# PK-Sim® Ontogeny Database

## Version 7.3

## Table of contents

# 1 Aim

This document represents a summary of literature data to ontogeny of enzymes, and other ADME relevant proteins as well as fit results used for implementation of ontogeny functions in PK-Sim®.

# 2 Data management

## 2.1 Literature data

Used literature data are referenced in the respective enzyme sections.

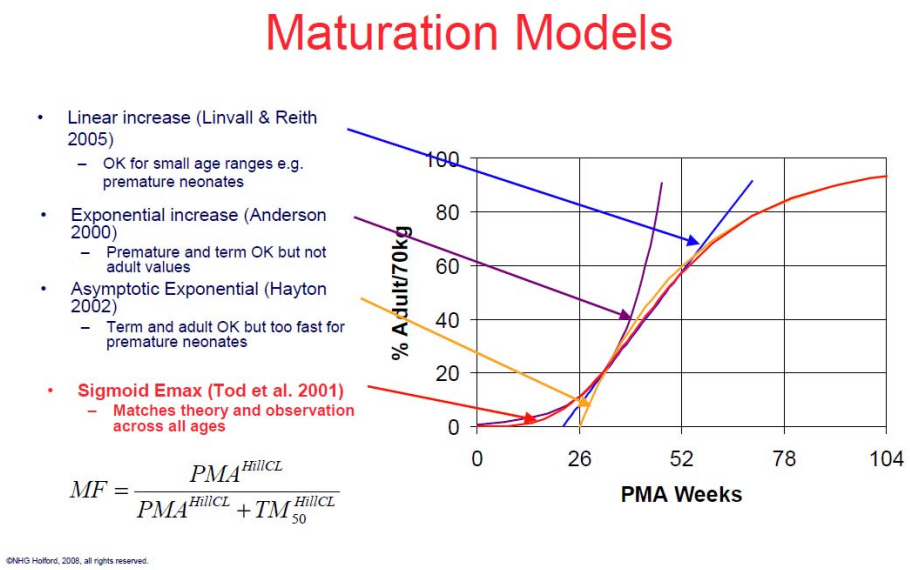
## 2.2 Fit results

Fit results and figures are illustrated in the respective enzyme sections.

# 3 Methods

A maturation model based on a sigmoidal Emax model (corresponding to the Hill-equation), published by Tod et al. 2008 (Clin Pharmacokinet. 47(4):231-43) presents the best description of age dependent development of e.g. proteins (Fig. 1). This model was also presented at the EMEA Workshop on Modelling in Paediatric Medicines in 2008 (Presentation 'Prof. N. Holford, 2008, 'Mechanism-Based Concepts of Size and Maturity', www.ema.europa.eu/docs/en_GB/document_library/Agenda/2009/11/WC500010017.pdf).

**Figure 1.** Slide taken from 'http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500009792.pdf')




Fitting of ontogeny data was therefore performed using the following Hill equation (Equation 1):

$$A = PMA^n / ( PMA^n + A_{0.5}^n) \quad (1)$$

With:
PMA = Post-menstrual age in weeks
A = Relative activity at PMA

$A_{0.5}$ = PMA (in weeks) at 50 % activity compared to adult
n = Hill coefficient

In the case of proteins showing decreased expression with increasing age, the following inverse fit function was applied (Equation 2):

$$A = 1 - PMA^n / (A_{0.5}^n + PMA^n) + offset \quad (2)$$

With offset = activity in adults

For fitting the ontogeny including variability, constituting variability in ontogeny as well as activity, a virtual population with 10000 individuals was created. Fitted were then the geometric mean and geometric standard deviation of the Hill coefficient (GeoSD n), the geometric mean and geometric standard deviation of PMA at 50% activity compared to adult (GeoSD $A_{0.5}$), and a geometric standard deviation as an activity variability factor (GeoSD adult).

All illustrated figures are shown in full age-length and a zoom-in version in the first period after birth. The presented tables are the implemented tables in PK-Sim, which are created from the fitted Hill equations.

# 4 Results

## 4.3 CYP Enzymes in the liver

## A.1 CYP1A2 in liver

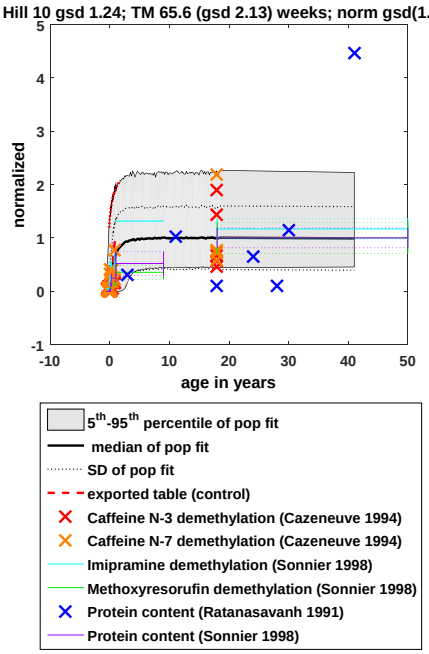
### A.1.1 Original data

| Reference | Used for fit |
|---|---|
| Br J Clin Pharmacol. 1994 May;37(5):405-12.; Biotransformation of caffeine in human liver microsomes from foetuses, neonates, infants and adults.;Cazeneuve C, Pons G, Rey E, Treluyer JM, Cresteil T, Thiroux G, D'Athis P, Olive G.<br><br>Digital Object Identifyer (DOI): 10.1111/j.1365-2125.1994.tb05706.x<br><br>→ Table 2 (Caffeine N-3 demethylation, and Caffeine N-7 demethylation) | Yes |
| Eur J Biochem. 1998 Feb 1;251(3):893-8.; Delayed ontogenesis of CYP1A2 in the human liver.; Sonnier M, Cresteil T.<br><br>Digital Object Identifyer (DOI): 10.1046/j.1432-1327.1998.2510893.x<br><br>→ Figure 2a<br>→ Figure 2b<br>→ Figure 3 | <br><br><br><br><br><br>Yes<br>Yes<br>Yes |
| Hepatology. 1991 Jun;13(6):1142-51.; Intralobular distribution and quantitation of cytochrome P-450 enzymes in human liver as a function of age.; Ratanasavanh D1, Beaune P, Morel F, Flinois JP, Guengerich FP, Guillouzo A.<br><br>Digital Object Identifyer (DOI): 10.1002/hep.1840130622<br><br>→Table 2 (protein content) | <br><br><br><br><br><br>Yes |

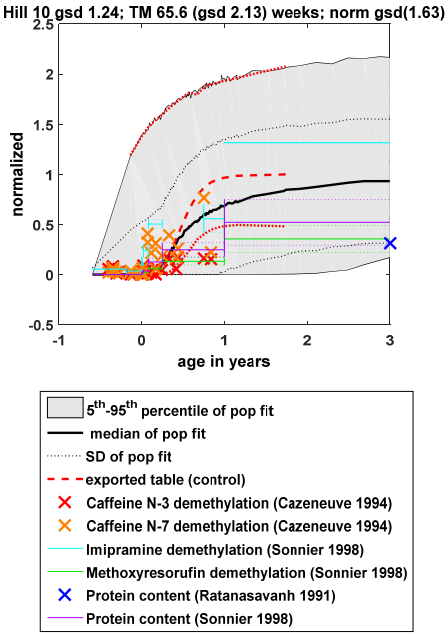
### A.1.2 Fit results

#### A.1.2.1 Figure

Full range-plot




Zoom-in, x-axis




#### A.1.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

**Fit Result:**
n = 10.015
$A_{0.5}$ = 65.639

GeoSD n = 1.241
GeoSD $A_{0.5}$ = 2.130
GeoSD adult = 1.628

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

#### A.1.2.3 Description for PK-Sim®

Values for CYP1A2 ontogeny are based on information to age dependency of Caffeine N-3 demethylation, Caffeine N-7 demethylation, Methoxyresorufin demethylation, Imipramine demethylation, and protein content, derived from the papers as mentioned in table A.1.1.

#### A.1.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP1A2 | Standard Deviation |
|---|---|---|
| 0.629999995 | 0.00099 | 74.55000305 |
| 0.769999981 | 0.007 | 24.93000031 |
| 0.879999995 | 0.026000001 | 11.80000019 |
| 0.980000019 | 0.071000002 | 6.539999962 |
| 1.049999952 | 0.140000001 | 4.420000076 |
| 1.139999986 | 0.25999999 | 3.150000095 |
| 1.340000033 | 0.649999976 | 1.870000005 |
| 1.440000057 | 0.790000021 | 1.639999986 |
| 1.549999952 | 0.879999995 | 1.590000033 |
| 1.610000014 | 0.920000017 | 1.549999952 |
| 1.74000001 | 0.959999979 | 1.529999971 |
| 1.929999948 | 0.99000001 | 1.519999981 |
| 2.519999981 | 1 | 1.559999943 |

## A.2 CYP2C18 in liver

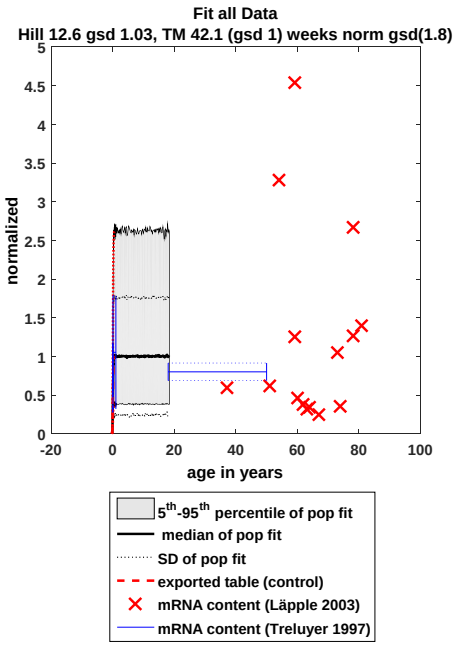
### A.2.1 Original data

| Reference | Used for fit |
|---|---|
| Pharmacogenetics. 1997 Dec;7(6):441-52.; Developmental expression of CYP2C and CYP2C-dependent activities in the human liver: in-vivo/in-vitro correlation and inducibility.; Treluyer JM, Gueret G, Cheron G, Sonnier M, Cresteil T.<br><br>Pubmed ID (PMID): 9429229 (DOI not available)<br><br>→ Figure 5 (mRNA expression) | Yes |
| Pharmacogenetics. 2003 Sep;13(9):565-75.; Differential expression and function of CYP2C isoforms in human intestine and liver.; Läpple F, von Richter O, Fromm MF, Richter T, Thon KP, Wisser H, Griese EU, Eichelbaum M, Kivistö KT.<br><br>Digital Object Identifyer (DOI): 10.1097/01.fpc.0000054122.14659.1e<br><br>Pubmed ID (PMID): 12972955 (DOI not functioning)<br><br>→Table 3 (mRNA expression) | Yes |

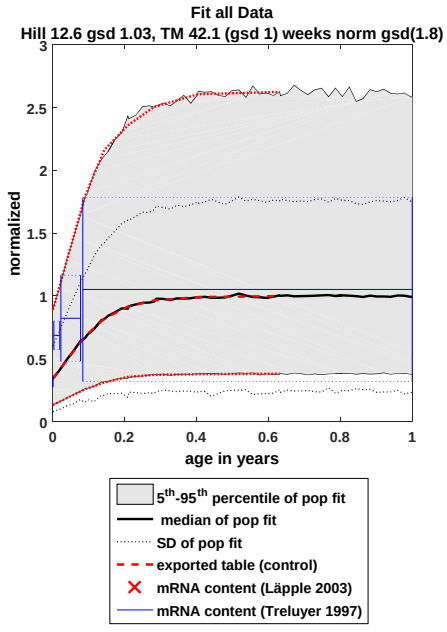
### A.2.2 Fit results

#### A.2.2.1 Figure

Full range-plot




Zoom-in, x-axis




**Comment:** For the intestine, the geometric standard deviation in activity observed in adults ('GeoSD adult') has been separately fitted and implemented with a GeoSD of 2.177.

