0	278.20	275.00	962.07	0.29	0.29	225.93	198.00	630.58	0.36	0.31	E16
dextrorphan-total†	AS=1.0	273.00	252.19	496.73	0.55	0.51	278.85	160.19	306.28	0.91	0.52	E17
dextrorphan-total†	AS=2.0	211.63	249.18	405.37	0.52	0.61	304.65	191.00	452.99	0.67	0.42	E18
dextrorphan-total†	AS=2.0	199.98	243.32	1614.43	0.12	0.15	280.19	179.57	1091.29	0.26	0.16	E20
dextrorphan-total†	AS=1.0	299.53	178.71	161.92	1.85	1.10	288.46	102.34	166.78	1.73	0.61	E21
dextrorphan-total†	AS=3.0	257.95	263.62	677.83	0.38	0.39	352.78	201.86	710.37	0.50	0.28	E23
dextrorphan-total†	AS=2.0	194.69	231.92	994.10	0.20	0.23	280.43	177.47	674.34	0.42	0.26	E24
dextrorphan-total†	AS=2.0	277.88	264.65	1646.27	0.17	0.16	313.71	195.66	1263.74	0.25	0.15	E25
dextrorphan-total†	AS=1.0	260.20	256.00	1015.63	0.26	0.25	216.48	187.46	666.61	0.32	0.28	E26
dextrorphan-total†	AS=2.0	198.01	187.34	1035.70	0.19	0.18	284.61	147.60	664.04	0.43	0.22	E27
dextrorphan-total†	AS=1.0	266.46	246.65	787.91	0.34	0.31	229.73	187.15	540.50	0.43	0.35	E28
dextrorphan-total†	AS=1.0	258.77	249.21	930.94	0.28	0.27	240.65	191.07	568.81	0.42	0.34	E30
GMFE (dextrorphan-total†)		population k_{cat}			2.63 (1.00–8.33) 35/69 with GMFE ≤ 2					1.84 (1.01–5.26) 48/70 with GMFE ≤ 2		
		ind. optim. k_{cat}				2.58 (1.00–6.67) 35/69 with GMFE ≤ 2					2.41 (1.01–6.67) 34/70 with GMFE ≤ 2	
Overall GMFE		population k_{cat}			2.45 (1.00–14.70) 131/210 with GMFE ≤ 2					2.21 (1.00–20.00) 133/212 with GMFE ≤ 2		

*: no AUC_{last} calculated due to insufficient amount of observed data points, -: not available, †: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 2 for studies D and E) and should be interpreted with caution, AS: CYP2D6 activity score, AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

Table S6.7.4: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors (continued)

Molecule	CYP2D6 status	AUC_{last} [ng·h/mL]					C_{max} [ng/mL]					Subject ID
		Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs		
		population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	
		ind. optim. k_{cat}				1.94 (1.00–14.70) 166/210 with GMFE $\leq$ 2					1.94 (1.00–8.53) 152/212 with GMFE $\leq$ 2	

*: no AUC_{last} calculated due to insufficient amount of observed data points, -: not available, †: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 2 for studies D and E) and should be interpreted with caution, AS: CYP2D6 activity score, AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6, obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

S6.8 GMFE of Predicted AUC_{last} and C_{max} Values Grouped by Study and Activity Score

Table S6.8.5: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors grouped by study and activity score

