# Open Systems Pharmacology Suite - 11 Folder Comparison

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# Chapter 1

# Folder Comparison Results

Overall Comparison Result: Invalid Number of Compared Files: 155

# 1.1 Comparison Results

**Overall Comparison Result** 

Invalid

# Old Folder

 $D:\Outputs_10.0$ 

#### New Folder

D:\Outputs\_11.0

#### Using exclusions

\*\*|drug|Fraction of oral drug mass absorbed into mucosa segment

# 1.1.1 Invalid Simulations (13/155)

 $Simulation: \ DDI\_Multiple Combinations \textbf{-} 21\_1st\_Competitive\_Competitive$ 

Result of the validation: Invalid Absolute Tolerance: 1.00E-8 Relative Tolerance: 1.00E-4

# $Output\ Path:\ Organism | Small Intestine | Mucosa | Upper Jejunum | Intracellular | C1 | Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|UpperJejunum|Intracellular|C1|Concentration in container' is 6.24% and is greater than the allowed max. tolerance of 3.00%

<sup>\*\*|</sup>Receptor Occupancy-drug-BIND-Lab Complex

# Organism | Small | Intracellular | C1 | Concentration in container 100 100 100 100 0.01 0.001

Figure 1.1

0.2

Time [h]

0.25

0.3

0.35

0.4

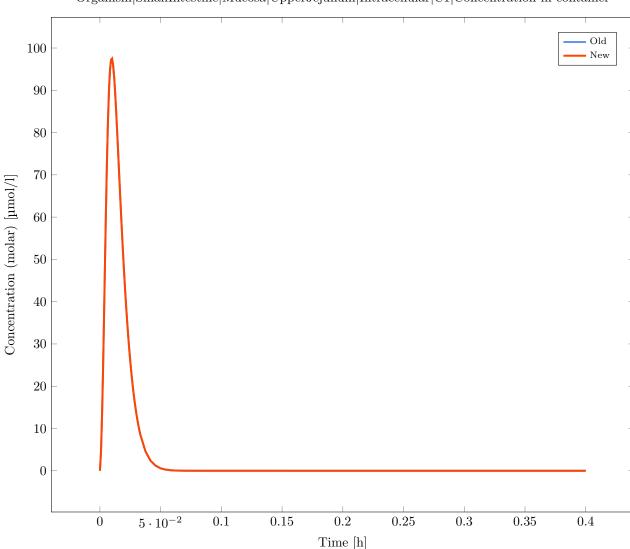
0.15

0.0001

 $5 \cdot 10^{-2}$ 

0.1

0



#### Organism | Small Intestine | Mucosa | Upper Jejunum | Intracellular | C1 | Concentration in container

Figure 1.2

# $Simulation: \ Human\_MultipleIV\_PGPB a solateral-Human\_MultipleIV\_PGPB a solateral$

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

#### Output Path: Organism|Heart|Intracellular|drug|Concentration in container

Deviation for 'Organism|Heart|Intracellular|drug|Concentration in container' is 13.22% and is greater than the

allowed max. tolerance of 3.00%

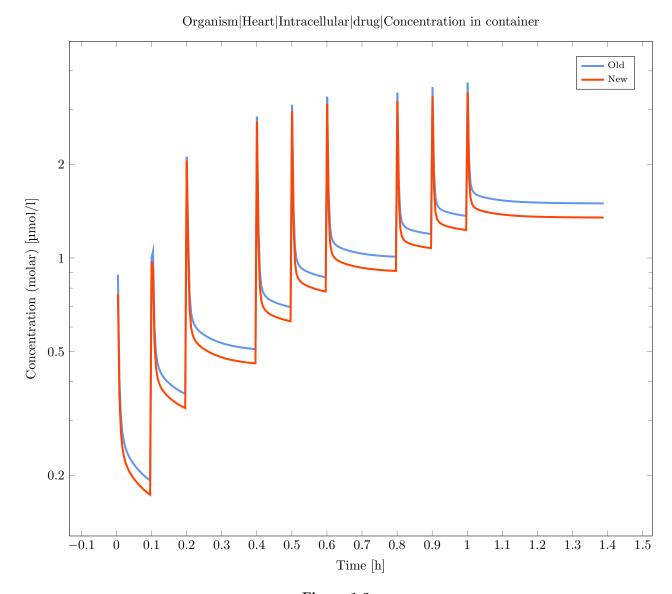


Figure 1.3

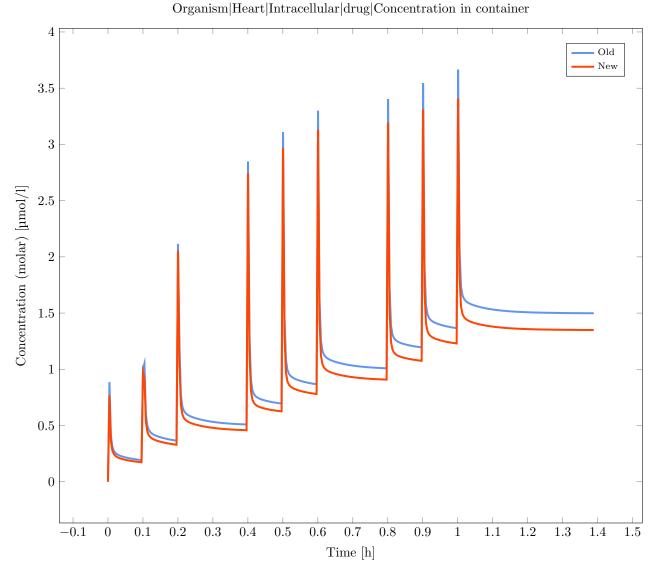


Figure 1.4

# Output Path: Organism|Heart|drug|Intracellular Unbound

Deviation for 'Organism|Heart|drug|Intracellular Unbound' is 13.22% and is greater than the allowed max. tolerance of 3.00%

# Organism | Heart | drug | Intracellular Unbound Old | New | Old | New |

Figure 1.5

0.6

0.7

Time [h]

0.8

0.9

1.1

1.2

1.3

1.4

1.5

0

-0.1

0.1

0.2

0.3

0.4

0.5

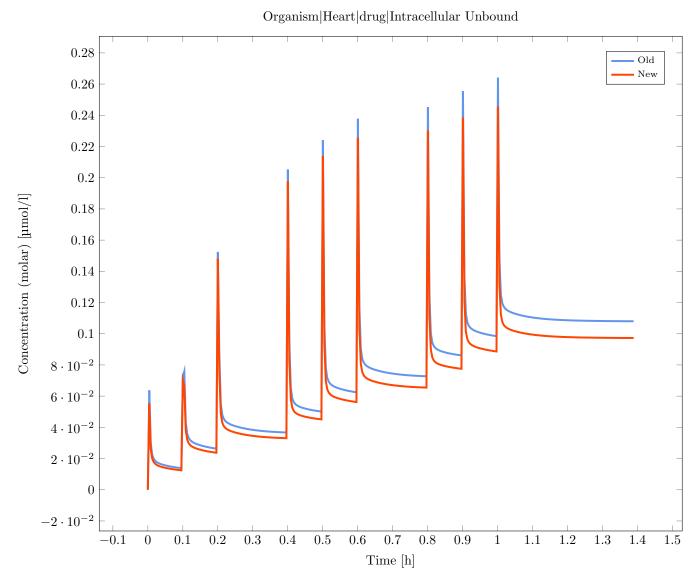


Figure 1.6

# Output Path: Organism|Heart|drug|Tissue

Deviation for 'Organism |Heart|drug|Tissue' is 13.13% and is greater than the allowed max. tolerance of 3.00% Deviation: 0.13

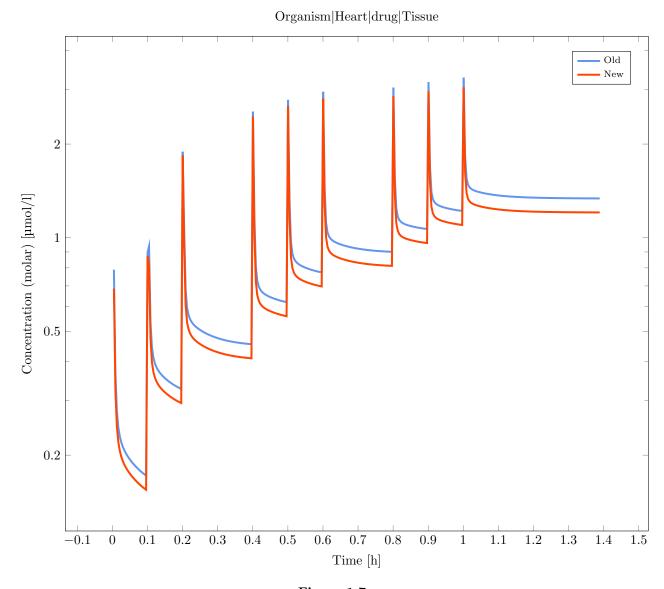


Figure 1.7

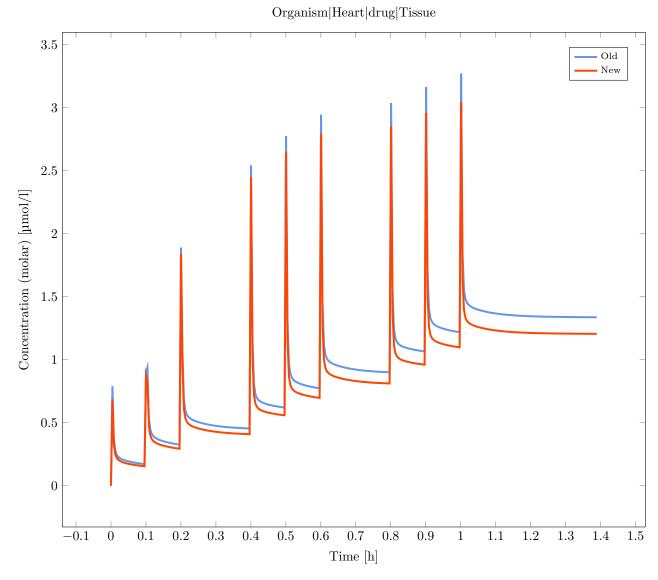


Figure 1.8

# Output Path: Organism|Heart|drug|Interstitial Unbound

Deviation for 'Organism |Heart|drug|Interstitial Unbound' is 7.51% and is greater than the allowed max. tolerance of 3.00%

# Organism|Heart|drug|Interstitial Unbound

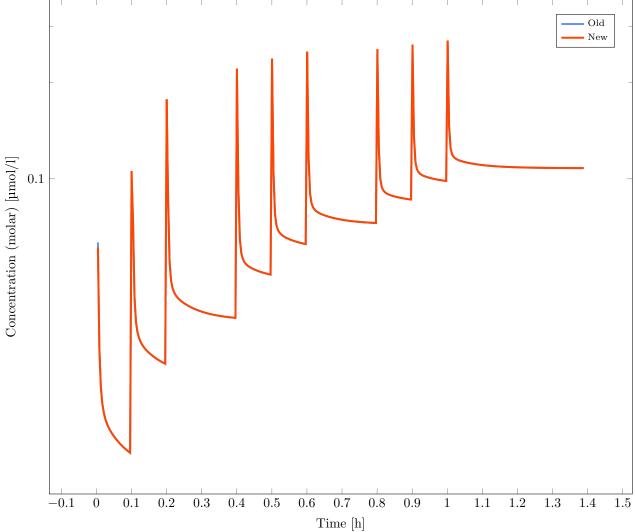


Figure 1.9

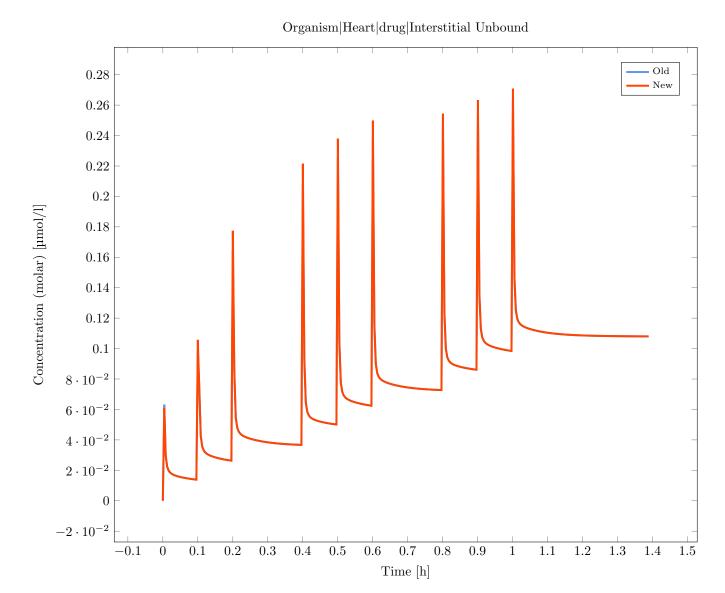


Figure 1.10

# $Output\ Path:\ Organism | Heart | Interstitial | drug | Concentration\ in\ container$

Deviation for 'Organism|Heart|Interstitial|drug|Concentration in container' is 7.51% and is greater than the allowed max. tolerance of 3.00%