### A.2.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

**Fit Result:**
n = 12.590
$A_{0.5}$ = 42.134

GeoSD n = 1.034
GeoSD $A_{0.5}$ = 1.002
GeoSD adult = 1.795

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

### A.2.2.3 Description for PK-Sim®

Values for CYP2C18 ontogeny are based on information to age dependency of mRNA expression, derived from the papers as mentioned in table A.2.1.

### A.2.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP2C18 | Standard Deviation |
|---|---|---|
| 0.469999999 | 0.00098 | 1.870000005 |
| 0.600000024 | 0.022 | 1.809999943 |
| 0.680000007 | 0.090999998 | 1.789999962 |
| 0.730000019 | 0.200000003 | 1.799999952 |
| 0.769999981 | 0.340000004 | 1.789999962 |
| 0.860000014 | 0.680000007 | 1.809999943 |
| 0.910000026 | 0.819999993 | 1.799999952 |
| 0.980000019 | 0.920000017 | 1.779999971 |
| 1.049999952 | 0.959999979 | 1.789999962 |
| 1.169999957 | 0.99000001 | 1.799999952 |
| 1.399999976 | 1 | 1.799999952 |

## A.3 CYP2C19 in liver

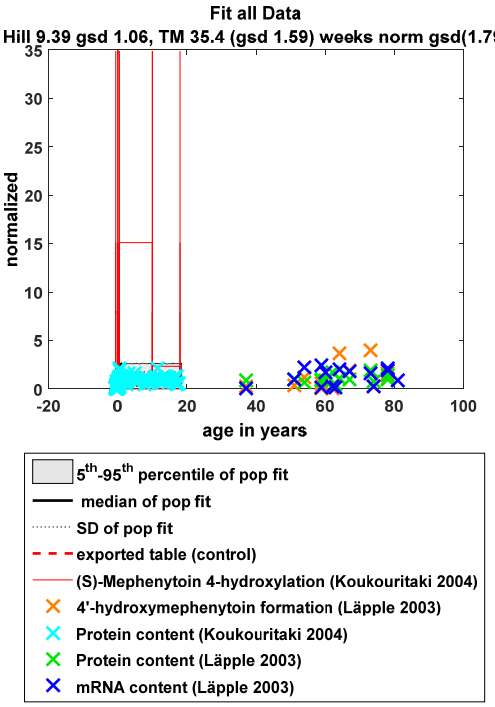
### A.3.1 Original data

| Reference | Used for fit |
|---|---|
| J Pharmacol Exp Ther. 2004 Mar;308(3):965-74. Epub 2003 Nov 21.; Developmental expression of human hepatic CYP2C9 and CYP2C19.; Koukouritaki SB, Manro JR, Marsh SA, Stevens JC, Rettie AE, McCarver DG, Hines RN.<br><br>Digital Object Identifyer (DOI): 10.1124/jpet.103.060137<br><br>→ Figure 3 (protein content)<br>→ Table 2 ((S)-Mephenytoin 4-hydroxylation) | <br><br><br><br><br><br><br>Yes<br>Yes |
| Pharmacogenetics. 2003 Sep;13(9):565-75.; Differential expression and function of CYP2C isoforms in human intestine and liver.; Läpple F, von Richter O, Fromm MF, Richter T, Thon KP, Wisser H, Griese EU, Eichelbaum M, Kivistö KT.<br><br>Digital Object Identifyer (DOI): 10.1097/01.fpc.0000054122.14659.1e<br><br>Pubmed ID (PMID): 12972955 (DOI not functioning)<br><br>→ Table 3 (mRNA expression)<br>→ Table 6 (protein content) | <br><br><br><br><br><br><br><br><br>Yes<br>Yes |

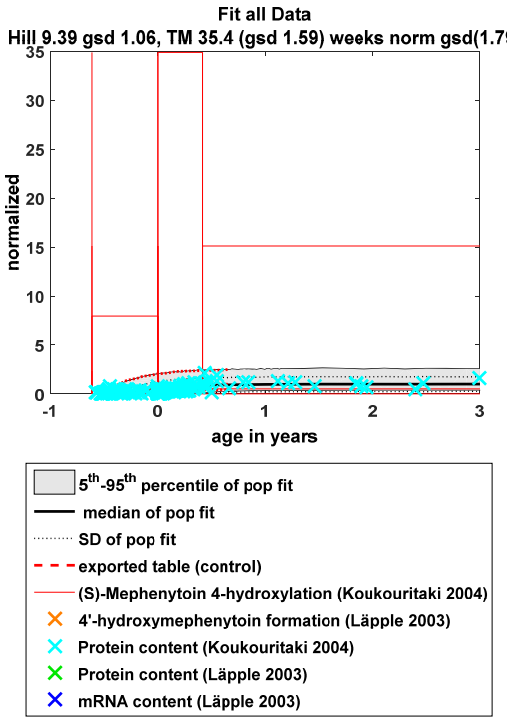
### A.3.2 Fit results

#### A.3.2.1 Figure

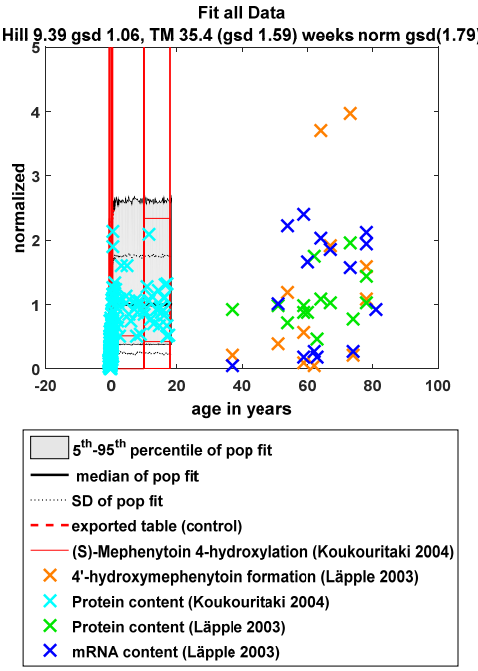
Full range-plot



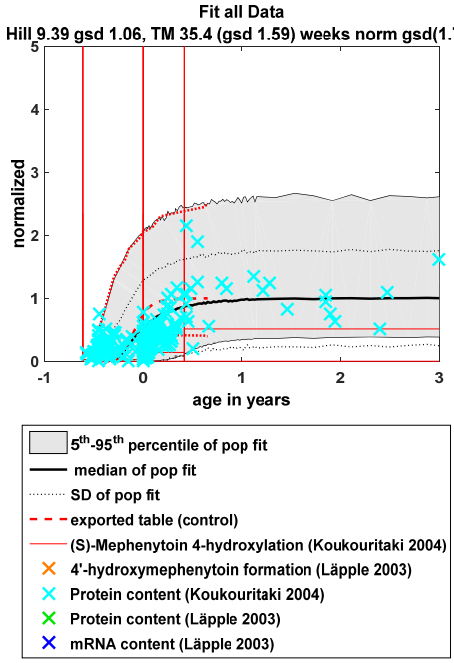

Zoom-in, x-axis




Zoom-in, y-axis




Zoom-in, x-axis and y-axis




**Comment:**

For the intestine, the geometric standard deviation in activity observed in adults ('GeoSD adult') has been separately fitted and implemented with a GeoSD of 2.883.

### A.3.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

**Fit Result:**
n = 9.390
$A_{0.5}$ = 35.447

GeoSD n = 1.055
GeoSD $A_{0.5}$ = 1.592
GeoSD adult = 1.793

### A.3.2.3 Description for PK-Sim®

Values for CYP2C1* ontogeny are based on information to age dependency of mRNA expression, protein content and (S)-Mephenytoin 4-hydroxylation derived from the papers as mentioned in table A.3.1.

### A.3.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP2C19 | Standard Deviation |
|---|---|---|
| 0.33 | 0.001 | 46.35 |
| 0.47 | 0.03 | 10.04 |
| 0.53 | 0.09 | 5.56 |
| 0.58 | 0.18 | 3.76 |
| 0.62 | 0.3 | 2.96 |
| 0.72 | 0.64 | 1.96 |
| 0.77 | 0.76 | 1.84 |
| 0.81 | 0.83 | 1.75 |
| 0.87 | 0.91 | 1.68 |
| 0.94 | 0.95 | 1.71 |
| 1.09 | 0.99 | 1.69 |
| 1.39 | 1 | 1.72 |
| 1.42 | 1 | 1.75 |

## A.4 CYP2C8 in liver

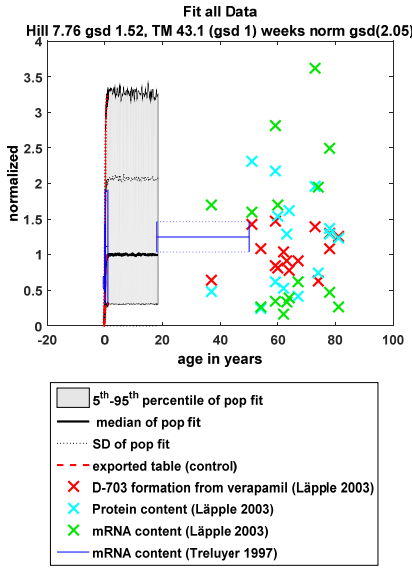
### A.4.1 Original data

| Reference | Used for fit |
|---|---|
| Pharmacogenetics. 1997 Dec;7(6):441-52.; Developmental expression of CYP2C and CYP2C-dependent activities in the human liver: in-vivo/in-vitro correlation and inducibility.; Treluyer JM, Gueret G, Cheron G, Sonnier M, Cresteil T.<br><br>Pubmed ID (PMID): 9429229 (DOI not available)<br><br>→ Figure 5 (mRNA expression) | Yes |
| Pharmacogenetics. 2003 Sep;13(9):565-75.; Differential expression and function of CYP2C isoforms in human intestine and liver.; Läpple F, von Richter O, Fromm MF, Richter T, Thon KP, Wisser H, Griese EU, Eichelbaum M, Kivistö KT.<br><br>Digital Object Identifyer (DOI): 10.1097/01.fpc.0000054122.14659.1e<br><br>Pubmed ID (PMID): 12972955 (DOI not functioning)<br><br>→Table 3 (mRNA expression)<br>→Table 4(protein content, D-703 formation from verapamil) | <br><br><br><br><br><br><br><br>Yes<br>Yes |

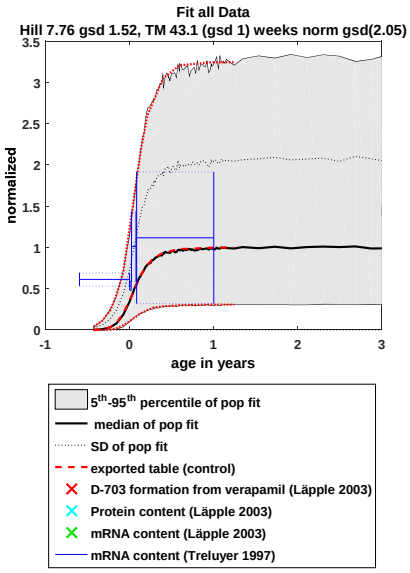
### A.4.2 Fit results

#### A.4.2.1 Figure

Full range-plot




Zoom-in, x-axis




**Comment:**

For the intestine, the geometric standard deviation in activity observed in adults ('GeoSD adult') has been separately fitted and implemented with a GeoSD of 2.903

### A.4.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

**Fit Result:**
n = 7.758
$A_{0.5}$ = 43.084

GeoSD n = 1.522
GeoSD $A_{0.5}$ = 1.000
GeoSD adult = 2.054

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

### A.4.2.3 Description for PK-Sim®

Values for CYP2C8 ontogeny are based on information to age dependency of mRNA expression, protein content and D-703 formation from verapamil, derived from the papers as mentioned in table A.4.1.