Study	Molecule	CYP2D6 Activity Score	n	AUC_{last} [ng·h/mL]					C_{max} [ng/mL]				
				Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs	
				population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}
A	dextromethorphan	0	1	156.79	146.08	162.42	0.97	0.9	15.85	14.08	16.37	0.97	0.86
		0.25	1	131.51	138.87	146.34	0.90	0.95	14.33	11.92	12.59	0.83	0.88
		1	7	13.15 (0.99)	6.32 (1.37)	5.68 (1.50)	2.44 (0.59)	1.12 (0.08)	1.02 (0.32)	2.07 (0.23)	0.95 (0.23)	2.13 (0.41)	0.96 (0.18)
		1.5	1	7.84	14.67	17.31	0.45	0.85	4.53	1.30	2.07	0.29	0.46
		2	3	1.34 (0.40)	0.79 (0.70)	0.64 (0.53)	2.74 (1.16)	1.22 (0.06)	0.25 (0.19)	0.55 (0.03)	0.24 (0.16)	3.36 (2.45)	1.01 (0.15)
		3	2	0.54 (0.24)	0.40 (0.22)	0.39 (0.15)	1.37 (0.11)	1 (0.17)	0.17 (0.01)	0.26 (0.03)	0.17 (0.03)	1.55 (0.05)	1.02 (0.12)
GMFE dextromethorphan, study A							2.16	1.13				2.32	1.17
A	dextrorphan	0.25	1	3.80	3.05	3.20	1.19	0.95	0.38	0.34	0.27	0.90	0.71
		1	7	13.67 (1.31)	13.97 (1.27)	19.62 (3.44)	0.71 (0.12)	0.73 (0.12)	5.11 (1.88)	2.52 (0.3)	2.92 (0.39)	0.54 (0.18)	0.62 (0.20)
		1.5	1	15.45	15.23	23.58	0.66	0.65	6.20	3.59	2.73	0.58	0.44
		2	4	14.09 (0.75)	14.05 (0.75)	19.05 (5.09)	0.78 (0.2)	0.78 (0.2)	5.63 (1.37)	3.2 (0.18)	3.33 (0.26)	0.6 (0.18)	0.63 (0.19)
		3	2	14.57 (3.25)	14.5 (3.29)	18.26 (7.09)	0.9 (0.53)	0.9 (0.53)	3.85 (0.53)	4.25 (0.06)	4.24 (0.05)	1.12 (0.17)	1.11 (0.17)
GMFE dextrorphan, study A							1.33	1.31				1.64	1.57
A	dextrorphan-total[†]	0.25	1	74.20	58.21	161.67	0.46	0.36	150.57	29.23	23.13	0.19	0.15
		1	7	386.58 (82.34)	370.4 (83.06)	321.18 (106.87)	1.33 (0.64)	1.28 (0.64)	216.35 (50.44)	205.71 (19.72)	212.57 (33.57)	0.99 (0.23)	1.01 (0.14)
		1.5	1	454.99	475.88	601.15	0.76	0.79	357.76	279.59	240.73	0.78	0.67
		2	4	334.27 (101.83)	320.94 (101.04)	325.8 (78.04)	1.02 (0.24)	0.98 (0.26)	218 (42.38)	250.29 (11.37)	192.89 (41.08)	1.18 (0.25)	0.88 (0.09)
		3	2	402.05 (14.91)	396.78 (15.89)	333.51 (72.56)	1.24 (0.31)	1.22 (0.31)	244.12 (76.98)	318.76 (5.94)	243.17 (2.08)	1.37 (0.41)	1.05 (0.34)
GMFE dextrorphan-total, study A							1.29	1.30				1.40	1.44
Overall GMFE, study A							1.59	1.24				1.80	1.31
C	dextromethorphan	0.5	1	49.56	63.17	62.68	0.79	1.01	10.39	6.45	7.53	0.62	0.72
		1	1	14.86	6.01	5.05	2.94	1.19	1.09	2.53	1.03	2.33	0.95
		1.5	4	6.23 (0.87)	4.33 (2.75)	3.49 (2.31)	2.49 (1.62)	1.26 (0.04)	0.82 (0.67)	1.11 (0.14)	0.71 (0.48)	2.23 (1.76)	0.94 (0.13)
		2	4	1.68 (0.30)	0.50 (0.19)	0.45 (0.16)	3.99 (1.00)	1.11 (0.08)	0.2 (0.07)	0.58 (0.05)	0.15 (0.05)	3.19 (0.97)	0.78 (0.18)
		3	1	0.13	0.08	0.07	1.79	1.15	0.11	0.21	0.13	1.93	1.18
GMFE dextromethorphan, study C							2.90	1.17				2.50	1.18
C	dextrorphan	0.5	1	10.52	9.41	12.19	0.86	0.77	4.14	1.48	1.20	0.36	0.29
		1	1	14.89	15.25	24.67	0.6	0.62	8.85	2.85	3.44	0.32	0.39
		1.5	4	13.07 (1.47)	13.08 (1.44)	15.32 (5.82)	1.01 (0.61)	1.02 (0.61)	4.37 (2.57)	2.97 (0.43)	3.11 (0.36)	1.06 (1.02)	1.14 (1.12)
		2	4	14.23 (1.32)	14.13 (1.27)	10.04 (1.53)	1.43 (0.1)	1.42 (0.1)	3.92 (1.11)	3.48 (0.42)	3.66 (0.43)	0.94 (0.26)	0.99 (0.27)
		3	1	13.53	13.49	10.29	1.31	1.31	4.63	3.61	3.61	0.78	0.78