# $\label{eq:concentration} Organism | Heart | Interstitial | drug | Concentration \ in \ container$

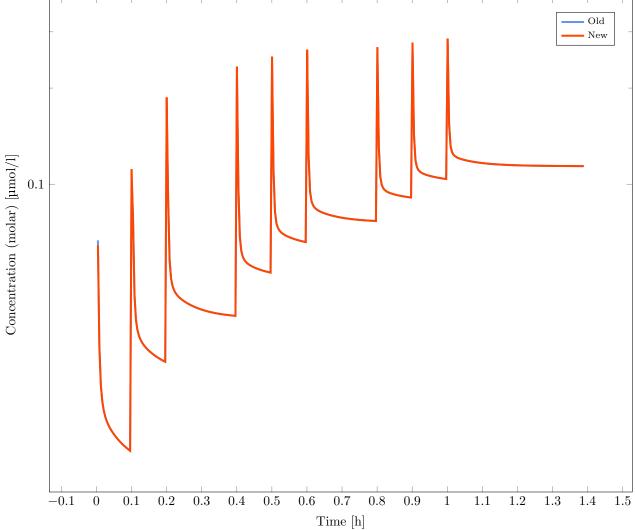
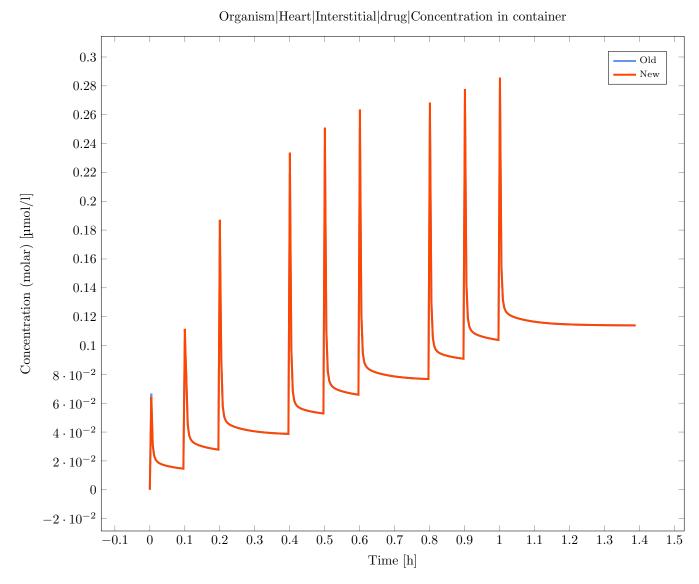


Figure 1.11



# Figure 1.12

#### Simulation: Human\_MultipleIV\_PGP-Human\_MultipleIV\_PGP

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

#### Output Path: Organism|Heart|drug|Intracellular Unbound

 $Deviation \ for \ 'Organism | Heart| drug | Intracellular \ Unbound' \ is \ 13.93\% \ and \ is \ greater \ than \ the \ allowed \ max. \ tollowed \ max.$ 

erance of 3.00%Deviation: 0.14

# ${\bf Organism|Heart|drug|Intracellular~Unbound}$

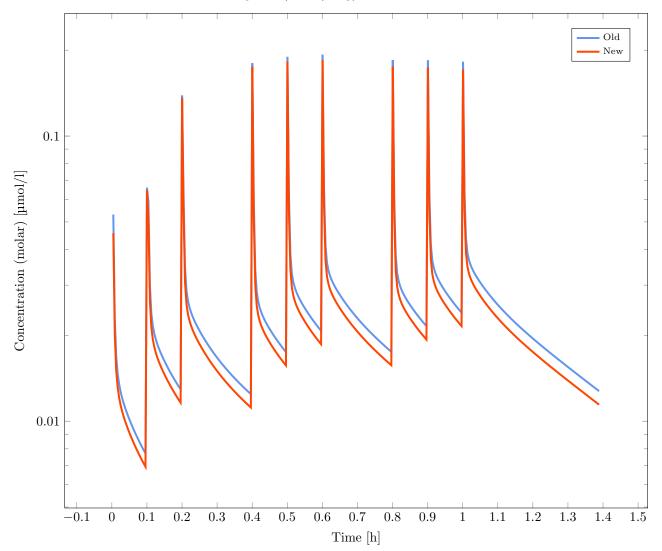


Figure 1.13

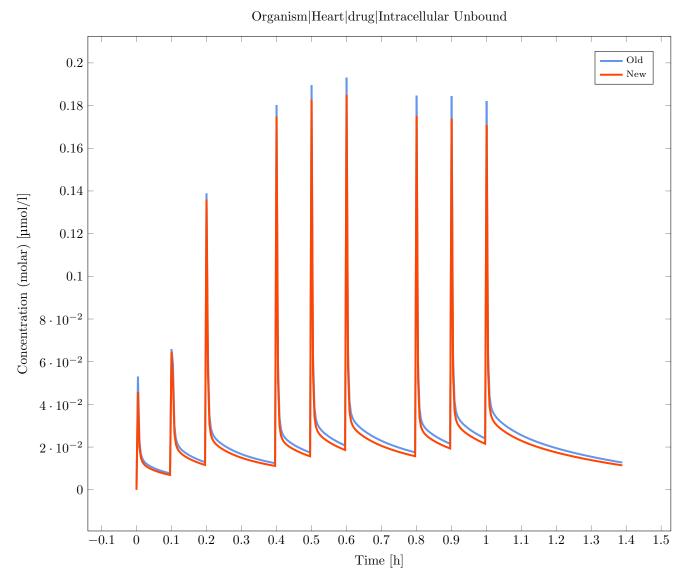


Figure 1.14

# Output Path: Organism|Heart|Intracellular|drug|Concentration in container

Deviation for 'Organism|Heart|Intracellular|drug|Concentration in container' is 13.93% and is greater than the allowed max. tolerance of 3.00%

# ${\bf Organism|Heart|Intracellular|drug|Concentration\ in\ container}$ Old New 2 Concentration (molar) $[\mu]$ 1 0.5 0.1 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.1 1.2 1.3 1.4 -0.11.5

 ${\bf Figure~1.15}$ 

Time [h]

### Organism|Heart|Intracellular|drug|Concentration in container 2.8 OldNew 2.6 2.4 2.2 2 Concentration (molar) $[\mu]$ 1.8 1.6 1.4 1.2 1 0.8 0.6 0.4 0.2 0 -0.20.2 0.3 0.4 0.5 0.7 0.8 0.9 1.1 1.2 1.3 -0.10 0.1 0.6 1 1.4 1.5 Time [h]

Figure 1.16

# Output Path: Organism|Heart|drug|Tissue

Deviation for 'Organism |Heart|drug|Tissue' is 13.83% and is greater than the allowed max. tolerance of 3.00% Deviation: 0.14

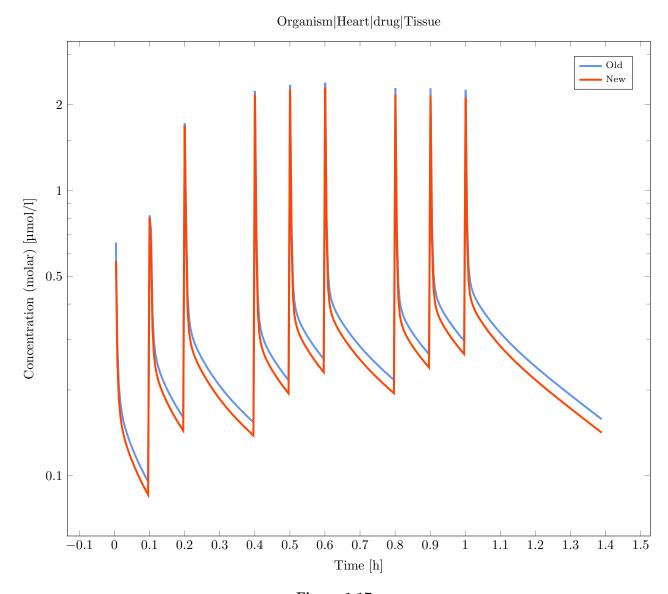


Figure 1.17

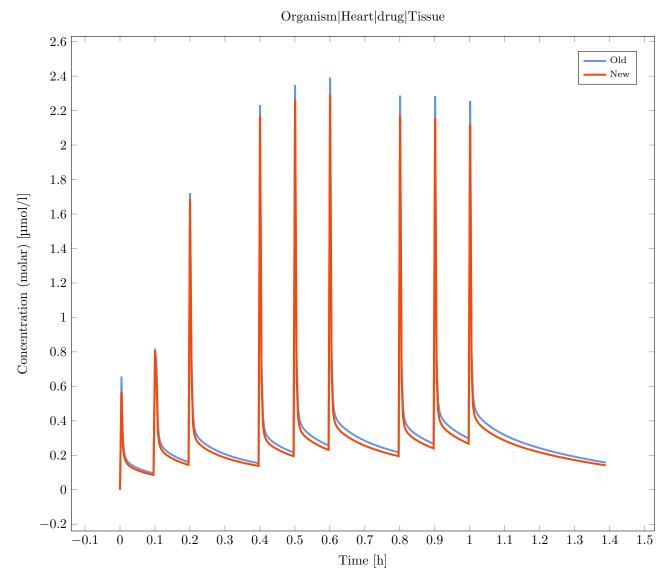


Figure 1.18

# Output Path: Organism|Heart|drug|Interstitial Unbound

Deviation for 'Organism |Heart|drug|Interstitial Unbound' is 8.18% and is greater than the allowed max. tolerance of 3.00%

# ${\bf Organism|Heart|drug|Interstitial\ Unbound}$

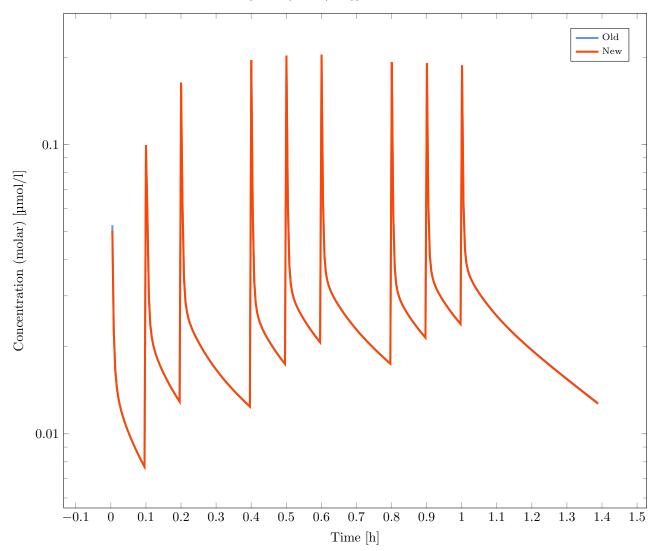


Figure 1.19

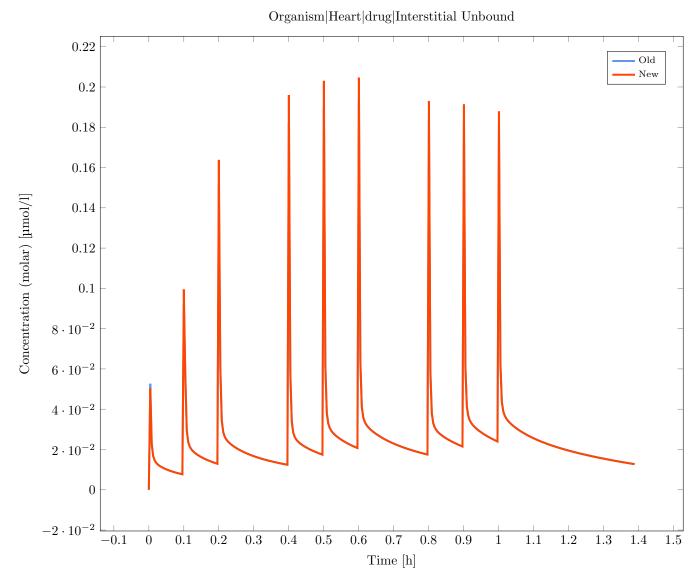


Figure 1.20

# Output Path: Organism|Heart|Interstitial|drug|Concentration in container

Deviation for 'Organism|Heart|Interstitial|drug|Concentration in container' is 8.18% and is greater than the allowed max. tolerance of 3.00%