### A.4.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP2C8 | Standard Deviation |
|---|---|---|
| 0.34 | 0.001 | 9.23 |
| 0.45 | 0.0087 | 4.92 |
| 0.54 | 0.035 | 3.23 |
| 0.61 | 0.089 | 2.62 |
| 0.69 | 0.2 | 2.15 |
| 0.77 | 0.36 | 2.12 |
| 0.9 | 0.66 | 2.06 |
| 0.98 | 0.79 | 2.06 |
| 1.05 | 0.87 | 2.03 |
| 1.17 | 0.93 | 2.05 |
| 1.36 | 0.98 | 2.06 |
| 1.74 | 1 | 2.05 |

## A.5 CYP2C9 in liver

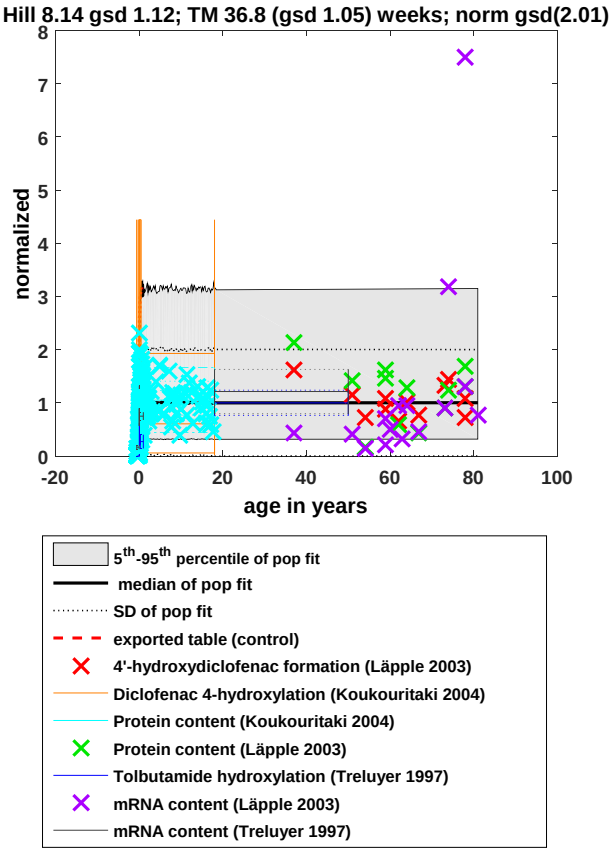
### A.5.1 Original data

| Reference | Used for fit |
|---|---|
| J Pharmacol Exp Ther. 2004 Mar;308(3):965-74. Epub 2003 Nov 21.; Developmental expression of human hepatic CYP2C9 and CYP2C19.; Koukouritaki SB, Manro JR, Marsh SA, Stevens JC, Rettie AE, McCarver DG, Hines RN.<br><br>Digital Object Identifyer (DOI): 10.1124/jpet.103.060137<br><br>→ Figure 2 (protein content)<br>→ Table 1 (Diclofenac 4-hydroxylation)<br>→ Figure 5 | <br><br><br><br><br><br><br>Yes<br>Yes<br>No |
| Pharmacogenetics. 1997 Dec;7(6):441-52.; Developmental expression of CYP2C and CYP2C-dependent activities in the human liver: in-vivo/in-vitro correlation and inducibility.; Treluyer JM, Gueret G, Cheron G, Sonnier M, Cresteil T.<br><br>Pubmed ID (PMID): 9429229 (DOI not available)<br><br>→ Figure 3 (Tolbutamide hydroxylation)<br>→ Figure 5 (mRNA expression) | <br><br><br><br><br><br>Yes<br>Yes |
| Pharmacogenetics. 2003 Sep;13(9):565-75.; Differential expression and function of CYP2C isoforms in human intestine and liver.; Läpple F, von Richter O, Fromm MF, Richter T, Thon KP, Wisser H, Griese EU, Eichelbaum M, Kivistö KT.<br><br>Digital Object Identifyer (DOI): 10.1097/01.fpc.0000054122.14659.1e<br>Pubmed ID (PMID): 12972955 (DOI not functioning)<br><br>→Table 3 (mRNA expression)<br>→Table 5 (4'hydroxydiclofenac formation, protein content) | <br><br><br><br><br><br><br>Yes<br>Yes |

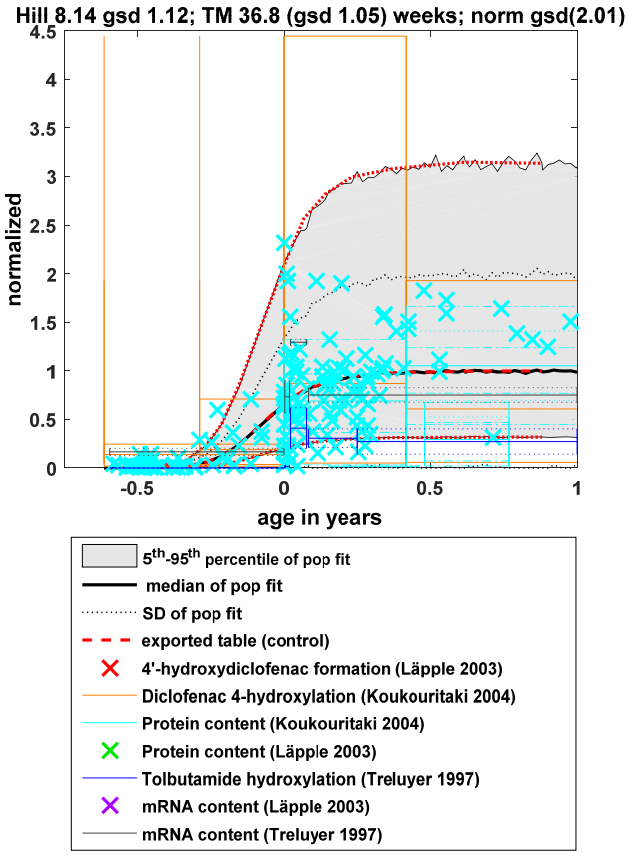
### A.5.2 Fit results

#### A.5.2.1 Figure

Full range-plot




Zoom-in, x-axis




**Comment:**

For the intestine, the geometric standard deviation in activity observed in adults ('GeoSD adult') has been separately fitted and implemented with a GeoSD of 4.016

### A.5.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

**Fit Result:**
n = 8.135
$A_{0.5}$ = 36.773

GeoSD n = 1.118
GeoSD $A_{0.5}$ = 1.049
GeoSD adult = 2.006

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

### A.5.2.3 Description for PK-Sim®

Values for CYP2C9 ontogeny are based on information to age dependency of mRNA expression, protein content, tolbutamide hydroxylation, and 4'hydroxydiclofenac formation, derived from the papers as mentioned in table A.5.1.

### A.5.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP2C9 | Standard Deviation |
|---|---|---|
| 0.3 | 0.00098 | 2.91 |
| 0.44 | 0.019 | 2.4 |
| 0.51 | 0.061 | 2.33 |
| 0.55 | 0.12 | 2.22 |
| 0.62 | 0.24 | 2.15 |
| 0.77 | 0.66 | 2.01 |
| 0.84 | 0.8 | 2.03 |
| 0.91 | 0.89 | 2.02 |
| 1 | 0.94 | 2.02 |
| 1.15 | 0.98 | 2.01 |
| 1.39 | 1 | 2.01 |

## A.6 CYP2D6 in liver

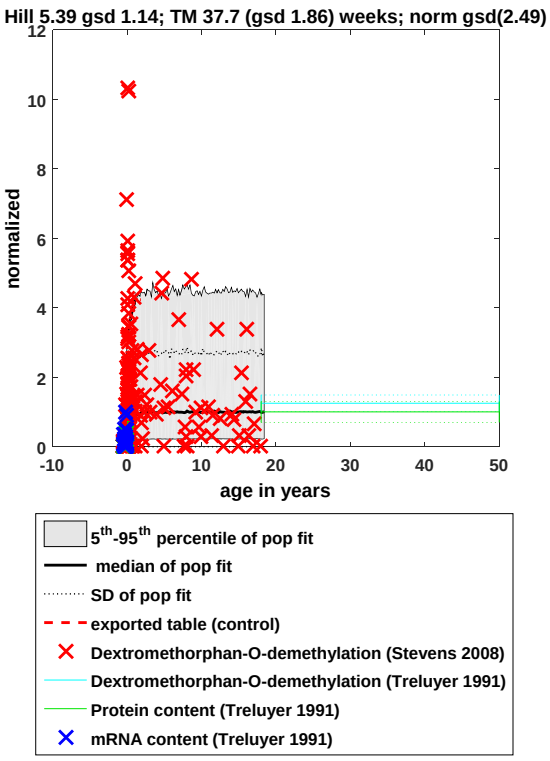
### A.6.1 Original data

| Reference | Used for fit |
|---|---|
| Drug Metab Dispos. 2008 Aug;36(8):1587-93. doi: 10.1124/dmd.108.021873. Epub 2008 May 12.; Developmental changes in human liver CYP2D6 expression.; Stevens JC, Marsh SA, Zaya MJ, Regina KJ, Divakaran K, Le M, Hines RN.<br><br>Digital Object Identifyer (DOI): 10.1124/dmd.108.021873<br><br>→ Figure 1A (Dextromethorphan-O-demethylation)<br>→ Figure 1B (Dextromethorphan-O-demethylation)<br>→ Figure 1C (Dextromethorphan-O-demethylation) | <br><br><br><br><br><br>Yes<br>Yes<br>Yes |
| Eur J Biochem. 1991 Dec 5;202(2):583-8.; Expression of CYP2D6 in developing human liver.; Treluyer JM, Jacqz-Aigrain E, Alvarez F, Cresteil T.<br><br>Digital Object Identifyer (DOI): 10.1111/j.1432-1033.1991.tb16411.x<br><br>→ Figure 1 (protein content)<br>→ Figure 5 (Dextromethorphan-O-demethylation) | <br><br><br><br><br><br>Yes<br>Yes |

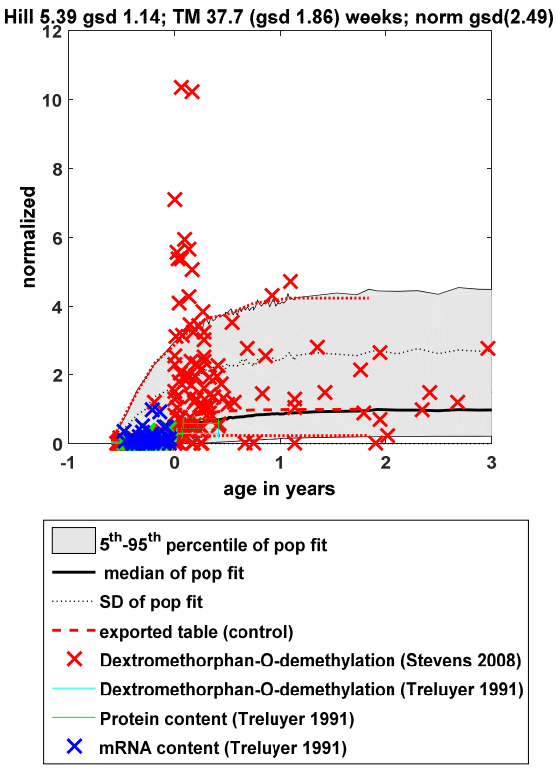
### A.6.2 Fit results

#### A.6.2.1 Figure

Full range-plot




Zoom-in, x-axis



### A.6.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

**Fit Result:**
n = 5.391
$A_{0.5}$ = 37.706

GeoSD n = 1.139
GeoSD $A_{0.5}$ = 1.859
GeoSD adult = 2.488

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

### A.6.2.3 Description for PK-Sim®

Values for CYP2D6 ontogeny are based on information to age dependency of protein content and dextromethorphan-O-demethylation activity, derived from the papers as mentioned in table A.6.1.