All values are given as mean (SD). [†]: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 3 for studies D and E) and should be interpreted with caution,
AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6
obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

Table S6.8.5: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors (continued)

Study	Molecule	CYP2D6 Activity Score	n	AUC_{last} [ng·h/mL]					C_{max} [ng/mL]				
				Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs	
				population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}
GMFE dextrorphan, study C							1.26	1.27				1.43	1.45
C	dextrorphan-total†	0.5	1	298.66	257.64	361.64	0.83	0.71	161.12	123.96	100.89	0.77	0.63
		1	1	453.27	434.5	501.42	0.9	0.87	247.34	220.11	241.79	0.89	0.98
		1.5	4	399.31 (31.86)	383.98 (40.17)	527.97 (140.95)	0.78 (0.15)	0.75 (0.12)	265.42 (79.52)	237.71 (25.6)	221 (22.76)	0.94 (0.20)	0.87 (0.18)
		2	4	345.18 (104.11)	324.43 (97.07)	386.37 (198.52)	0.98 (0.36)	0.93 (0.34)	304.74 (98.17)	269.41 (25.24)	221.63 (15.94)	0.93 (0.21)	0.77 (0.19)
		3	1	381.95	376.42	374.65	1.02	1.00	177.33	288.07	225.95	1.62	1.27
GMFE dextrorphan-total, study C							1.14	1.20				1.15	1.24
Overall GMFE, study C							1.77	1.21				1.69	1.29
D	dextromethorphan	1	4	13.15 (0.44)	13.44 (10.27)	14.60 (15.26)	1.57 (0.90)	1.09 (0.23)	2.42 (1.91)	2.26 (0.10)	2.12 (1.49)	1.35 (0.74)	0.93 (0.16)
		1.5	2	6.97 (0.10)	14.11 (11.25)	16.43 (16.21)	0.82 (0.80)	1.02 (0.32)	3.34 (3.03)	1.24 (0.02)	2.26 (1.7)	0.63 (0.57)	0.76 (0.18)
		2	5	2.70 (1.50)	4.92 (5.63)	4.25 (5.15)	1.99 (1.86)	1.15 (0.12)	0.8 (0.79)	0.6 (0.07)	0.87 (0.88)	1.8 (1.78)	1.04 (0.11)
GMFE dextromethorphan, study D							1.70	1.11				1.60	1.10
D	dextrorphan	1	4	13.98 (0.44)	13.89 (0.58)	16.64 (4.42)	0.88 (0.23)	0.88 (0.22)	4.54 (0.66)	2.82 (0.08)	2.78 (0.43)	0.63 (0.10)	0.62 (0.09)
		1.5	2	13.67 (0.50)	13.50 (0.76)	39.71 (15.84)	0.38 (0.16)	0.37 (0.17)	9.48 (2.75)	3.19 (0.03)	2.74 (0.64)	0.35 (0.10)	0.31 (0.16)
		2	5	14.40 (1.39)	14.34 (1.33)	12.89 (8.11)	1.63 (1.21)	1.63 (1.21)	3.93 (1.54)	3.72 (0.35)	3.43 (0.52)	1.18 (0.77)	1.13 (0.87)
GMFE dextrorphan, study D							1.64	1.64				1.63	1.69
D	dextrorphan-total†	1	3	237.95 (14.15)	232.23 (20.53)	896.25 (241.03)	0.28 (0.09)	0.28 (0.10)	580.39 (155.53)	224.72 (9.93)	174.22 (12.12)	0.41 (0.14)	0.32 (0.09)
		1.5	2	215.52 (0.56)	223.87 (17.05)	888.27 (345.7)	0.26 (0.1)	0.28 (0.13)	532.78 (174.72)	245.54 (2.79)	165.35 (1.04)	0.49 (0.15)	0.33 (0.11)
		2	5	209.91 (4.25)	214.36 (19.22)	945.08 (205.84)	0.23 (0.05)	0.23 (0.05)	596.61 (130.43)	283.65 (27.14)	165.29 (14.85)	0.49 (0.11)	0.29 (0.06)
GMFE dextrorphan-total, study D							3.99	3.93				2.17	3.28
Overall GMFE, study D							2.39	2.17				1.80	2.02
E	dextromethorphan	0	1	124.38	98.69	97.59	1.27	1.01	10.67	15.8	10.94	1.48	1.03
		1	13	13.05 (1.58)	23.99 (29.30)	36.4 (57.39)	1.2 (0.74)	1.02 (0.29)	4.87 (6.97)	2.2 (0.32)	3.29 (3.43)	1.21 (0.78)	0.99 (0.32)
		2	13	3.46 (0.48)	9.31 (6.53)	8.73 (6.96)	0.88 (0.84)	1.16 (0.20)	2.48 (3.61)	0.58 (0.05)	1.55 (1.08)	0.83 (0.9)	1.01 (0.45)
		3	1	1.97	2.79	2.30	0.85	1.21	0.35	0.24	0.39	0.67	1.10
GMFE dextromethorphan, study E							1.18	1.09				1.23	1.02
E	dextrorphan	1	13	13.67 (2.44)	12.84 (1.86)	15.74 (5.92)	1.21 (1.33)	1.02 (0.74)	3.74 (1.67)	2.83 (0.5)	2.41 (0.51)	1.18 (1.53)	0.79 (0.44)
		2	13	14.13 (2.32)	14.11 (2.09)	18.48 (8.75)	0.92 (0.38)	0.92 (0.38)	4.97 (2.05)	3.8 (0.43)	3.19 (0.67)	0.89 (0.36)	0.76 (0.37)