# ${\bf Organism|Heart|Interstitial|drug|Concentration\ in\ container}$

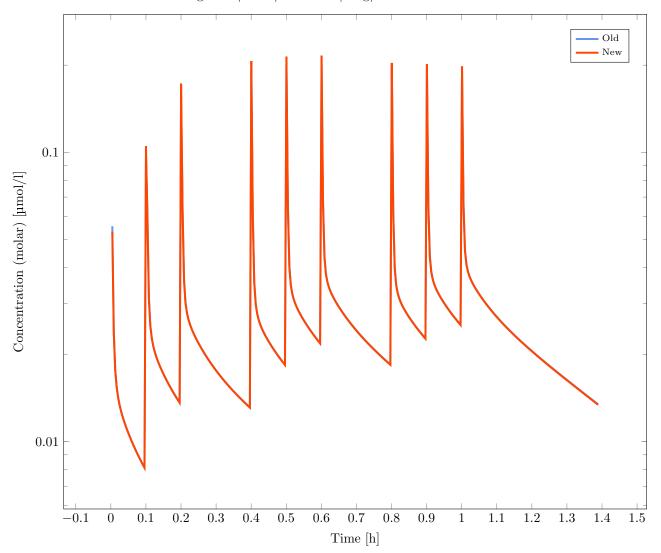


Figure 1.21

# Organism|Heart|Interstitial|drug|Concentration in container $\operatorname{Old}$ 0.22New 0.20.180.16Concentration (molar) $[\mu mol/1]$ 0.14 0.120.1 $8\cdot 10^{-2}$ $6\cdot 10^{-2}$ $4\cdot 10^{-2}$ $2\cdot 10^{-2}$ 0 $-2\cdot 10^{-2}$ 0.3 1.2 0.1 0.2 0.40.5 0.6 0.7 0.8 0.9 1.1 1.3 1.4 1.5 Time [h]

# Figure 1.22

# $Simulation: Human\_Oral\_BiDaily\_Table Formulation-S2\_NoSuspension$

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

#### Output Path: Organism|Lumen|Duodenum|C1|Concentration in lumen

Deviation for 'Organism|Lumen|Duodenum|C1|Concentration in lumen' is 22.20% and is greater than the al-

lowed max. tolerance of 3.00%

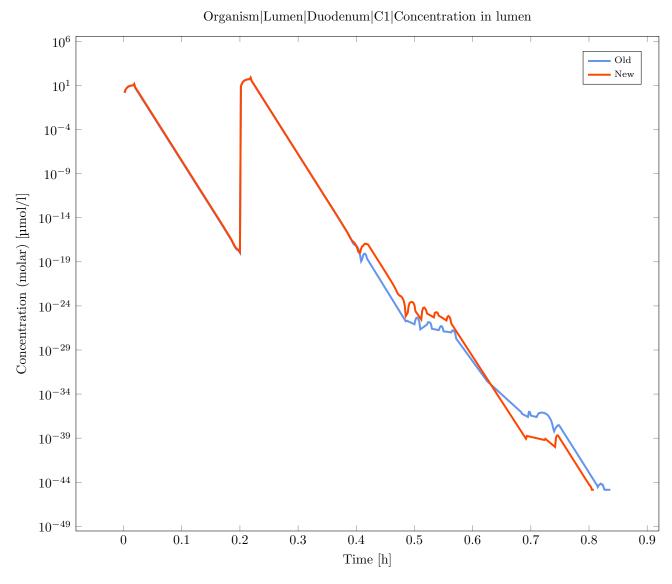


Figure 1.23

# Organism|Lumen|Duodenum|C1|Concentration in lumen Old 80 New 70 60Concentration (molar) [µmol/1] 50 40 3020 10 0 0.1 0.2 0.3 0.7 0.8 1.1 1.2 -0.10 0.4 0.5 0.6 0.9 1.3 Time [h]

# **Figure 1.24**

# Output Path: Organism|Lumen|Stomach|C1|Concentration in lumen

Deviation for 'Organism |Lumen|Stomach |C1|Concentration in lumen' is 22.20% and is greater than the allowed max. tolerance of 3.00%

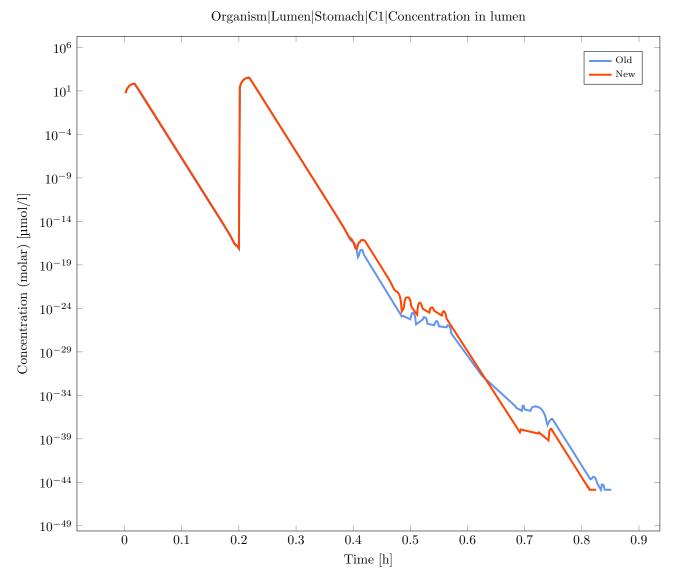
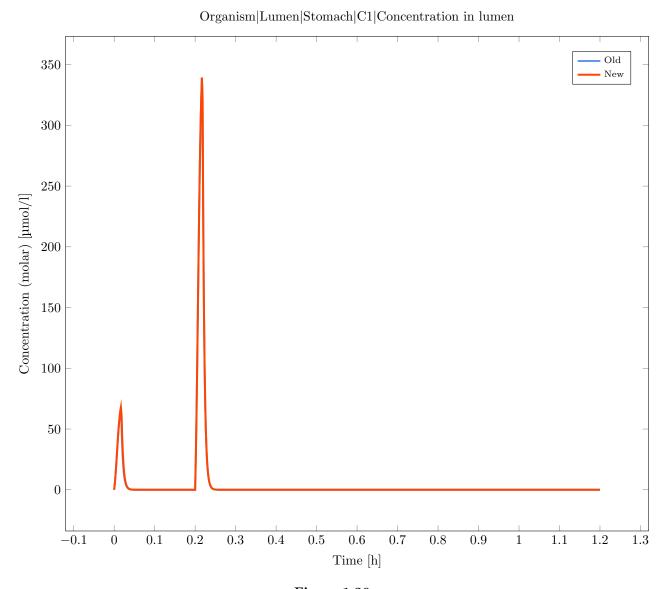


Figure 1.25



# **Figure 1.26**

# Output Path: Organism|Lumen|LowerIleum|C1|Concentration in lumen

Deviation for 'Organism|Lumen|LowerIleum|C1|Concentration in lumen' is 13.15% and is greater than the allowed max. tolerance of 3.00%

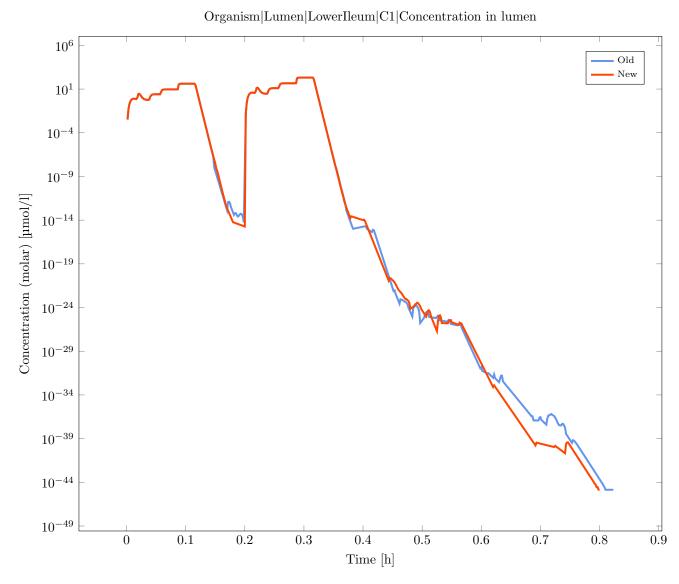
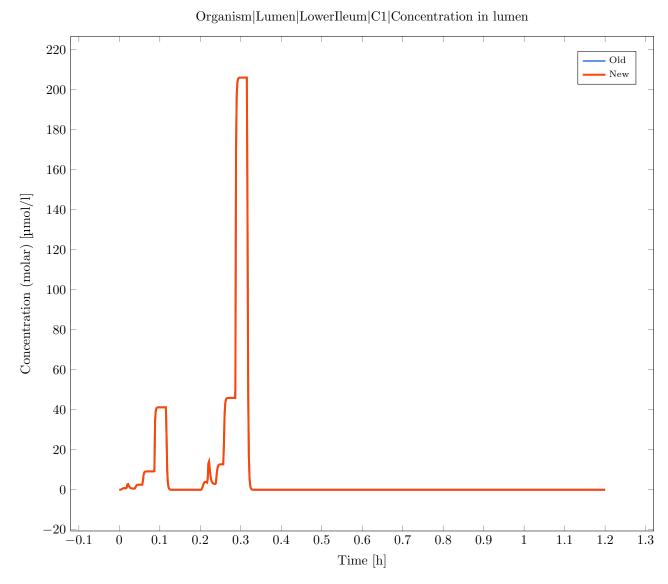


Figure 1.27



# Figure 1.28

# Output Path: Organism|Lumen|UpperJejunum|C1|Concentration in lumen

Deviation for 'Organism|Lumen|UpperJejunum|C1|Concentration in lumen' is 7.78% and is greater than the allowed max. tolerance of 3.00%

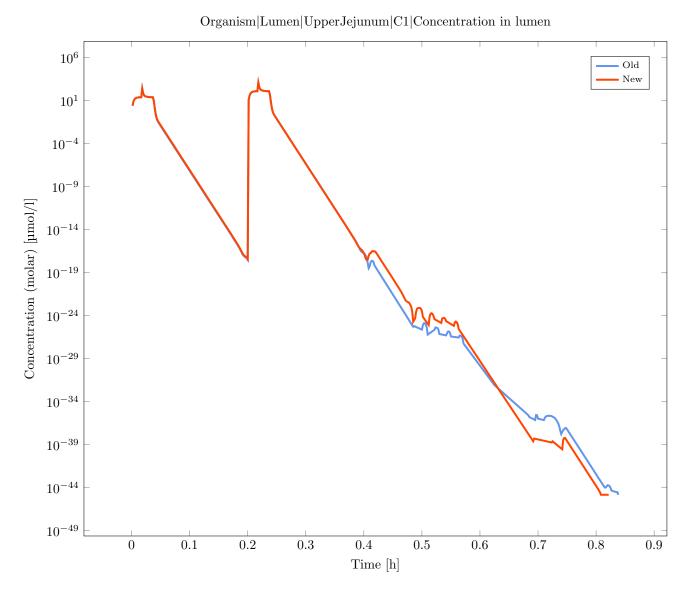


Figure 1.29

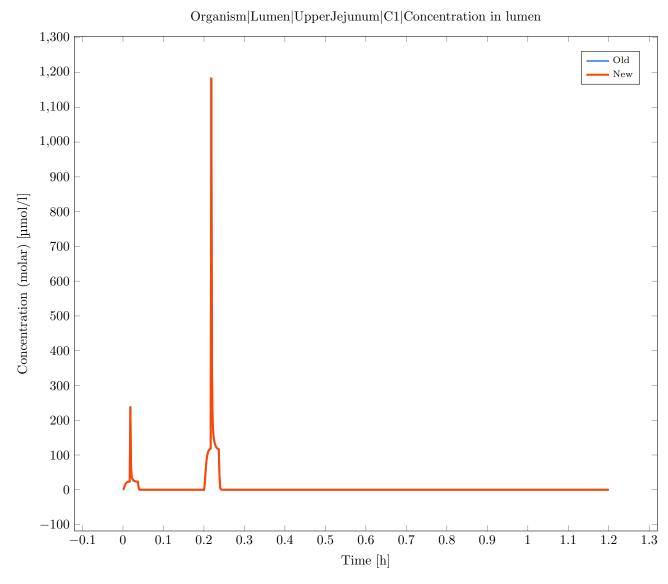


Figure 1.30

# Output Path: Organism|Lumen|Rectum|C1|Concentration in lumen

Deviation for 'Organism|Lumen|Rectum|C1|Concentration in lumen' is 6.77% and is greater than the allowed max. tolerance of 3.00%