### A.6.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP2D6 | Standard Deviation |
|---|---|---|
| 0.2 | 0.001 | 27.88 |
| 0.32 | 0.012 | 14.29 |
| 0.41 | 0.046 | 8.25 |
| 0.49 | 0.1 | 5.76 |
| 0.58 | 0.23 | 4.13 |
| 0.77 | 0.58 | 2.65 |
| 0.86 | 0.71 | 2.46 |
| 0.96 | 0.82 | 2.38 |
| 1.09 | 0.9 | 2.35 |
| 1.26 | 0.95 | 2.3 |
| 1.52 | 0.98 | 2.38 |
| 1.86 | 0.99 | 2.41 |
| 2.61 | 1 | 2.41 |

## A.7 CYP2E1 in liver

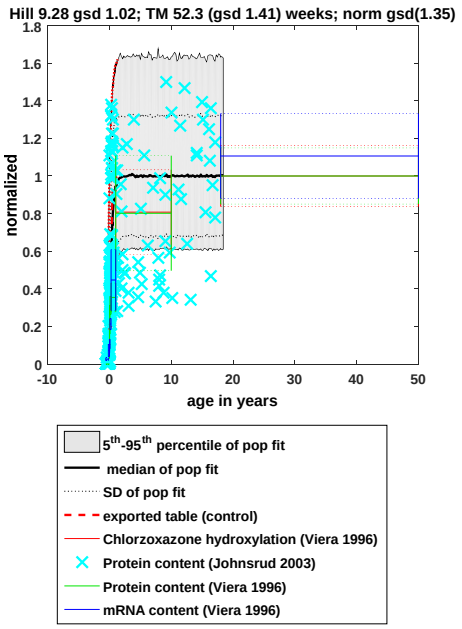
### A.7.1 Original data

| Reference | Used for fit |
|---|---|
| J Pharmacol Exp Ther. 2003 Oct;307(1):402-7.; Human hepatic CYP2E1 expression during development.; Johnsrud EK, Koukouritaki SB, Divakaran K, Brunengraber LL, Hines RN, McCarver DG.<br><br>Digital Object Identifyer (DOI): 10.1124/jpet.102.053124<br>Pubmed ID (PMID): 12972955 (DOI not functioning)<br><br>→ Figure 2A (protein content)<br>→ Figure 2B (protein content)<br>→ Figure 3 (protein content) | <br><br><br><br><br><br><br>Yes<br>Yes<br>Yes |
| Eur J Biochem. 1996 Jun 1;238(2):476-83.; Developmental expression of CYP2E1 in the human liver. Hypermethylation control of gene expression during the neonatal period.; Vieira I, Sonnier M, Cresteil T.<br><br>Digital Object Identifyer (DOI): 10.1111/j.1432-1033.1996.0476z.x<br><br>→ Figure 1 (protein content)<br>→ Figure 2 (Chlorzoxazone hydroxylation)<br>→ Figure 3 (mRNA expression) | <br><br><br><br><br><br><br>Yes<br>Yes<br>Yes |

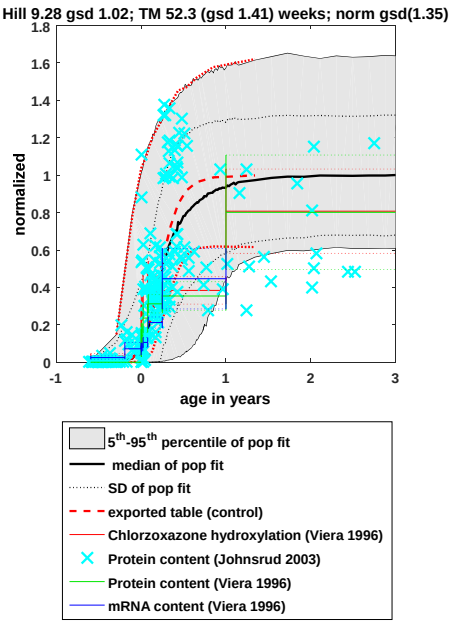
### A.7.2 Fit results

#### A.7.2.1 Figure

Full range-plot




Zoom-in, x-axis



### A.7.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

**Fit Result:**
n = 9.277
$A_{0.5}$ = 52.268

GeoSD n = 1.022
GeoSD $A_{0.5}$ = 1.409
GeoSD adult = 1.350

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

### A.7.2.3 Description for PK-Sim®

Values for CYP2E1 ontogeny are based on information to age dependency of mRNA expression, protein content and chlorzoxazone hydroxylation activity, derived from the papers as mentioned in table A.7.1.

### A.7.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP2E1 | Standard Deviation |
|---|---|---|
| 0.48 | 0.00099 | 21.07 |
| 0.66 | 0.021 | 9.07 |
| 0.77 | 0.077 | 4.85 |
| 0.82 | 0.13 | 3.67 |
| 0.9 | 0.26 | 2.51 |
| 1.05 | 0.6 | 1.63 |
| 1.12 | 0.73 | 1.47 |
| 1.21 | 0.85 | 1.39 |
| 1.3 | 0.92 | 1.33 |
| 1.43 | 0.96 | 1.32 |
| 1.62 | 0.99 | 1.33 |
| 2.12 | 1 | 1.34 |

## A.8 CYP3A4 in liver

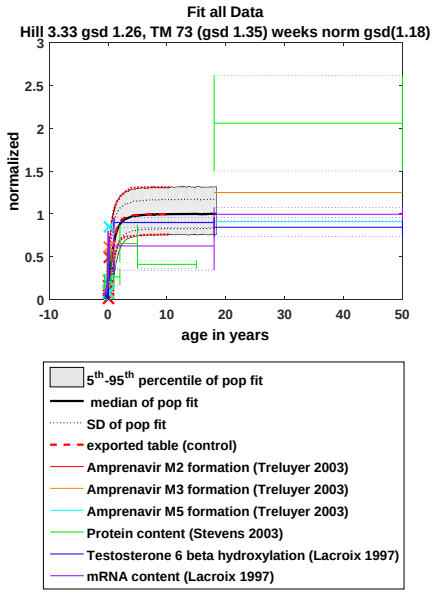
### A.8.1 Original data

| Reference | Used for fit |
|---|---|
| Eur J Biochem. 1997 Jul 15;247(2):625-34.; Expression of CYP3A in the human liver--evidence that the shift between CYP3A7 and CYP3A4 occurs immediately after birth.; Lacroix D, Sonnier M, Moncion A, Cheron G, Cresteil T.<br><br>Digital Object Identifyer (DOI): 10.1111/j.1432-1033.1997.00625.x<br><br>→ Figure 3 (mRNA expression)<br>→ Figure 4A-B (Testosterone 6 beta hydroxylation) | <br><br><br><br><br><br>Yes<br>Yes |
| Drug Metab Dispos. 2003 Mar;31(3):275-81.; Oxidative metabolism of amprenavir in the human liver. Effect of the CYP3A maturation.; Tréluyer JM, Bowers G, Cazali N, Sonnier M, Rey E, Pons G, Cresteil T.<br><br>Digital Object Identifyer (DOI): 10.1124/dmd.31.3.275<br><br>→ Table 5 (Amprenavir M2, M3 and M5 and formation) | <br><br><br><br><br><br>Yes |
| J Pharmacol Exp Ther. 2003 Nov;307(2):573-82. Epub 2003 Sep 15.; Developmental expression of the major human hepatic CYP3A enzymes.; Stevens JC, Hines RN, Gu C, Koukouritaki SB, Manro JR, Tandler PJ, Zaya MJ.<br><br>Digital Object Identifyer (DOI): 10.1124/jpet.103.054841<br><br>→ Figure 8 (protein content) | <br><br><br><br><br><br>Yes |
| Drug Metab Dispos. 2000 Apr;28(4):379-82.; Human cytochrome P450 maximal activities in pediatric versus adult liver.; Blanco JG1, Harrison PL, Evans WE, Relling MV.<br><br>PMID: 10725303 (DOI not available)<br><br>→ Figure 2 (Midazolam 1' hydroxylation) | <br><br><br><br><br><br>No |
| Pharmacogenetics. 1997 Dec;7(6):441-52.; Developmental expression of CYP2C and CYP2C-dependent activities in the human liver: in-vivo/in-vitro correlation and inducibility.; Treluyer JM, Gueret G, Cheron G, Sonnier M, Cresteil T.<br><br>Pubmed ID (PMID): 9429229 (DOI not available)<br><br>→ Figure 4B (Diazepam hydroxylation) | <br><br><br><br><br><br>No |

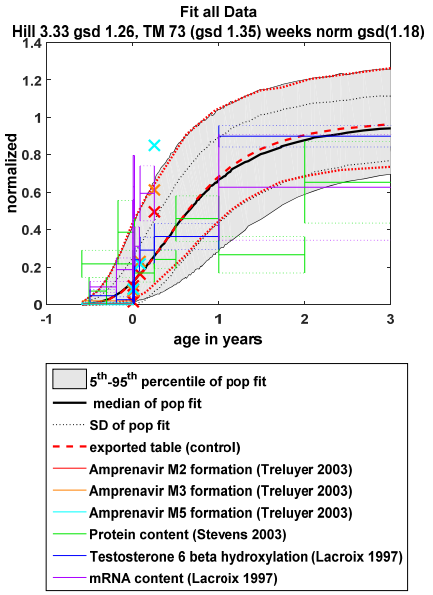
### A.8.2 Fit results

#### A.8.2.1 Figure

Full range-plot




Zoom-in, x-axis




**Comment:**

The old PK-Sim® version was not fitted using the Hill equation but using spline functions allowing for the 'overshoot' of relative expression compared to adults. According to Edginton et al. 2006 an ontogeny factor of 1.3 was found for children from 1-3 y.

Reassessing in the light of additional data, the references quoted by Edginton et al 2006, such a high expression value for this age range could not be confirmed. The only CYP-mediated process found to yield an ontogeny factor of approx. 1.44 for children aged 3-12 months was reported by Treluyer et al. 1997 for the hydroxylation of diazepam (Fig. 4B). This metabolization, however, is not specific for CYP3A4 but is also mediated by CYP2C19 as reported by Riss et al. 2008 (Acta Neurol Scand. 118(2):69-86). Therefore, the age-dependency of this process was not considered for fitting CYP3A4 ontogeny in liver. Nevertheless, even if this dataset would have been considered, due to the different fit function the new ontogeny profile of CYP3A4 in liver would be significantly different than the old one.

#### A.8.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

**Fit Result:**
n = 3.331
$A_{0.5}$ = 73.019

GeoSD n = 1.255
GeoSD $A_{0.5}$ = 1.345
GeoSD adult = 1.182

### A.8.2.3 Description for PK-Sim®

Values for CYP3A4 ontogeny in liver are based on information to age dependency of mRNA content, testosterone 6 beta hydroxylation activity, protein content as well as amprenavir metabolite formation, derived from the papers as mentioned in table A.8.1.