All values are given as mean (SD). †: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 3 for studies D and E) and should be interpreted with caution,
AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6
obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

Table S6.8.5: Predicted and observed AUC_{last} and C_{max} values and geometric mean fold errors (continued)

Study	Molecule	CYP2D6 Activity Score	n	AUC_{last} [ng·h/mL]					C_{max} [ng/mL]				
				Pred		Obs	Pred/Obs		Pred		Obs	Pred/Obs	
				population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}	population k_{cat}	ind. optim. k_{cat}		population k_{cat}	ind. optim. k_{cat}
		3	1	16.36	16.40	18.37	0.89	0.89	5.02	4.32	4.24	0.86	0.84
GMFE dextrorphan, study E							1.15	1.06				1.56	1.29
E	dextrorphan-total[†]	1	13	252.59 (23.27)	237.71 (24.05)	681.27 (311.13)	0.52 (0.44)	0.46 (0.27)	444.65 (192.2)	231.46 (26.03)	171.3 (24.94)	0.67 (0.43)	0.46 (0.22)
		2	13	219.21 (27.82)	239.99 (25.11)	944.98 (363.07)	0.26 (0.10)	0.29 (0.12)	641.47 (262.92)	298.28 (28.04)	181.96 (19.27)	0.52 (0.16)	0.32 (0.1)
		3	1	257.95	263.62	677.83	0.38	0.39	710.37	352.78	201.86	0.50	0.28
GMFE dextrorphan-total, study E							2.86	2.81				1.72	2.69
Overall GMFE, study E							1.72	1.65				1.36	1.66