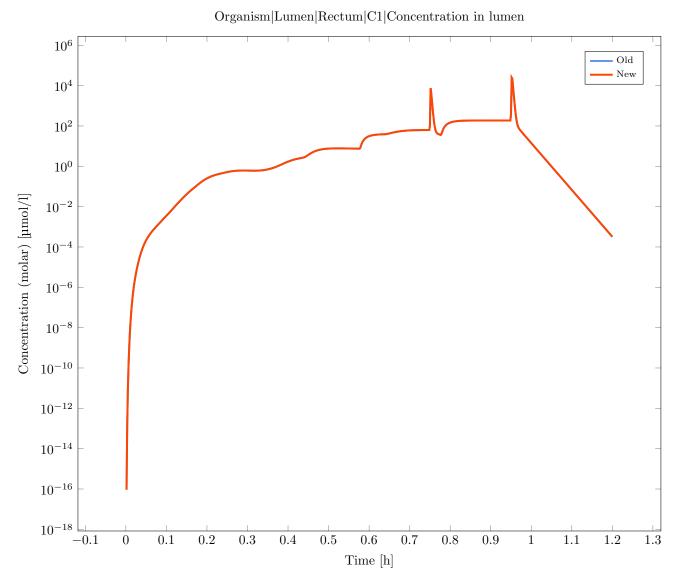


Figure 1.31

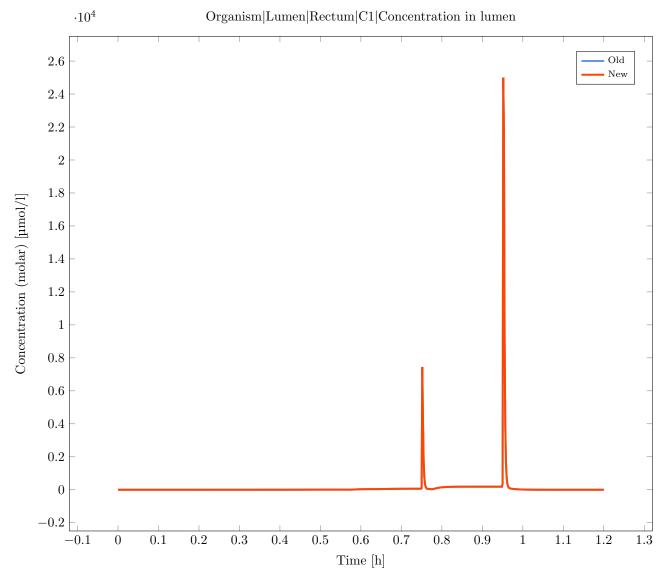


Figure 1.32

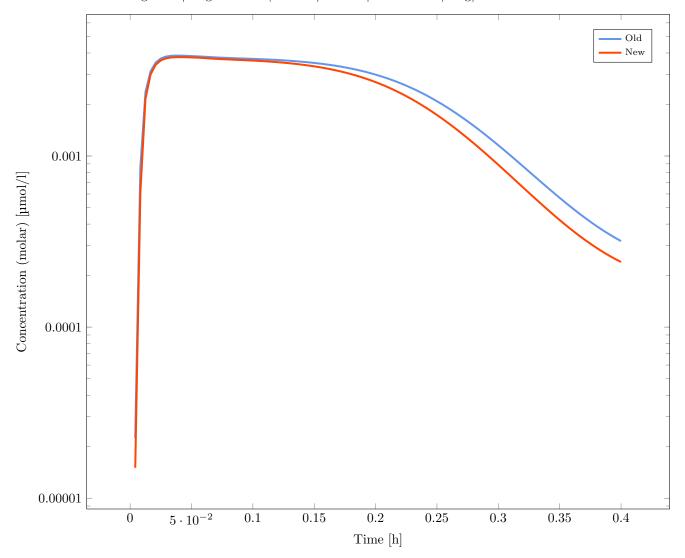
# $Simulation: Human\_SingleORAL\_MonoParticles\_AsSuspention-Human\_SingleORAL\_MonoParticles\_AsSuspention\\$

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

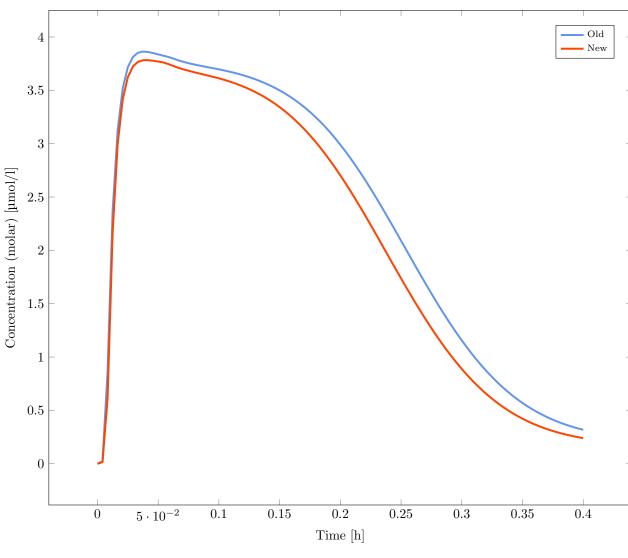
# $\label{eq:contraction} Output \ Path: \ Organism | Large Intestine | Mucosa | Caecum | Intracellular | drug | Concentration in container$

Deviation for 'Organism|LargeIntestine|Mucosa|Caecum|Intracellular|drug|Concentration in container' is 32.90% and is greater than the allowed max. tolerance of 3.00%

# $Organism | Large Intestine | Mucosa | Caecum | Intracellular | drug | Concentration \ in \ container$



 ${\bf Figure~1.33}$ 



 $\cdot 10^{-3}\ \mathrm{Organism} | \mathrm{LargeIntestine} | \mathrm{Mucosa} | \mathrm{Caecum} | \mathrm{Intracellular} | \mathrm{drug} | \mathrm{Concentration\ in\ container}$ 

Figure 1.34

## $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism | Small Intestine | Mucosa | Lower I leum | Intracellular | drug | Concentration in container' is 32.82% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower Ileum | Intracellular | drug | Concentration \ in \ container$

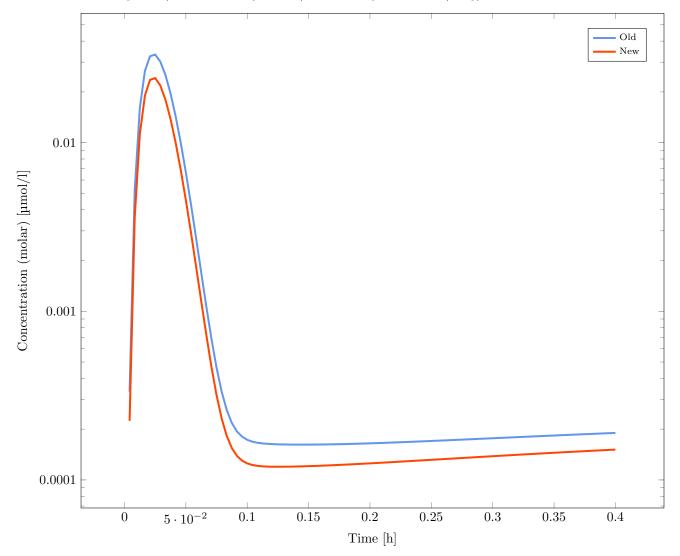
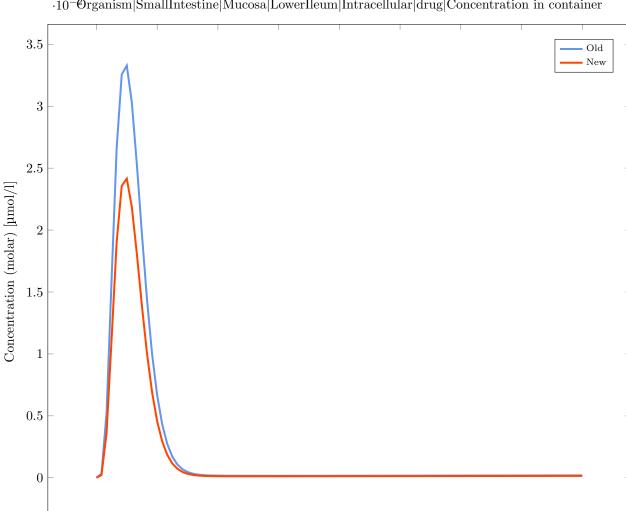


Figure 1.35



#### $\cdot 10^{-0} \text{Organism} | \text{SmallIntestine} | \text{Mucosa} | \text{LowerIleum} | \text{Intracellular} | \text{drug} | \text{Concentration in container} | \text{Concentration} | \text{Concentra$

Figure 1.36

0.2

Time [h]

0.25

0.3

0.35

0.4

0.15

0.1

## $Output\ Path:\ Organism | Small Intestine | Mucosa | Lower I leum | Interstitial | drug | Concentration\ in\ concentration | Concentration\ in\ concentration\ in\$

 $Deviation for \ 'Organism | Small Intestine | Mucosa | Lower I leum | Interstitial | drug | Concentration in container' is 32.71\% | drug | Concentration | Container' | Containe$ and is greater than the allowed max. tolerance of 3.00%

Deviation: 0.33

0

 $5\cdot 10^{-2}$ 

### $Organism | Small Intestine | Mucosa | Lower Ileum | Interstitial | drug | Concentration \ in \ container$

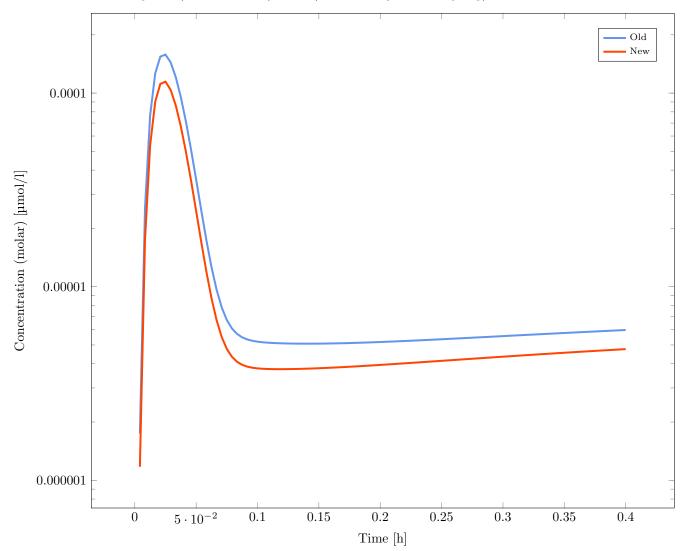


Figure 1.37

### $\cdot 10^{-4} Organism | Small Intestine | Mucosa | Lower Ileum | Interstitial | drug | Concentration in container | Concentration | Concentrati$