### A.8.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP3A4 | Standard Deviation |
|---|---|---|
| 0.18 | 0.001 | 4.63 |
| 0.37 | 0.011 | 3.22 |
| 0.5 | 0.03 | 2.73 |
| 0.63 | 0.064 | 2.46 |
| 0.77 | 0.12 | 2.22 |
| 0.92 | 0.2 | 1.92 |
| 1.39 | 0.49 | 1.45 |
| 1.55 | 0.58 | 1.37 |
| 1.73 | 0.67 | 1.31 |
| 1.91 | 0.74 | 1.26 |
| 2.08 | 0.79 | 1.23 |
| 2.26 | 0.83 | 1.22 |
| 2.5 | 0.87 | 1.19 |
| 2.84 | 0.91 | 1.18 |
| 3.19 | 0.94 | 1.18 |
| 3.81 | 0.97 | 1.18 |
| 4.69 | 0.98 | 1.19 |
| 6.48 | 0.99 | 1.18 |
| 11.17 | 1 | 1.18 |

## A.9 CYP3A5 in liver

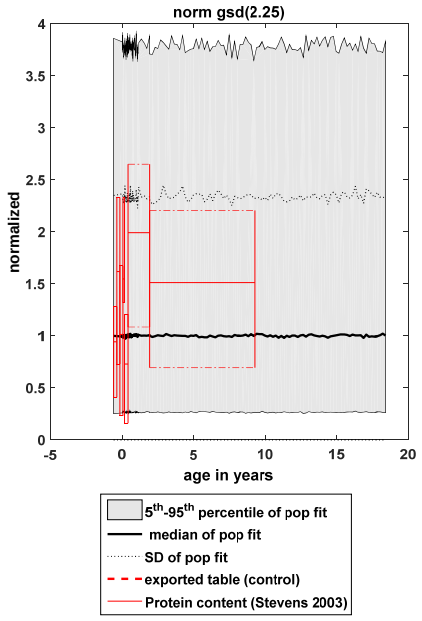
### A.9.1 Original data

| Reference | Used for fit |
|---|---|
| J Pharmacol Exp Ther. 2003 Nov;307(2):573-82. Epub 2003 Sep 15.; Developmental expression of the major human hepatic CYP3A enzymes.; Stevens JC, Hines RN, Gu C, Koukouritaki SB, Manro JR, Tandler PJ, Zaya MJ.<br><br>Digital Object Identifyer (DOI): 10.1124/jpet.103.054841<br><br>→ Figure 2 (protein content) | yes<br>→Although, no ontogeny visible for this protein. |

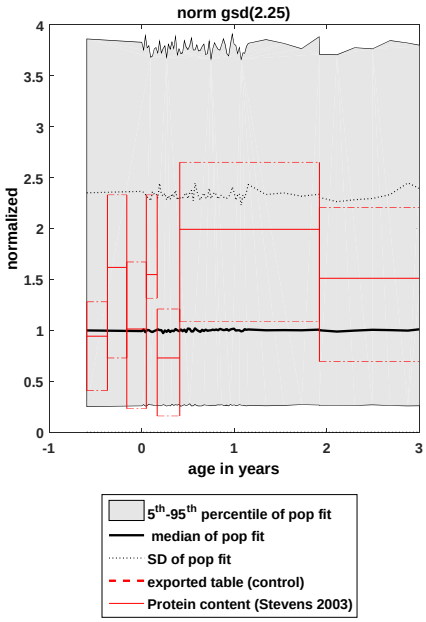
### A.9.2 Fit results

#### A.9.2.1 Figure

Full range-plot




Zoom-in, x-axis




**Comment:**

Due to the variability of the data, no ontogeny fit for CYP3A5 is possible. The ontogeny function for this enzyme therefore is equal to one for all age groups.

#### A.9.2.2 Fit function

The ontogeny is equal to 1 for all ages. The geometric standard deviation in activity observed in adults is 2.246.

#### A.9.2.3 Description for PK-Sim®

CYP3A5 activity in liver is assumed to be at 100 % adult activity at all ages based on the data from Stevens et al. 2003 J Pharmacol Exp Ther 307(2):573-82.

#### A.9.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP3A5 | Standard Deviation |
|---|---|---|
| 0 | 1 | 2.25 |
| 0.77 | 1 | 2.25 |

## CYP3A7 in liver

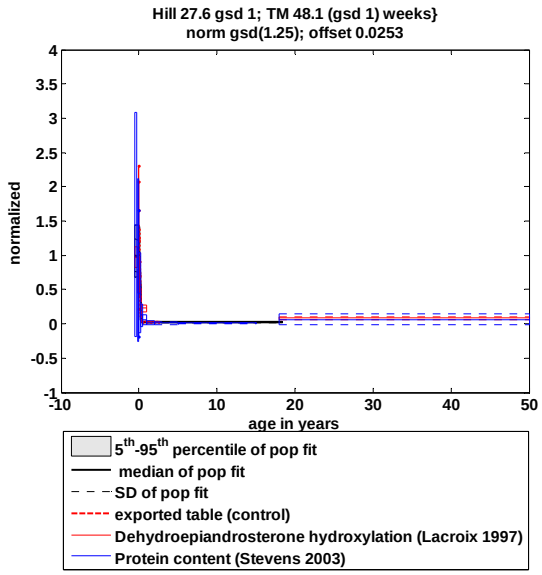
### A.9.3 Original data

| Reference | Used for fit |
|---|---|
| Eur J Biochem. 1997 Jul 15;247(2):625-34.; Expression of CYP3A in the human liver--evidence that the shift between CYP3A7 and CYP3A4 occurs immediately after birth.; Lacroix D, Sonnier M, Moncion A, Cheron G, Cresteil T.<br><br>Digital Object Identifyer (DOI): 10.1111/j.1432-1033.1997.00625.x<br><br>→ Figure 4A-B (Dehydroepiandrosterone hydroxylation) | Yes |
| J Pharmacol Exp Ther. 2003 Nov;307(2):573-82. Epub 2003 Sep 15.; Developmental expression of the major human hepatic CYP3A enzymes.; Stevens JC, Hines RN, Gu C, Koukouritaki SB, Manro JR, Tandler PJ, Zaya MJ.<br><br>Digital Object Identifyer (DOI): 10.1124/jpet.103.054841<br><br>→ Figure 8 (protein content) | Yes |

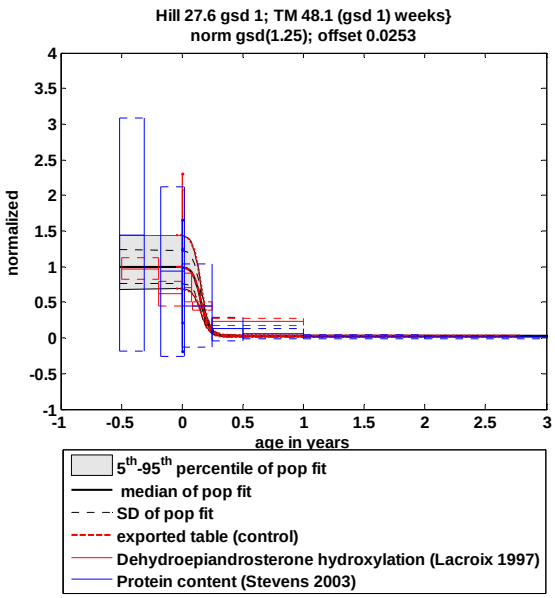
### A.9.4 Fit results

#### A.9.4.1 Figure

Full range-plot




Zoom-in, x-axis



### A.9.4.2 Fit function

**Fit Result:**
n = 27.615
$A_{0.5}$ = 48.051

GeoSD $A_{0.5}$ = 1
GeoSD n = 1
GeoSD adult = 1.254
Offset = 0.0253

$A = 1-PMA^n/(A_{0.5}{}^n + PMA^n) + offset$

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults
Offset = activity in adults

### A.9.4.3 Description for PK-Sim®

Values for CYP3A7 ontogeny are based on information to age dependency of protein content and dehydroepiandrosterone hydroxylation activity, derived from the papers as mentioned in table A.10.1.

### A.9.4.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP3A7 | Standard Deviation |
|---|---|---|
| 0.72 | 1 | 1.25 |
| 0.77 | 0.99 | 1.25 |
| 0.83 | 0.95 | 1.26 |
| 0.87 | 0.85 | 1.25 |
| 0.9 | 0.71 | 1.25 |
| 0.95 | 0.36 | 1.25 |
| 0.98 | 0.2 | 1.26 |
| 1.02 | 0.078 | 1.25 |
| 1.05 | 0.054 | 1.26 |
| 1.12 | 0.03 | 1.25 |
| 1.83 | 0.025 | 1.26 |
| 3.36 | 0.025 | 1.25 |
| 3.41 | 0.025 | 1.25 |
| 3.56 | 0.025 | 1.26 |

## 4.4 UGT enzymes in liver

## A.1 UGT1A1 in liver

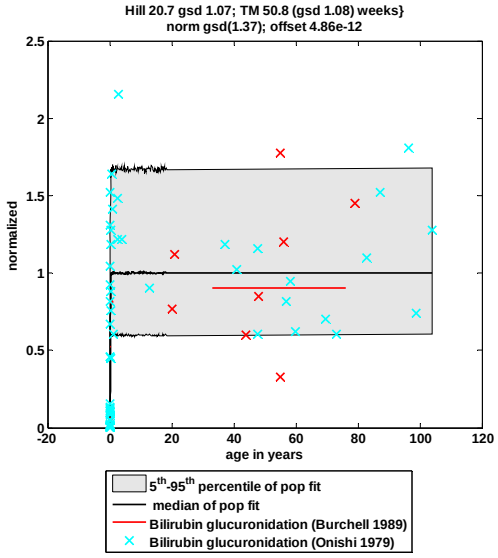
### A.1.1 Original data

| Reference | Used for fit |
|---|---|
| Dev Pharmacol Ther. 1989;13(2-4):70-7.; Development of human liver UDP-glucuronosyltransferases.; Burchell B, Coughtrie M, Jackson M, Harding D, Fournel-Gigleux S, Leakey J, Hume R.<br><br>Pubmed ID (PMID): 2515047 (DOI not available)<br><br>→ Table 1 (Bilirubin glucuronidation)<br>→ Table 2 (Bilirubin glucuronidation) | <br><br><br><br><br><br>No<br>Yes |
| Drug Metab Dispos. 2011 May;39(5):912-9. doi: 10.1124/dmd.110.037192. Epub 2011 Jan 25.; The development of UDP-glucuronosyltransferases 1A1 and 1A6 in the pediatric liver.; Miyagi SJ, Collier AC.<br><br>Digital Object Identifyer (DOI): 10.1124/dmd.110.037192<br><br>→ Figure 1A (Bilirubin glucuronidation) | <br><br><br><br><br>No |
| Gut. 2002 Feb;50(2):259-65.; Developmental aspects of human hepatic drug glucuronidation in young children and adults.; Strassburg CP, Strassburg A, Kneip S, Barut A, Tukey RH, Rodeck B, Manns MP.<br><br>Digital Object Identifyer (DOI): 10.1136/gut.50.2.259<br><br>→ Figure 2 (mRNA expression) | <br><br><br><br><br>No |
| Biochem J. 1979 Dec 15;184(3):705-7.; Postnatal development of uridine diphosphate glucuronyltransferase activity towards bilirubin and 2-aminophenol in human liver.; Onishi S, Kawade N, Itoh S, Isobe K, Sugiyama S.<br><br>Digital Object Identifyer (DOI): 10.1042/bj1840705<br><br>→ Figure 1 (Bilirubin glucuronidation) | <br><br><br><br><br>Yes |

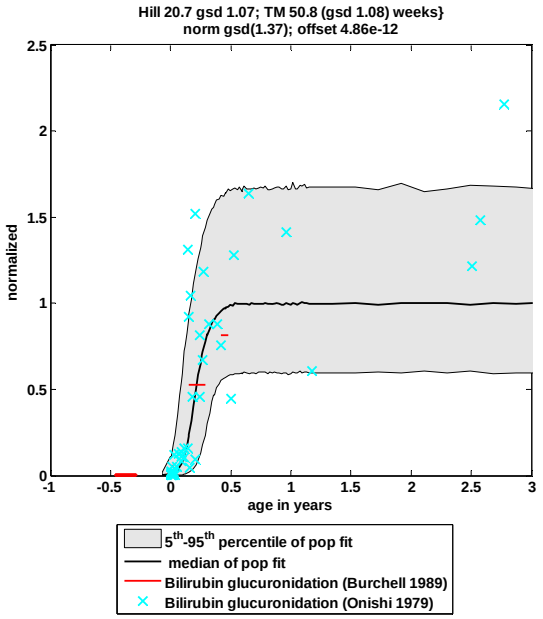
### A.1.2 Fit results

#### A.1.2.1 Figure

Full range-plot




Zoom-in, x-axis




#### A.1.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

**Fit Result:**
n = 20.670
$A_{0.5}$ = 50.754

GeoSD n = 1.066
GeoSD $A_{0.5}$ = 1.084
GeoSD adult = 1.367

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

#### A.1.2.3 Description for PK-Sim®

Values for UGT1A1 ontogeny are based on information to age dependency of mRNA expression, and bilirubin glucuronidation activity, derived from the papers as mentioned in table A.2.1.