All values are given as mean (SD). [†]: AUC_{last} and C_{max} values as well as corresponding ratios were calculated based on a small number of observed data points (n = 3 for studies A and B, n = 3 for studies D and E) and should be interpreted with caution, AUC: area under the plasma concentration-time curve, AUC_{last}: AUC from the time of the first concentration measurement to the last time of concentration measurement, C_{max}: peak plasma concentration, CYP2D6: Cytochrome P450 2D6 obs: observed, po: oral, ind.: individual, optim.: optimized, pred: predicted.

S7 Summary

In this supplementary file, the development process of a whole-body PBPK model of dextromethorphan and its metabolites dextrorphan and dextrorphan *O*-glucuronide is documented. The model has been thoroughly evaluated to predict the pharmacokinetics of the modeled analytes including a wide range of CYP2D6 DGI scenarios. Moreover, the model was applied to predict individual plasma concentration-time profiles using the model k_{cat} values obtained during the DGI model building process. These were then compared to predictions using individual optimized k_{cat} values. For a tabular summary of model geometric mean fold error (GMFE) and mean relative deviation (MRD) values, refer to Table S7.0.1.

Table S7.0.1: Summary of quantitative performance metrics for the different model subsets

	AUC_{last}		C_{max}		MRD (range)	MRD $\leq$ 2
	GMFE (range)	GMFE $\leq$ 2	GMFE (range)	GMFE $\leq$ 2		
Population studies						
PBPK base model	1.57 (1.01–3.45)	18/23	1.61 (1.01–2.97)	17/22	2.21 (1.35–3.56)	12/23
DGI model	1.50 (1.05–2.33)	16/18	1.28 (1.01–2.22)	17/18	2.13 (1.10–4.26)	11/18
Overall (populations)	1.54 (1.01–3.45)	34/41	1.47 (1.01–2.97)	34/40	2.17 (1.10–4.26)	23/41
Individual profiles						
Population predictions	2.45 (1.00–14.70)	131/210	2.21 (1.00–20.00)	133/212	2.72 (1.08–14.00)	114/212
Individual predictions	1.94 (1.00–14.70)	166/210	1.94 (1.00–8.53)	152/212	1.94 (1.08–14.00)	152/212

AUC_{last}: AUC from the time of the first concentration measurement to the last time point of concentration measurement, C_{max}: peak plasma concentration, DGI: drug-gene interaction, GMFE: geometric mean fold error, MRD: mean relative deviation, PBPK: physiologically based pharmacokinetic.

S8 Abbreviations

AS	CYP2D6 activity score
AUC	Area under the plasma concentration-time curve
AUC_{last}	AUC from the time of the first concentration measurement to the last time point of concentration measurement
cap	Capsule
C_{max}	Peak plasma concentration
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DGI	Drug-gene interaction
EHC	Enterohepatic circulation
EM	Extensive metabolizer
f_u	Fraction unbound
GFR	Glomerular filtration rate
GMFE	Geometric mean fold error
ICRP	International Commission on Radiological Protection
IM	Intermediate metabolizer
inf	Infusion
iv	Intravenous
K_D	Dissociation constant
k_{cat}	Catalytic rate constant
K_M	Michaelis-Menten constant
k_{off}	Dissociation rate constant
MRD	Mean relative deviation
MW	Molecular weight
NHANES	Third National Health and Nutrition Examination Survey
NM	Normal metabolizer
PBPK	Physiologically based pharmacokinetic
pKa	Acid dissociation constant
PM	Poor metabolizer
po	Oral
sd	Single dose
sol	Oral solution
tab	Tablet
t_{max}	Time to reach Peak plasma concentration
UM	Ultrarapid metabolizer
UGT2B15	Uridine 5’-diphospho-glucuronosyltransferase family 2 member B15

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