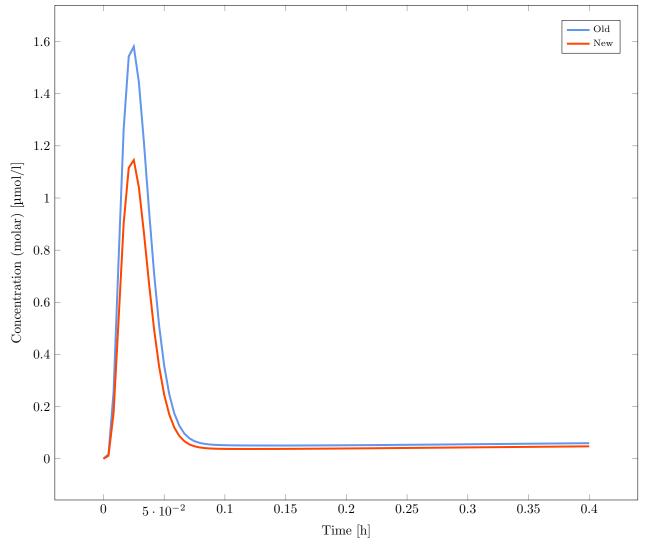


Figure 1.38

## $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration in container' is 32.71% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower Ileum | Plasma | drug | Concentration \ in \ container$

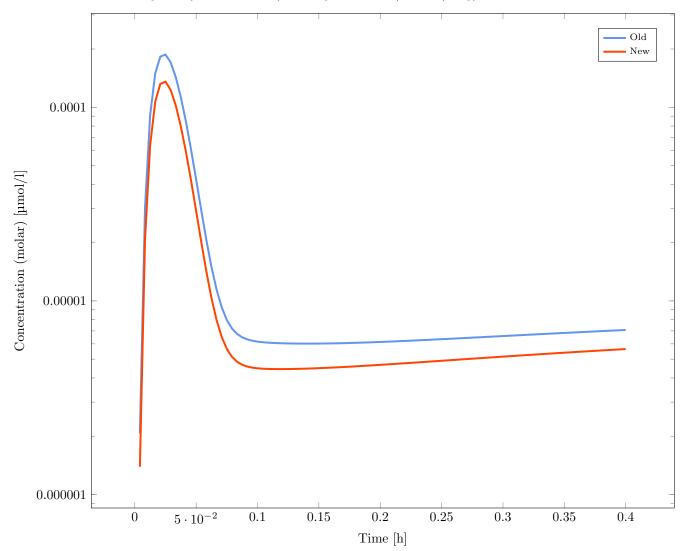
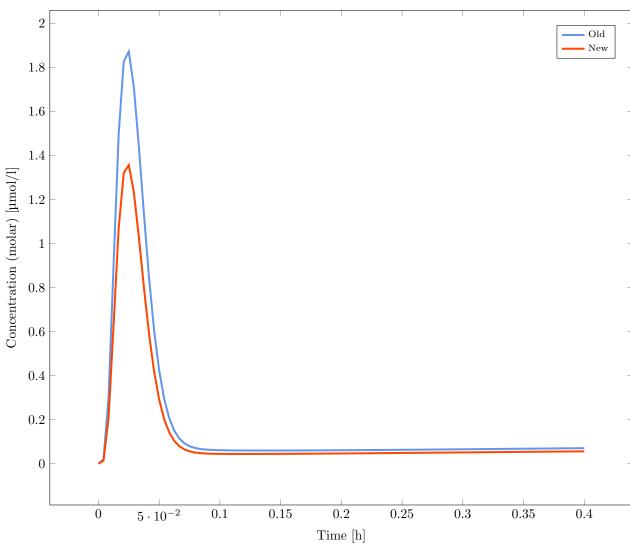


Figure 1.39



 $\cdot 10^{-4}$  Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration in container

Figure 1.40

### Output Path: Organism|Skin|drug|Intracellular Unbound

Deviation for 'Organism|Skin|drug|Intracellular Unbound' is 32.45% and is greater than the allowed max. tolerance of 3.00%

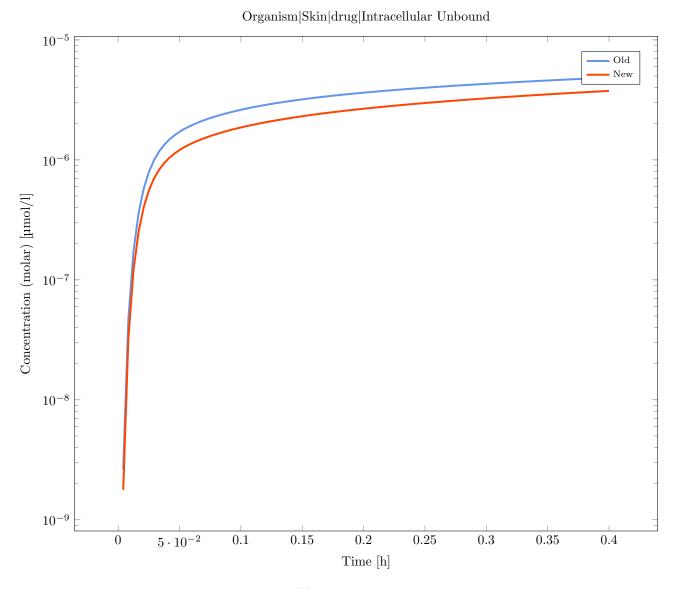
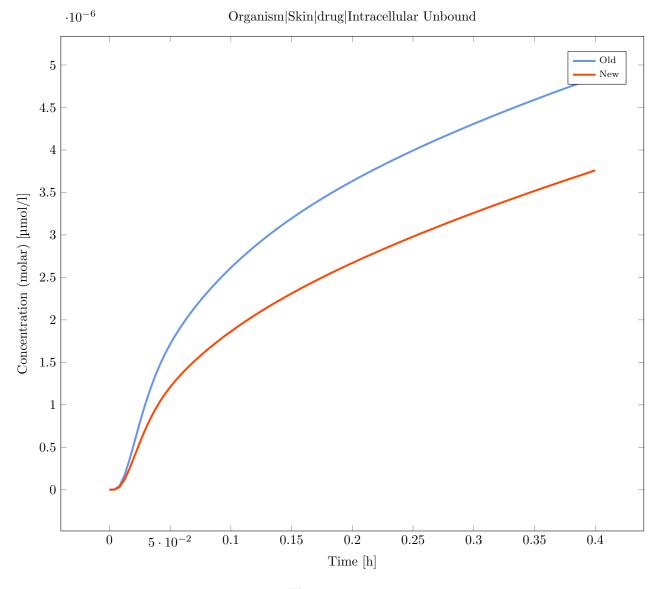


Figure 1.41



**Figure 1.42** 

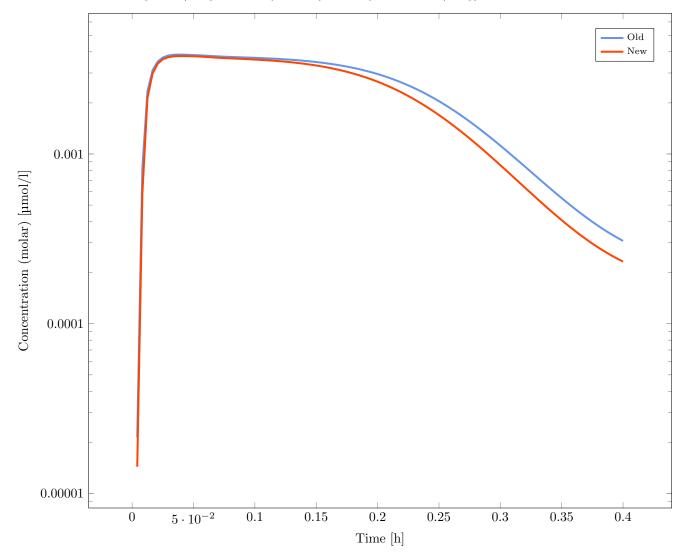
# $Simulation: Human\_SingleORAL\_PolyParticlesLogNormal\_AsSuspention-Human\_SingleORAL\_PolyParticlesLogNormal\_AsSuspention$

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

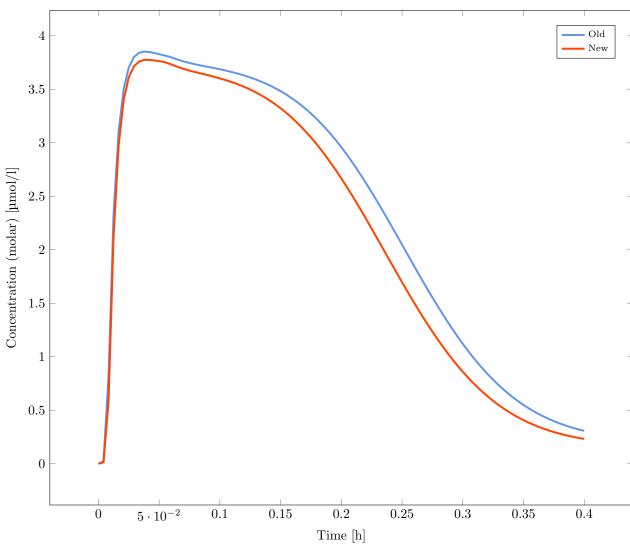
# $Output\ Path:\ Organism | Large Intestine | Mucosa | Caecum | Intracellular | drug | Concentration\ in\ container$

Deviation for 'Organism |LargeIntestine |Mucosa |Caecum |Intracellular |drug |Concentration in container' is 32.92% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Large Intestine | Mucosa | Caecum | Intracellular | drug | Concentration \ in \ container$



 $\mathbf{Figure}\ \mathbf{1.43}$ 



 $\cdot 10^{-3}\ \mathrm{Organism} | \mathrm{LargeIntestine} | \mathrm{Mucosa} | \mathrm{Caecum} | \mathrm{Intracellular} | \mathrm{drug} | \mathrm{Concentration\ in\ container}$ 

Figure 1.44

## $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism | Small Intestine | Mucosa | Lower I leum | Intracellular | drug | Concentration in container' is 32.84% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower Ileum | Intracellular | drug | Concentration \ in \ container$

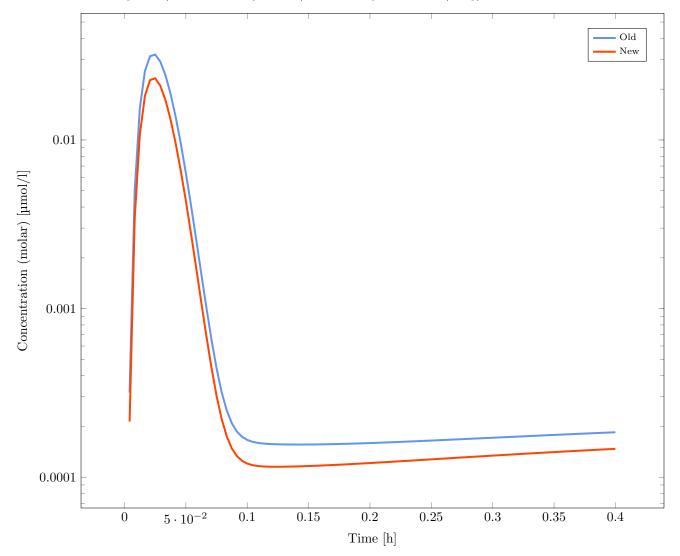
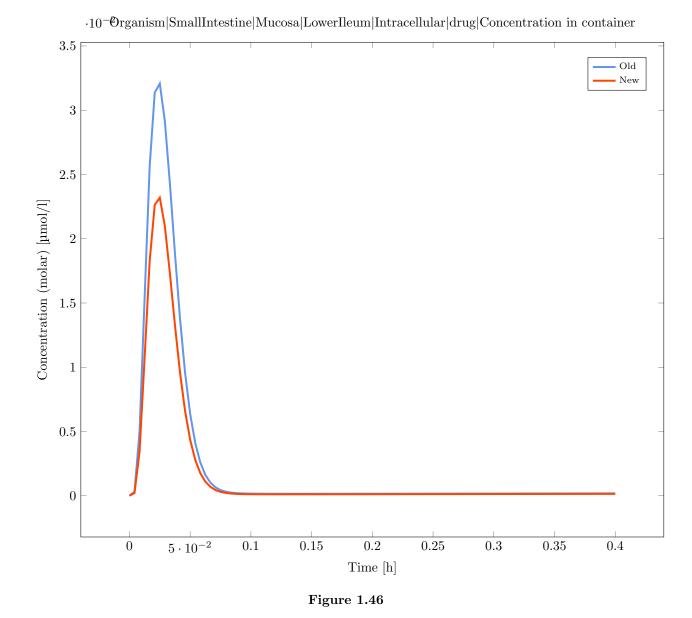