#### A.1.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for UGT1A1 | Standard Deviation |
|---|---|---|
| 0.698271871 | 0.000979058 | 2.552011728 |
| 0.769230783 | 0.007233677 | 2.38158989 |
| 0.858116925 | 0.064657465 | 2.010226488 |

| | | |
|---|---|---|
| 0.890073895 | 0.130265653 | 1.816496134 |
| 0.919260323 | 0.224505559 | 1.637136698 |
| 1.029093981 | 0.755379558 | 1.228398442 |
| 1.075121403 | 0.884206295 | 1.176906228 |
| 1.128819823 | 0.954406977 | 1.152582049 |
| 1.226630092 | 0.991511762 | 1.140699267 |
| 1.361833453 | 0.999002397 | 1.138464808 |

## A.2 UGT1A4 in liver

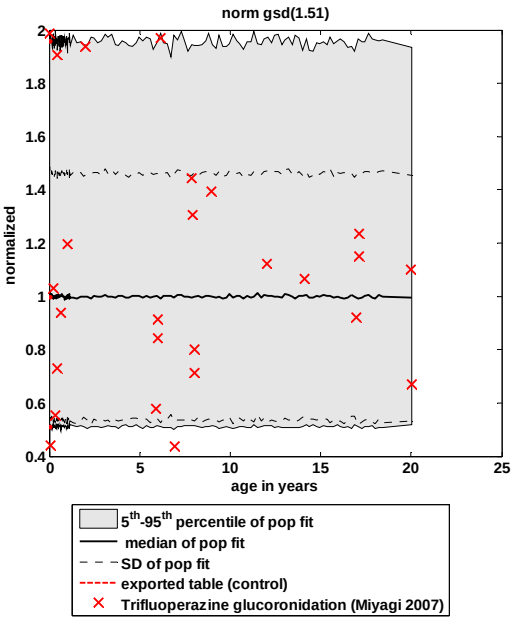
### A.2.1 Original data

| Reference | Used for fit |
|---|---|
| Drug Metab Dispos. 2007 Sep;35(9):1587-92. Epub 2007 Jun 7.; Pediatric development of glucuronidation: the ontogeny of hepatic UGT1A4.; Miyagi SJ, Collier AC.<br><br>Digital Object Identifyer (DOI): 10.1124/dmd.107.015214<br><br>→ Figure 3A (Trifluoperazine glucoronidation) | Yes<br>→ although no ontogeny visible for this protein |

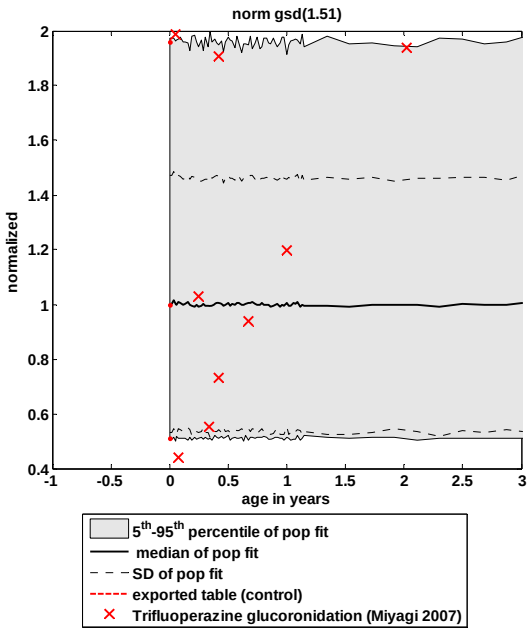
### A.2.2 Fit results

#### A.2.2.1 Figure

Full range-plot




Zoom-in, x-axis




**Comment:**

Due to the variability of the data, no ontogeny fit using the Hill equation for UGT1A4 is possible. The ontogeny function for this enzyme therefore is equal to one for all age groups.

The curve shown in Miyagi et al. 2007 is a result of modeling hepatic UGT1A4 liver clearance assuming a constant rate of development. It therefore does not represent a true fit.

#### A.2.2.2 Fit function

The ontogeny is equal to 1 for all ages. The geometric standard deviation in activity observed in adults is 1.506.

#### A.2.2.3 Description for PK-Sim®

UGT1A4 activity in liver is assumed to be at 100 % adult activity at all ages based on the data from Miyagi 2007 Drug Metab Dispos 35(9):1587-1592.

#### A.2.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for UGT1A4 | Standard Deviation |
|---|---|---|
| 0 | 1 | 1.51 |
| 0.77 | 1 | 1.51 |

## A.3 UGT1A6 in liver

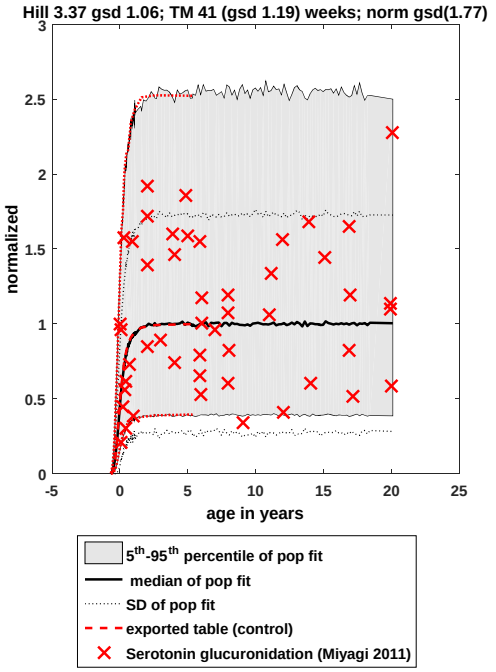
### A.3.1 Original data

| Reference | Used for fit |
|---|---|
| Drug Metab Dispos. 2011 May;39(5):912-9. doi: 10.1124/dmd.110.037192. Epub 2011 Jan 25.; The development of UDP-glucuronosyltransferases 1A1 and 1A6 in the pediatric liver.; Miyagi SJ, Collier AC.<br><br>Digital Object Identifyer (DOI): 10.1124/dmd.110.037192<br><br>→ Figure 2A (Serotonin glucuronidation) | Yes |

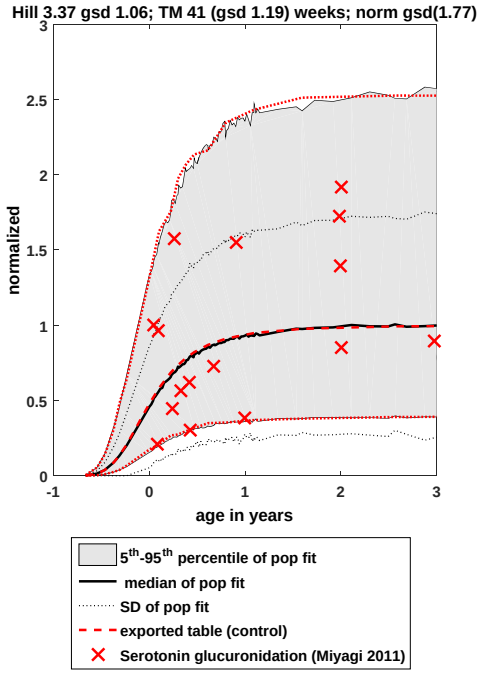
### A.3.2 Fit results

#### A.3.2.1 Figure

Full range-plot




Zoom-in, x-axis




**Comment:**

The old PK-Sim fit was based on in vivo data of paracetamol glucuruonidation, i.e. paracetamol glucuronide to sulfate ratios (Edginton et al. 2006). The fit using in vitro serotonin glucuronidation data, however, shows a similar representation of UGT1A6 ontogeny.

#### A.3.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

With:

PK-Sim® Ontogeny Database
Version 7.3

**Fit Result:**
n = 3.369
$A_{0.5}$ = 41.030

GeoSD n = 1.064
GeoSD $A_{0.5}$ = 1.192
GeoSD adult = 1.769

PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

#### A.3.2.3 Description for PK-Sim®

Values for UGT1A6 ontogeny are based on information to age dependency of serotonin glucuronidation as reported by Miyagi 2011 Drug Metab Dispos 39(5): 912-919.

#### A.3.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for UGT1A6 | Standard Deviation |
|---|---|---|
| 0.1 | 0.001 | 2.49 |
| 0.22 | 0.013 | 2.36 |
| 0.3 | 0.038 | 2.23 |
| 0.39 | 0.088 | 2.14 |
| 0.45 | 0.13 | 2.16 |
| 0.53 | 0.21 | 1.99 |
| 0.77 | 0.48 | 1.85 |
| 0.87 | 0.58 | 1.87 |
| 0.99 | 0.69 | 1.77 |
| 1.07 | 0.74 | 1.82 |
| 1.15 | 0.78 | 1.81 |
| 1.24 | 0.82 | 1.79 |
| 1.38 | 0.87 | 1.74 |
| 1.57 | 0.91 | 1.78 |
| 1.86 | 0.95 | 1.77 |
| 2.37 | 0.98 | 1.78 |
| 3.34 | 0.99 | 1.76 |
| 6.13 | 1 | 1.76 |

## A.4 UGT1A9 in liver

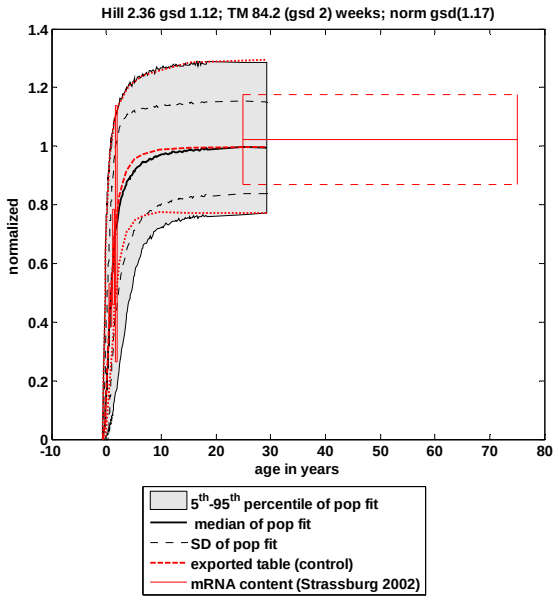
### A.4.1 Original data

| Reference | Used for fit |
|---|---|
| Gut. 2002 Feb;50(2):259-65.; Developmental aspects of human hepatic drug glucuronidation in young children and adults.; Strassburg CP, Strassburg A, Kneip S, Barut A, Tukey RH, Rodeck B, Manns MP.<br><br>Digital Object Identifyer (DOI): 10.1136/gut.50.2.259<br><br>→ Figure 2 (mRNA expression) | Yes |

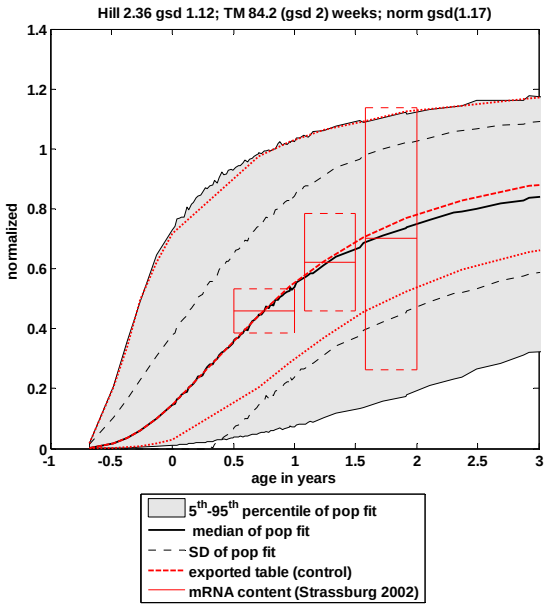
### A.4.2 Fit results

#### A.4.2.1 Figure

Full range-plot




Zoom-in, x-axis




#### A.4.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

**Fit Result:**
n = 2.362
$A_{0.5}$ = 84.220

GeoSD n = 1.122
GeoSD $A_{0.5}$ = 1.997
GeoSD adult = 1.169

### A.4.2.3 Description for PK-Sim®

Values for UGT1A9 ontogeny are based on information to age dependency of mRNA expression as reported by Strassburg et al. 2002 Gut 50:259–265.