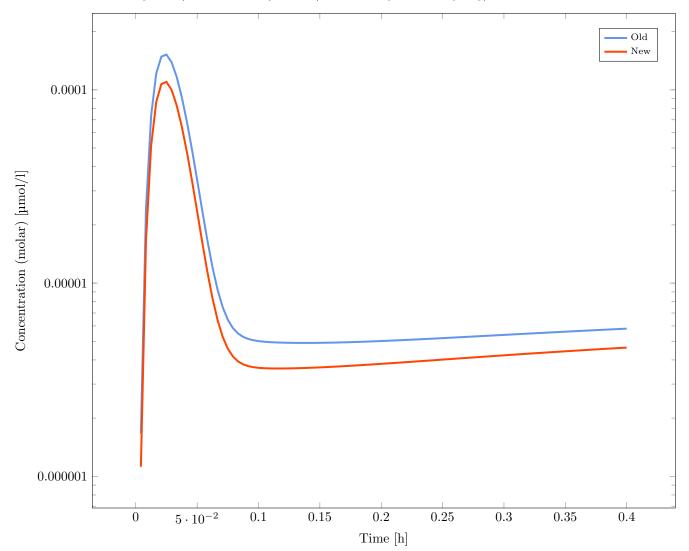
Figure 1.45



## $Output\ Path:\ Organism | Small Intestine | Mucosa | Lower I leum | Interstitial | drug | Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerIleum|Interstitial|drug|Concentration in container' is 32.74% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower Ileum | Interstitial | drug | Concentration \ in \ container$



**Figure 1.47** 

### $\cdot 10^{-4} Organism | Small Intestine | Mucosa | Lower I leum | Interstitial | drug | Concentration in container | Concentration | Concentrat$ 1.6 $\operatorname{Old}$ New 1.4 1.2 Concentration (molar) [µmol/l] 1 0.8 0.6 0.40.20 0.15 0.2 0.25 0.3 0.35 0 $5\cdot 10^{-2}$ 0.1 0.4

Figure 1.48

Time [h]

## $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration in container' is 32.74% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower Ileum | Plasma | drug | Concentration \ in \ container$

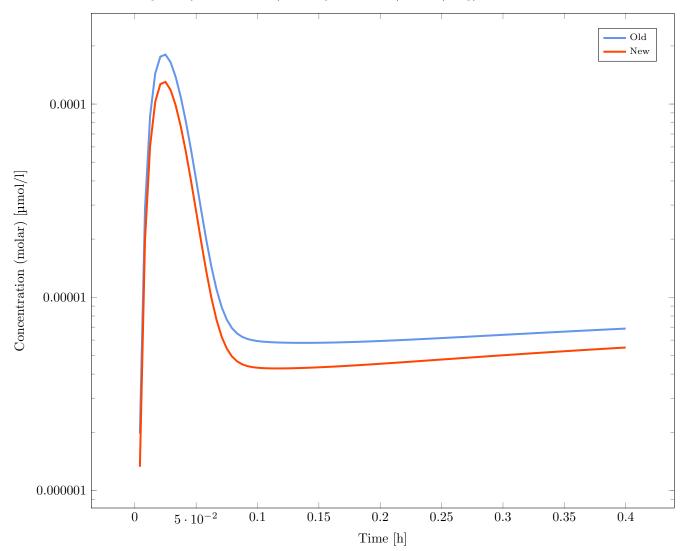
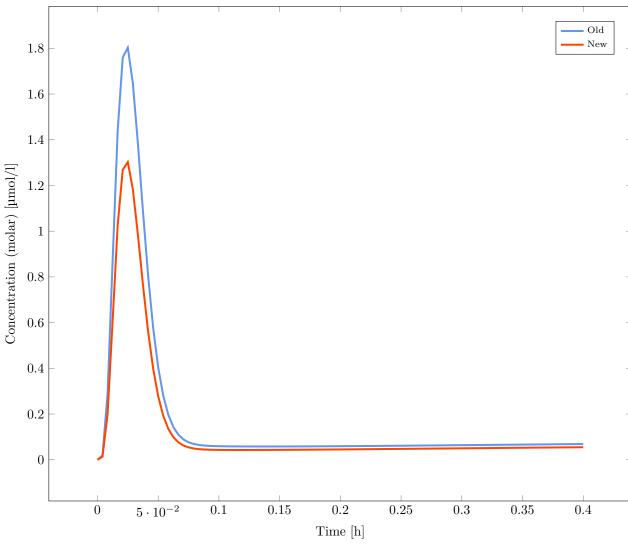


Figure 1.49



 $\cdot 10^{-4}$  Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration in container

Figure 1.50

#### Output Path: Organism|Skin|Intracellular|drug|Concentration in container

Deviation for 'Organism|Skin|Intracellular|drug|Concentration in container' is 32.49% and is greater than the allowed max. tolerance of 3.00%

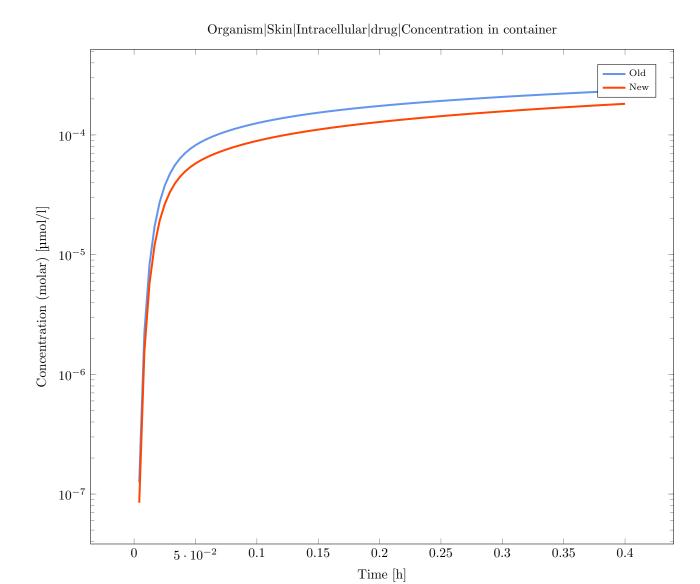


Figure 1.51

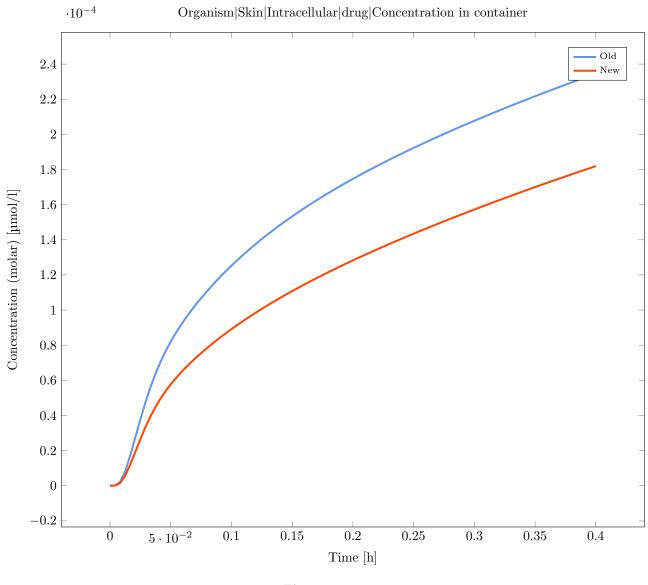


Figure 1.52

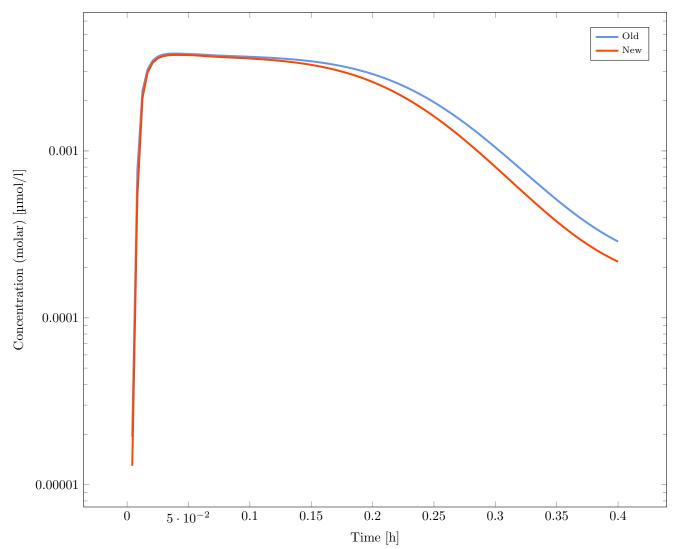
# $Simulation: Human\_SingleORAL\_PolyParticlesNormal\_AsSuspention-Human\_SingleORAL\_PolyParticlesNormal\_AsSuspention$

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

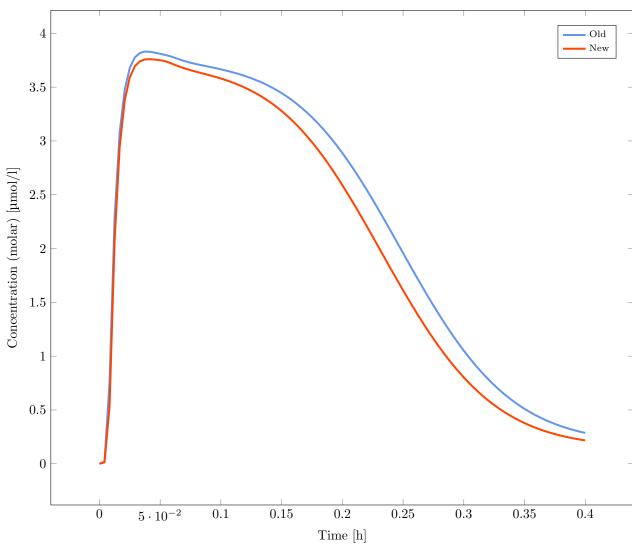
# $Output\ Path:\ Organism | Large Intestine | Mucosa | Caecum | Intracellular | drug | Concentration\ in\ container$

Deviation for 'Organism | Large Intestine | Mucosa | Caecum | Intracellular | drug | Concentration in container' is 32.96% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Large Intestine | Mucosa | Caecum | Intracellular | drug | Concentration \ in \ container$



 ${\bf Figure~1.53}$ 



 $\cdot 10^{-3}\ \mathrm{Organism} | \mathrm{LargeIntestine} | \mathrm{Mucosa} | \mathrm{Caecum} | \mathrm{Intracellular} | \mathrm{drug} | \mathrm{Concentration\ in\ container}$ 

Figure 1.54

## $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism | Small Intestine | Mucosa | Lower I leum | Intracellular | drug | Concentration in container' is 32.88% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower Ileum | Intracellular | drug | Concentration \ in \ container$

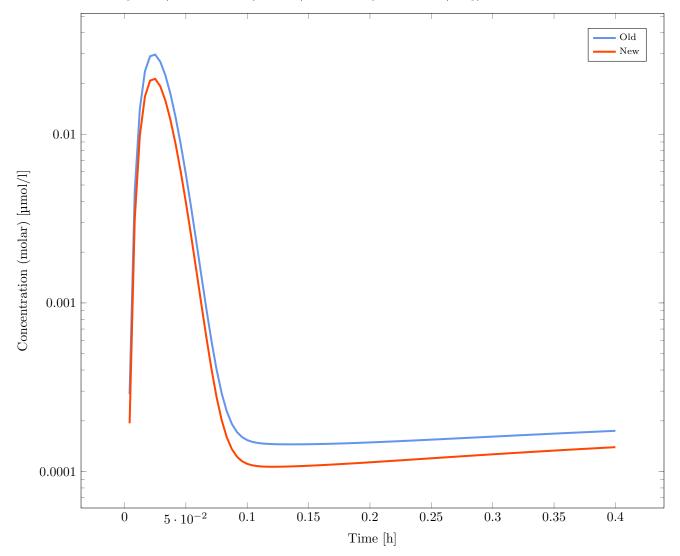
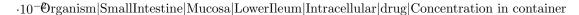