### A.4.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for UGT1A9 | Standard Deviation |
|---|---|---|
| 0.09 | 0.00099 | 5.48 |
| 0.29 | 0.016 | 4.63 |
| 0.4 | 0.035 | 3.99 |
| 0.5 | 0.059 | 3.64 |
| 0.64 | 0.1 | 3.03 |
| 0.77 | 0.15 | 2.62 |
| 1.47 | 0.44 | 1.61 |
| 1.74 | 0.54 | 1.47 |
| 2.01 | 0.63 | 1.38 |
| 2.34 | 0.7 | 1.3 |
| 2.69 | 0.77 | 1.26 |
| 3.14 | 0.83 | 1.22 |
| 3.7 | 0.88 | 1.19 |
| 4.47 | 0.92 | 1.17 |
| 5.03 | 0.94 | 1.17 |
| 5.95 | 0.96 | 1.16 |
| 7.45 | 0.97 | 1.16 |
| 10.49 | 0.99 | 1.16 |
| 16.12 | 1 | 1.17 |

## A.5 UGT2B4 in liver

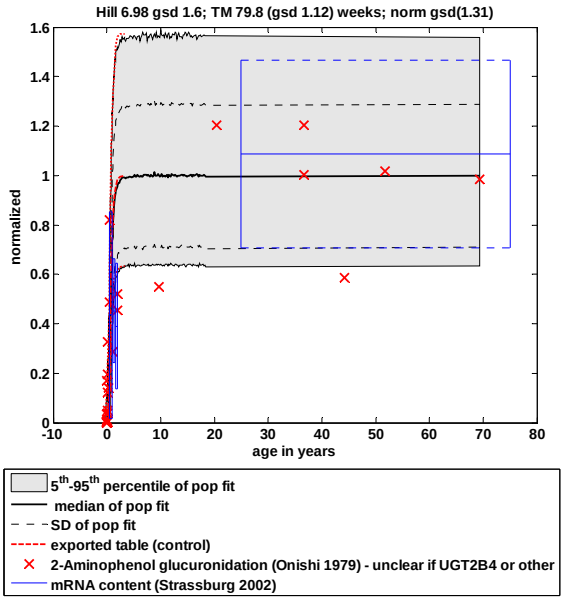
### A.5.1 Original data

| Reference | Used for fit |
|---|---|
| Biochem J. 1979 Dec 15;184(3):705-7.; Postnatal development of uridine diphosphate glucuronyltransferase activity towards bilirubin and 2-aminophenol in human liver.; Onishi S, Kawade N, Itoh S, Isobe K, Sugiyama S.<br><br>Digital Object Identifyer (DOI): 10.1042/bj1840705<br><br>→ Figure 2 (2-aminophenol glucuronidation) | Yes |
| Gut. 2002 Feb;50(2):259-65.; Developmental aspects of human hepatic drug glucuronidation in young children and adults.; Strassburg CP, Strassburg A, Kneip S, Barut A, Tukey RH, Rodeck B, Manns MP.<br><br>Digital Object Identifyer (DOI): 10.1136/gut.50.2.259<br><br>→ Figure 2 (mRNA expression) | Yes |

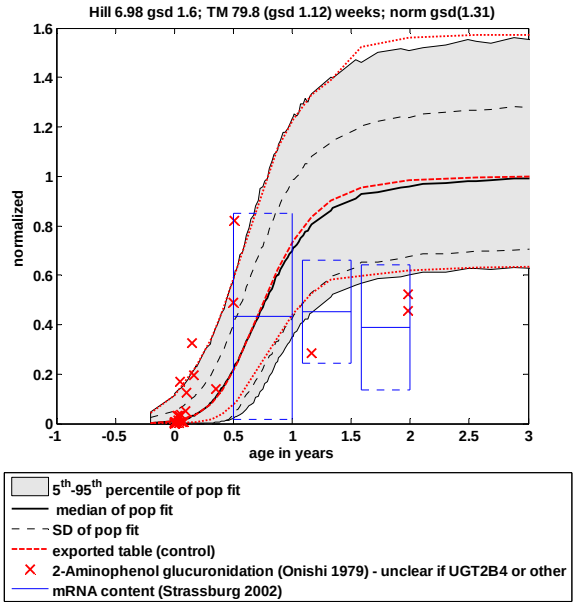
### A.5.2 Fit results

#### A.5.2.1 Figure

Full range-plot




Zoom-in, x-axis



### A.5.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

**Fit Result:**
n = 6.983
$A_{0.5}$ = 79.785

GeoSD n = 1.596
GeoSD $A_{0.5}$ = 1.125
GeoSD adult = 1.314

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

### A.5.2.3 Description for PK-Sim®

Values for UGT2B4 ontogeny are based on information to age dependency of 2-aminophenol Glucuronidation, and mRNA expression, derived from the papers as mentioned in table A.5.1.

### A.5.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for UGT2B7 | Standard Deviation |
|---|---|---|
| 0.479999989 | 0.00099 | 17.12999916 |
| 0.660000026 | 0.0073 | 12.78999996 |
| 0.769999981 | 0.02 | 8.729999542 |
| 0.910000026 | 0.057 | 5.679999828 |
| 1.029999971 | 0.119999997 | 3.970000029 |
| 1.149999976 | 0.219999999 | 2.960000038 |
| 1.24000001 | 0.310000002 | 2.480000019 |
| 1.5 | 0.620000005 | 1.769999981 |
| 1.639999986 | 0.74000001 | 1.669999957 |
| 1.75999999 | 0.819999993 | 1.610000014 |
| 1.889999986 | 0.879999995 | 1.570000052 |
| 2.069999933 | 0.930000007 | 1.539999962 |
| 2.349999905 | 0.970000029 | 1.519999981 |
| 2.859999895 | 0.99000001 | 1.559999943 |
| 4.010000229 | 1 | 1.590000033 |

## A.6 UGT2B7 in liver

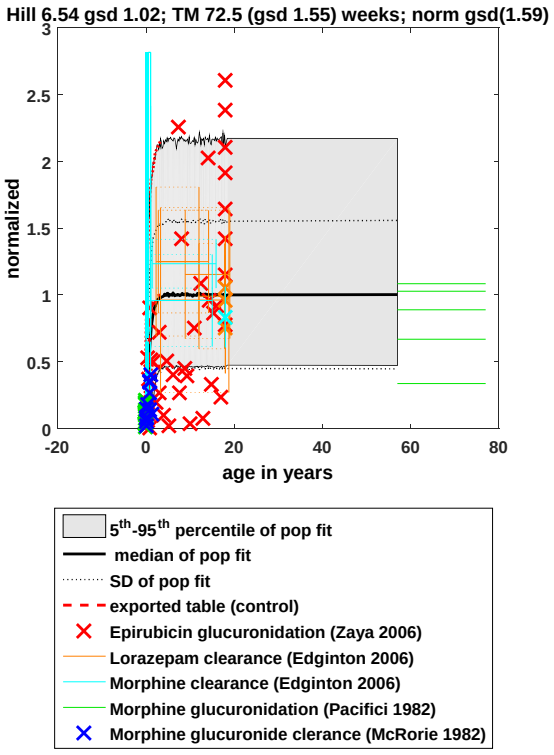
### A.6.1 Original data

| Reference | Used for fit |
|---|---|
| Gut. 2002 Feb;50(2):259-65.; Developmental aspects of human hepatic drug glucuronidation in young children and adults.; Strassburg CP, Strassburg A, Kneip S, Barut A, Tukey RH, Rodeck B, Manns MP.<br><br>Digital Object Identifyer (DOI): 10.1136/gut.50.2.259<br><br>→ Figure 2 (mRNA expression) | No |
| Drug Metab Dispos. 2006 Dec;34(12):2097-101.; Epub 2006 Sep 19. Epirubicin glucuronidation and UGT2B7 developmental expression.; Zaya MJ1, Hines RN, Stevens JC.<br><br>Digital Object Identifyer (DOI): 10.1124/dmd.106.011387<br><br>→ Figure 6 A (Epirubicin glucuronidation) | Yes |
| Eur J Clin Pharmacol. 1982;22(6):553-8.; Morphine glucuronidation in human fetal and adult liver.; Pacifici GM, Säwe J, Kager L, Rane A.<br><br>Digital Object Identifyer (DOI): 10.1007/BF00609630<br><br>→ Figure 2 (Morphine glucuronidation) | Yes |
| Am J Dis Child. 1992 Aug;146(8):972-6.; The maturation of morphine clearance and metabolism.; McRorie TI, Lynn AM, Nespeca MK, Opheim KE, Slattery JT.<br><br>Digital Object Identifyer (DOI): 10.1001/archpedi.1992.02160200094036<br><br>→ Figure 2 (Morphine glucuronide clearance) | Yes |
| Clin Pharmacokinet. 2006;45(10):1013-34.; Development and evaluation of a generic physiologically based pharmacokinetic model for children.; Edginton AN, Schmitt W, Willmann S.<br><br>Digital Object Identifyer (DOI): 10.2165/00003088-200645100-00005<br><br>→Table 3 (Lorazepam and morphine clearance) | Yes |

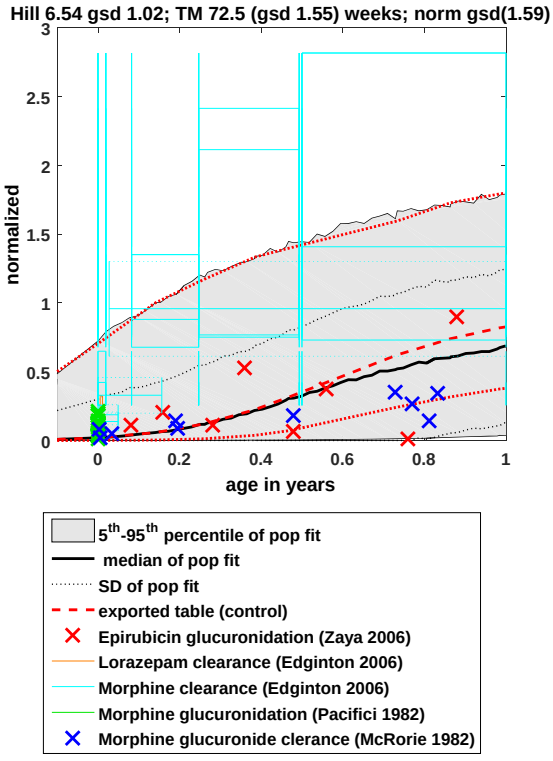
### A.6.2 Fit results

#### A.6.2.1 Figure

Full range-plot




Zoom-in, x-axis




#### A.6.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

**Fit Result:**
n = 6.543
$A_{0.5}$ = 72.533

GeoSD n = 1.023
GeoSD $A_{0.5}$ = 1.554
GeoSD adult = 1.595

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation
GeoSD adult = geometric standard deviation in activity observed in adults

#### A.6.2.3 Description for PK-Sim®

Values for UGT2B7 ontogeny are based on information to age dependency morphine glucuronidation activity, epirubicin glucuronidation activity, as well as in vivo morphine and lorazepam glucuronide clearance, derived from the papers as mentioned in table A.6.1.