Figure 1.55



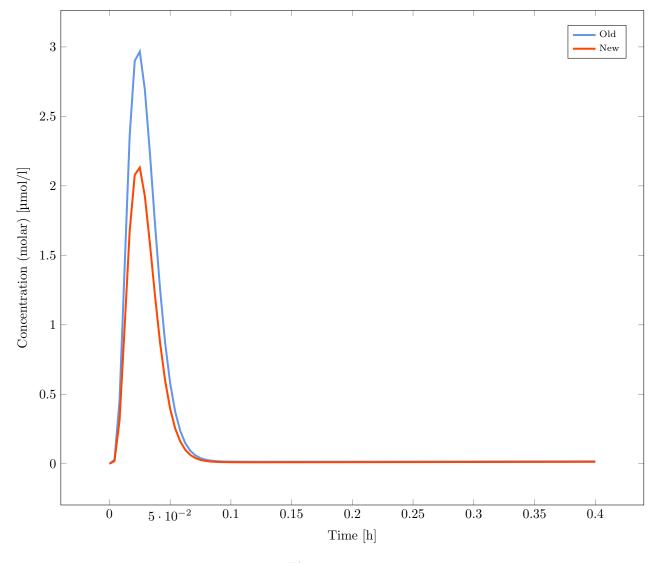


Figure 1.56

## $Output\ Path:\ Organism | Small Intestine | Mucosa | Lower I leum | Interstitial | drug | Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerIleum|Interstitial|drug|Concentration in container' is 32.80% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower I leum | Interstitial | drug | Concentration \ in \ container$

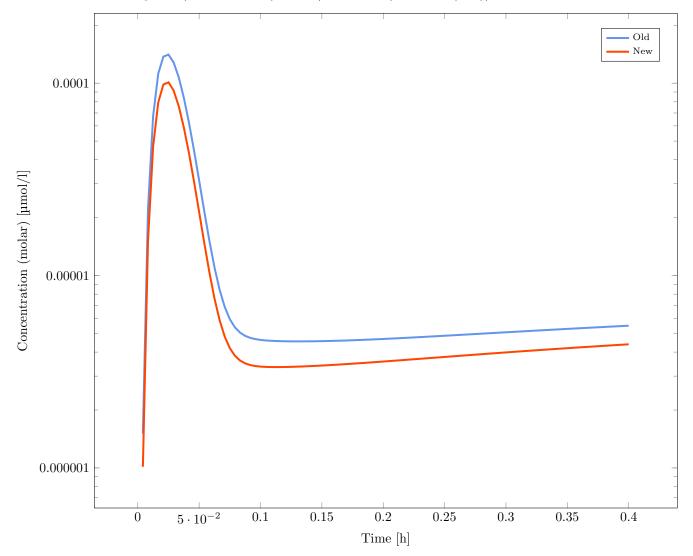


Figure 1.57

#### $\cdot 10^{-4} Organism | Small Intestine | Mucosa | Lower I leum | Interstitial | drug | Concentration in container | Concentration | Concentrat$

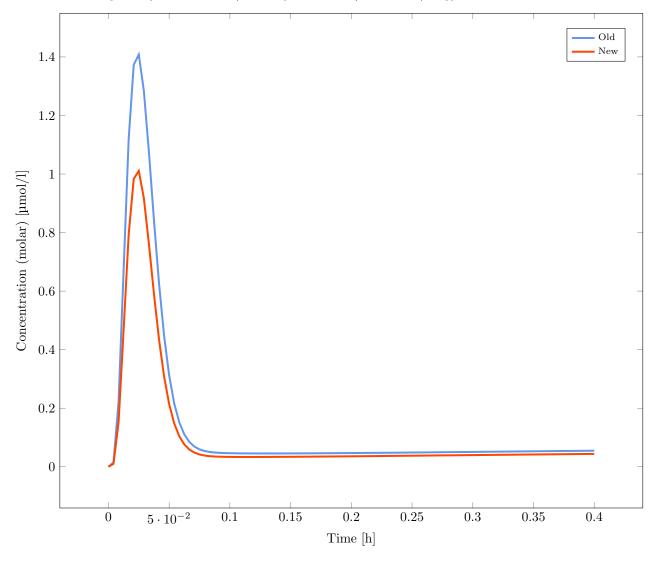


Figure 1.58

## $Output\ Path:\ Organism | Small Intestine | Mucosa | Lower Ileum | Plasma | drug | Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration in container' is 32.80% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower Ileum | Plasma | drug | Concentration \ in \ container$

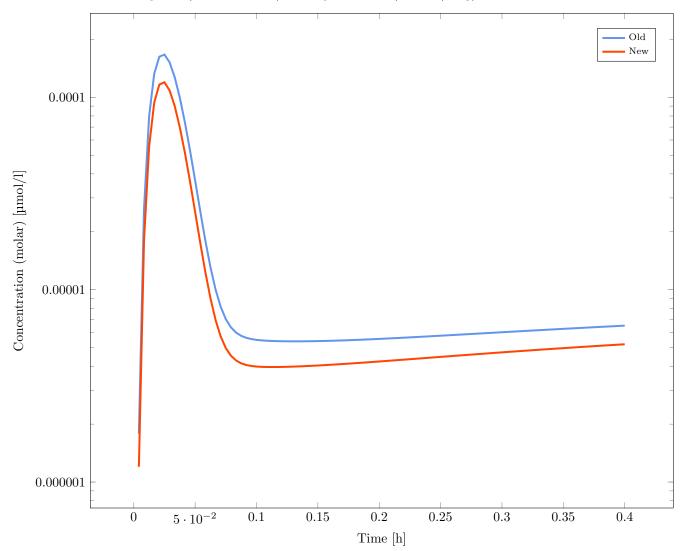
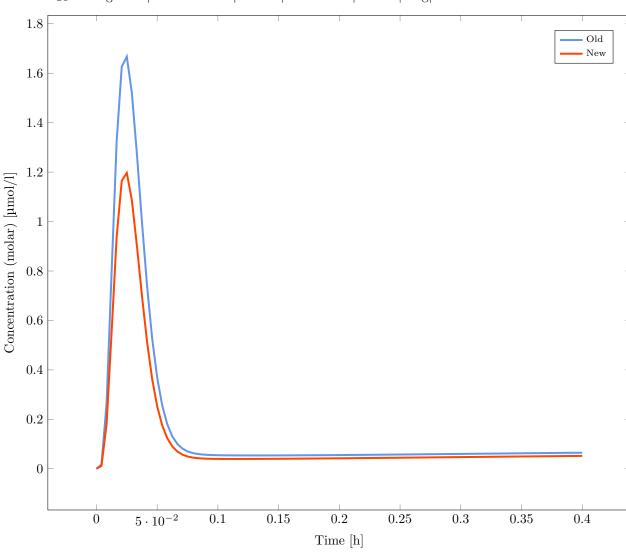


Figure 1.59



 $\cdot 10^{-4}$  Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration in container

Figure 1.60

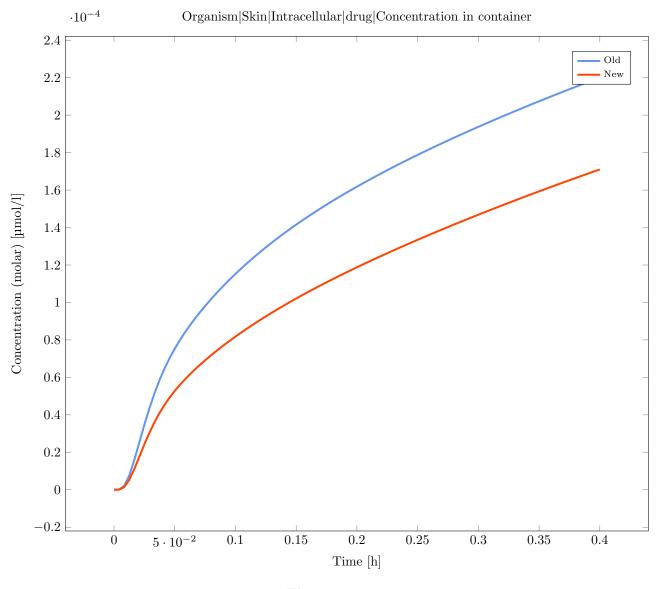
#### Output Path: Organism|Skin|Intracellular|drug|Concentration in container

Deviation for 'Organism|Skin|Intracellular|drug|Concentration in container' is 32.57% and is greater than the allowed max. tolerance of 3.00%

# $Organism | Skin | Intracellular | drug | Concentration \ in \ container$ Old New $10^{-4}$ Concentration (molar) $[\mu]$ $10^{-5}$ $10^{-6}$ $10^{-7}$ $5 \cdot 10^{-2}$ 0 0.1 0.15 0.2 0.25 0.3 0.35 0.4

Figure 1.61

Time [h]



**Figure 1.62** 

# $Simulation: Human\_SingleORAL\_PolyParticlesNormal\_AsSuspention-Human\_SingleORAL\_PolyParticlesNormal\_AsSuspention\_dissolved\_radius$

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

## $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration\ in\ container$

 $Deviation for \ 'Organism | Small Intestine | Mucosa | Lower I leum | Intracellular | drug | Concentration in container' is 29.81\% and is greater than the allowed max. tolerance of 3.00\%$ 

#### $Organism | Small Intestine | Mucosa | Lower Ileum | Intracellular | drug | Concentration \ in \ container$

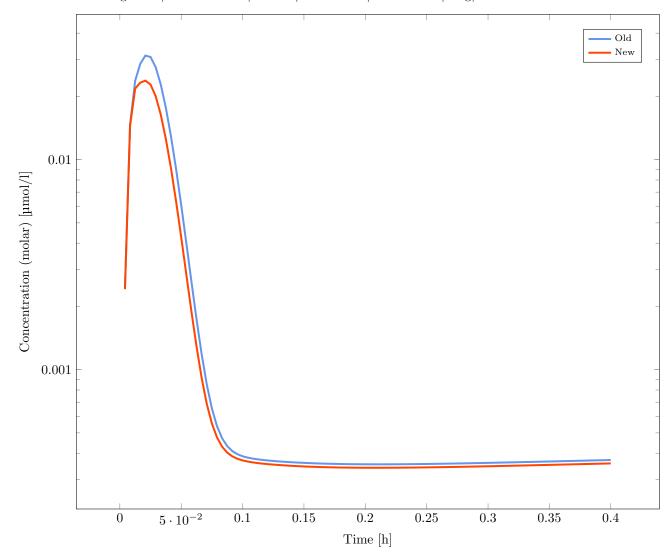
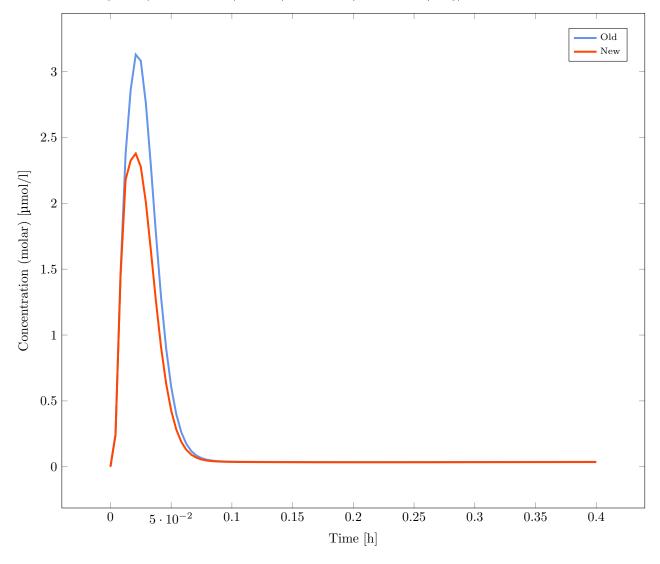


Figure 1.63





**Figure 1.64** 

#### Output Path: Organism|Lumen|Feces|drug|Fraction excreted to feces

Deviation for 'Organism |Lumen|Feces|drug|Fraction excreted to feces' is 29.80% and is greater than the allowed max. tolerance of 3.00%