#### A.6.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for UGT2B7 | Standard Deviation |
|---|---|---|
| 0.479999989 | 0.00099 | 17.12999916 |
| 0.660000026 | 0.0073 | 12.78999996 |

| | | |
|---|---|---|
| 0.769999981 | 0.02 | 8.729999542 |
| 0.910000026 | 0.057 | 5.679999828 |
| 1.029999971 | 0.119999997 | 3.970000029 |
| 1.149999976 | 0.219999999 | 2.960000038 |
| 1.24000001 | 0.310000002 | 2.480000019 |
| 1.5 | 0.620000005 | 1.769999981 |
| 1.639999986 | 0.74000001 | 1.669999957 |
| 1.75999999 | 0.819999993 | 1.610000014 |
| 1.889999986 | 0.879999995 | 1.570000052 |
| 2.069999933 | 0.930000007 | 1.539999962 |
| 2.349999905 | 0.970000029 | 1.519999981 |
| 2.859999895 | 0.99000001 | 1.559999943 |
| 4.010000229 | 1 | 1.590000033 |

## 4.5 CYP Enzymes in the intestine

## A.1 CYP3A4 in duodenum

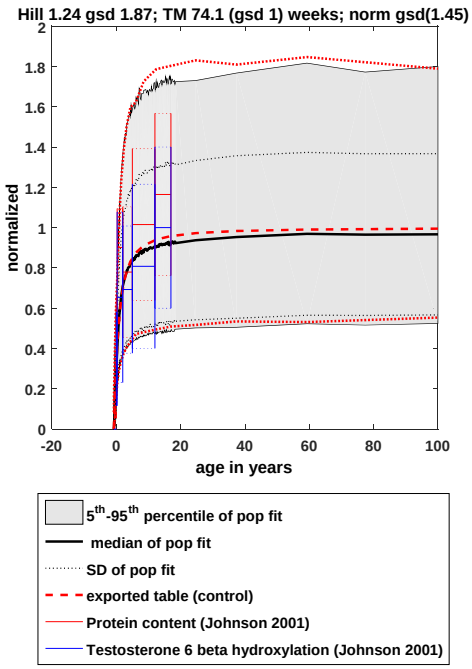
### A.1.1 Original data

| Reference | Used for fit |
|---|---|
| Br J Clin Pharmacol. 2001 May;51(5):451-60.; Enterocytic CYP3A4 in a paediatric population: developmental changes and the effect of coeliac disease and cystic fibrosis.; Johnson TN, Tanner MS, Taylor CJ, Tucker GT.<br><br>Digital Object Identifyer (DOI): 10.1046/j.1365-2125.2001.01370.x<br><br>→ Figure 2 (Protein content and Testosterone 6 beta hydroxylation) | Yes |

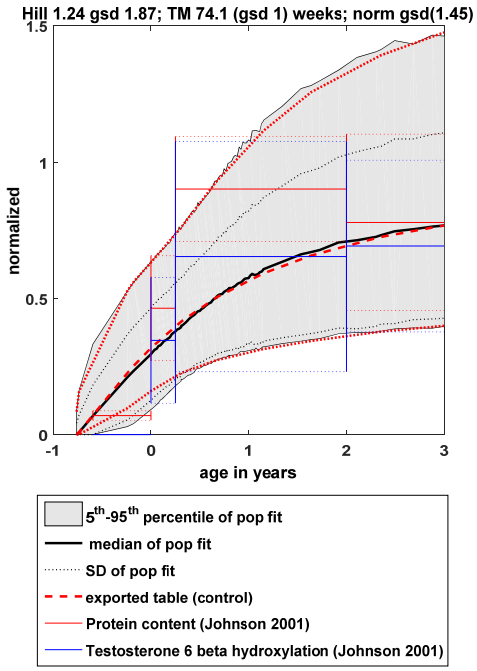
### A.1.2 Fit results

#### A.1.2.1 Figure

Full range-plot




Zoom-in, x-axis




#### A.1.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation

**Fit Result:**
n = 1.237
$A_{0.5}$ = 74.055

GeoSD n = 1.872
GeoSD $A_{0.5}$ = 1.000
GeoSD adult = 1.451

GeoSD adult = geometric standard deviation in activity observed in adults

#### A.1.2.3 Description for PK-Sim®

Values for CYP3A4 ontogeny in intestine are based on information to age dependency of protein content and testosterone 6 beta hydroxylation activity as described by Johnson et al. 2001 Br J Clin Pharmacol. 51(5):451-60.

#### A.1.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for CYP3A4 | Standard Deviation |
|---|---|---|
| 0.01 | 0.0011 | 13.99 |
| 0.03 | 0.0086 | 5.87 |
| 0.53 | 0.23 | 1.67 |
| 0.59 | 0.25 | 1.63 |
| 0.77 | 0.32 | 1.52 |
| 1.08 | 0.41 | 1.45 |
| 1.44 | 0.5 | 1.45 |
| 1.92 | 0.59 | 1.47 |
| 2.41 | 0.66 | 1.48 |
| 3.13 | 0.73 | 1.49 |
| 3.97 | 0.78 | 1.49 |
| 5.17 | 0.83 | 1.49 |
| 6.87 | 0.87 | 1.46 |
| 9.29 | 0.91 | 1.47 |
| 13.18 | 0.94 | 1.48 |
| 17.8 | 0.96 | 1.47 |
| 25.51 | 0.97 | 1.47 |
| 38.25 | 0.98 | 1.45 |
| 60.21 | 0.99 | 1.46 |
| 101.04 | 1 | 1.43 |

## 4.6 Plasma Proteins

## A.1 Human Serum albumin (HSA)

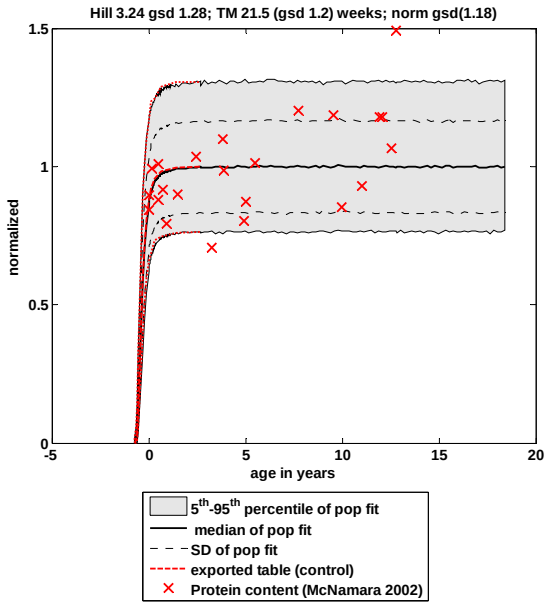
### A.1.1 Original data

| Reference | Used for fit |
|---|---|
| AAPS PharmSci. 2002;4(1):E4.; Protein binding predictions in infants.; McNamara PJ1, Alcorn J.<br><br>Digital Object Identifyer (DOI): 10.1208/ps040104<br><br>→ Figure 1 (serum protein concentrations) | <br><br><br><br>Yes |

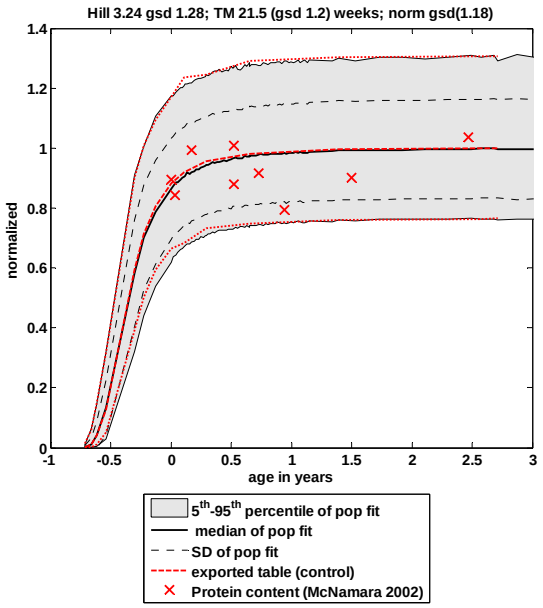
### A.1.2 Fit results

#### A.1.2.1 Figure

Full range-plot




Zoom-in, x-axis




#### A.1.2.2 Fit function

$A = PMA^n/(A_{0.5}{}^n + PMA^n)$

With:
PMA = Post-menstrual age in weeks
A = Activity at PMA
$A_{0.5}$ = PMA at 50 % activity compared to adult
n = Hill coefficient
GeoSD = geometric standard deviation

**Fit Result:**
n = 3.240
$A_{0.5}$ = 21.533

GeoSD n = 1.284
GeoSD $A_{0.5}$ = 1.205
GeoSD adult = 1.177

GeoSD adult = geometric standard deviation in activity observed in adults

#### A.1.2.3 Description for PK-Sim®

Values for Human Serum albumin ontogeny are based on information to age dependency of serum albumin concentrations, as reported by McNamara et al., AAPS PharmSci. 2002;4(1):E4.

#### A.1.2.4 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for HSA | Standard Deviation |
|---|---|---|
| 0.05 | 0.0011 | 4.46 |
| 0.1 | 0.011 | 2.8 |
| 0.16 | 0.04 | 2.2 |
| 0.23 | 0.13 | 1.74 |
| 0.46 | 0.59 | 1.29 |
| 0.55 | 0.71 | 1.24 |
| 0.64 | 0.81 | 1.2 |
| 0.77 | 0.88 | 1.19 |
| 0.88 | 0.92 | 1.2 |
| 1.06 | 0.96 | 1.17 |
| 1.42 | 0.98 | 1.18 |
| 2.17 | 1 | 1.18 |

## A.2 Alpha-1-acid glycoprotein (AAG)

A new ontogeny for AAG has been implemented. This ontogeny is recently published at the PAGE 2018 Conference which is linked below:

Mayer et al., A novel approach to estimate ontogenies for PBPK applications – From literature data to simulations.

https://www.page-meeting.org/default.asp?abstract=8583

### A.2.1.1 PK-Sim® Table

| Post menstrual age [year(s)] | Ontogeny for AAG | Standard Deviation |
|---|---|---|
| 0.766712298 | 0.254563711 | 1.829152038 |
| 0.770545289 | 0.288103739 | 1.881821245 |
| 0.77437828 | 0.320476631 | 1.840358216 |
| 0.785877253 | 0.404892648 | 1.715701843 |
| 0.797376226 | 0.47258055 | 1.628946923 |
| 0.805042209 | 0.510390851 | 1.588351585 |
| 0.816541182 | 0.558546687 | 1.54513096 |
| 0.831873146 | 0.610479462 | 1.508784277 |
| 0.847205111 | 0.652062602 | 1.486738469 |
| 0.889368013 | 0.732510638 | 1.459102868 |
| 0.946862879 | 0.798310922 | 1.447694197 |
| 1.035021675 | 0.855224822 | 1.443135263 |
| 1.169176363 | 0.900405864 | 1.441661523 |
| 1.387656856 | 0.935748949 | 1.441286708 |
| 1.721127082 | 0.96008023 | 1.441272349 |
| 3.032010039 | 0.987428363 | 1.441419782 |
| 13.60711841 | 1.002010167 | 1.441462514 |
| 30.76659822 | 1 | 1.440946066 |
| 90.45859001 | 0.986596986 | 1.443474188 |