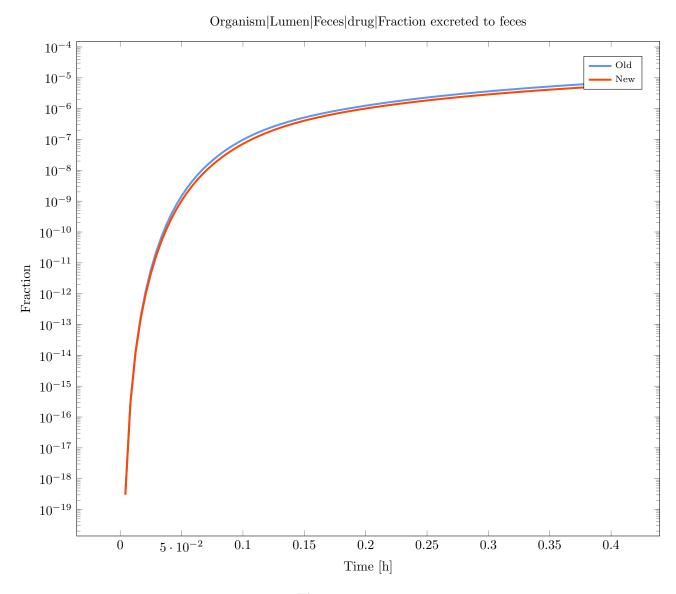
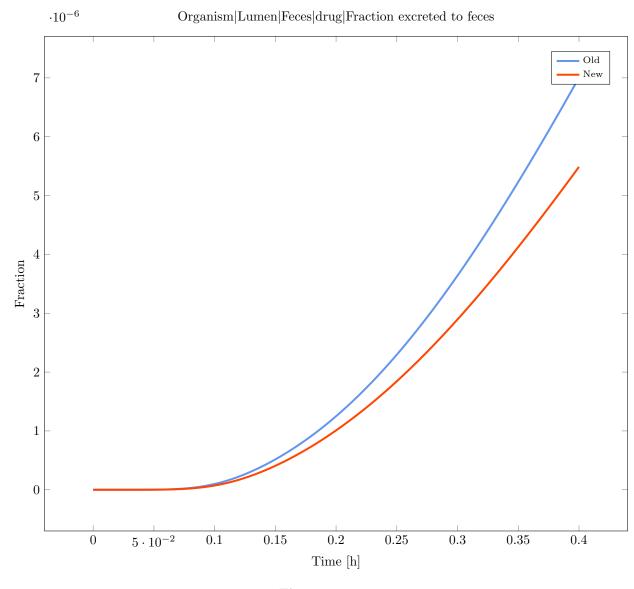


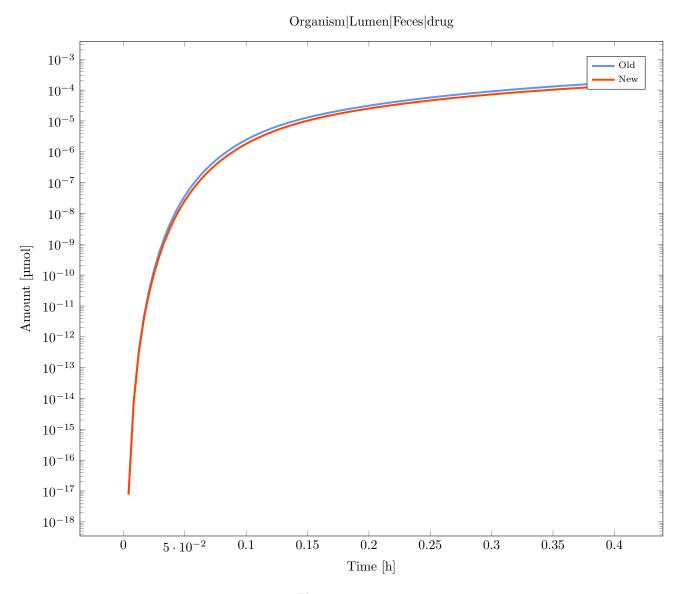
Figure 1.65



**Figure 1.66** 

### Output Path: Organism|Lumen|Feces|drug|

Deviation for 'Organism|Lumen|Feces|drug' is 29.80% and is greater than the allowed max. tolerance of 3.00% Deviation: 0.30



**Figure 1.67** 

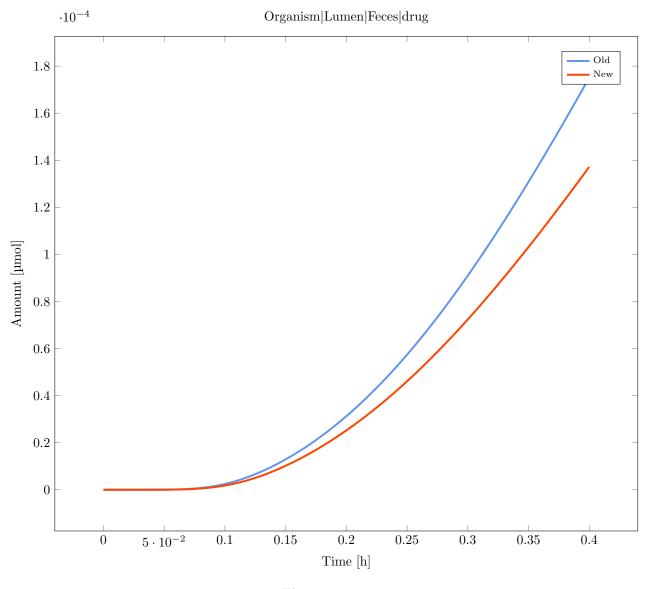


Figure 1.68

### Output Path: Organism | Lumen | Feces | drug | Concentration in feces

Deviation for 'Organism |Lumen|Feces|drug|Concentration in feces' is 29.80% and is greater than the allowed max. tolerance of 3.00%

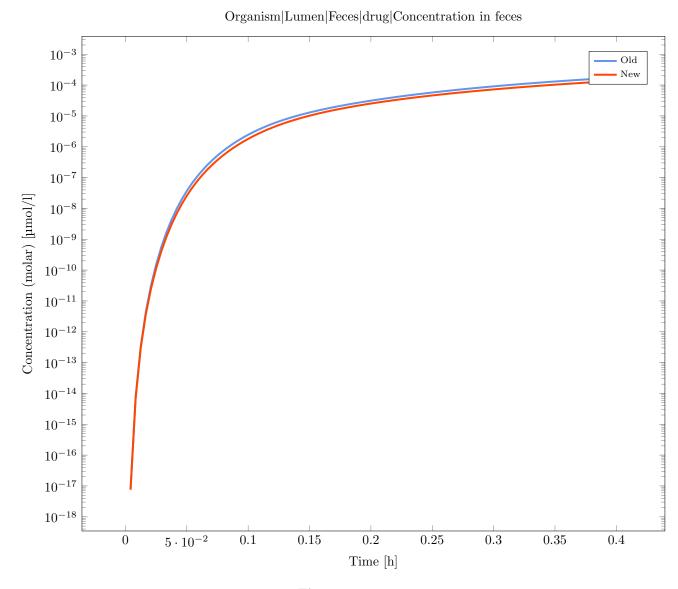
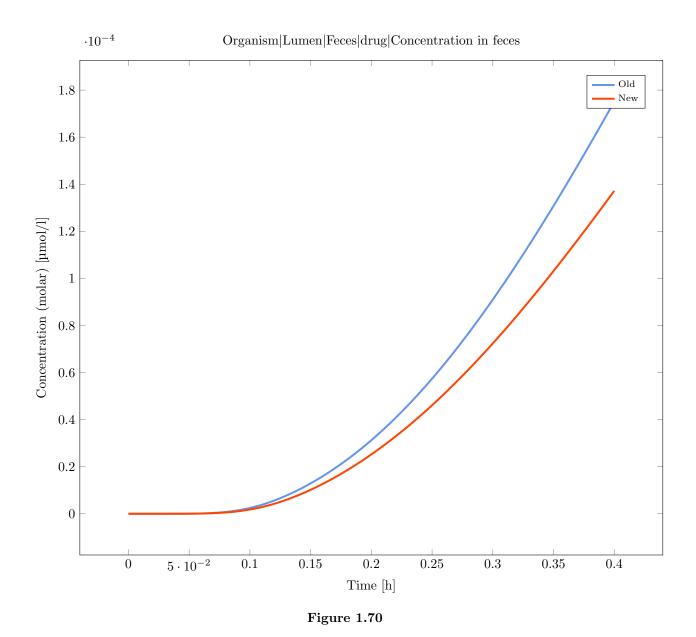


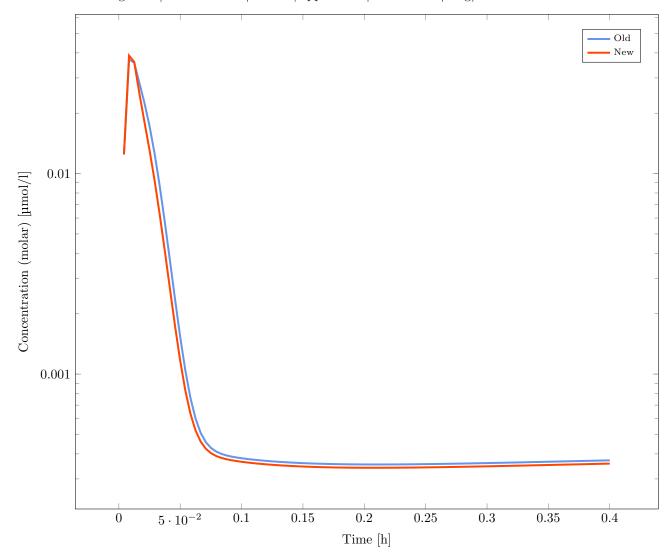
Figure 1.69



 $\label{thm:organism} Output \ Path: \ Organism | Small Intestine | Mucosa | Upper I leum | Intracellular | drug | Concentration in container$ 

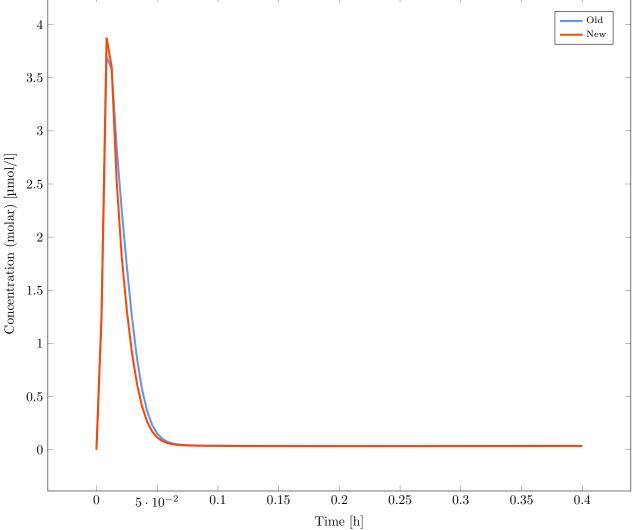
Deviation for 'Organism|SmallIntestine|Mucosa|UpperIleum|Intracellular|drug|Concentration in container' is 28.21% and is greater than the allowed max. tolerance of 3.00%

#### $Organism | Small Intestine | Mucosa | Upper I leum | Intracellular | drug | Concentration \ in \ container$



**Figure 1.71** 





**Figure 1.72** 

# $Simulation: Human\_SingleORAL\_PolyParticlesNormal\_AsSuspention-Human\_SingleORAL\_PolyParticlesNormal\_AsSuspention\_treat\_precipated\_drug\_as\_soluble$

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

# $Output\ Path:\ Organism | Large Intestine | Mucosa | Caecum | Intracellular | drug | Concentration\ in\ container$

Deviation for 'Organism |LargeIntestine |Mucosa |Caecum |Intracellular |drug |Concentration in container' is 32.96% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Large Intestine | Mucosa | Caecum | Intracellular | drug | Concentration \ in \ container$

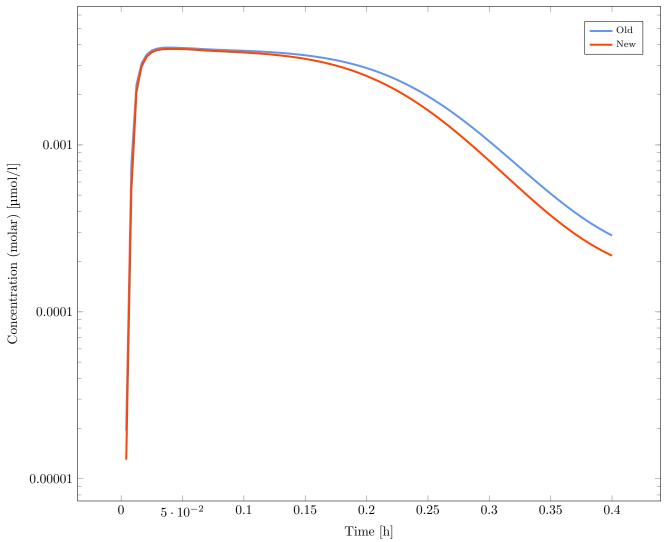
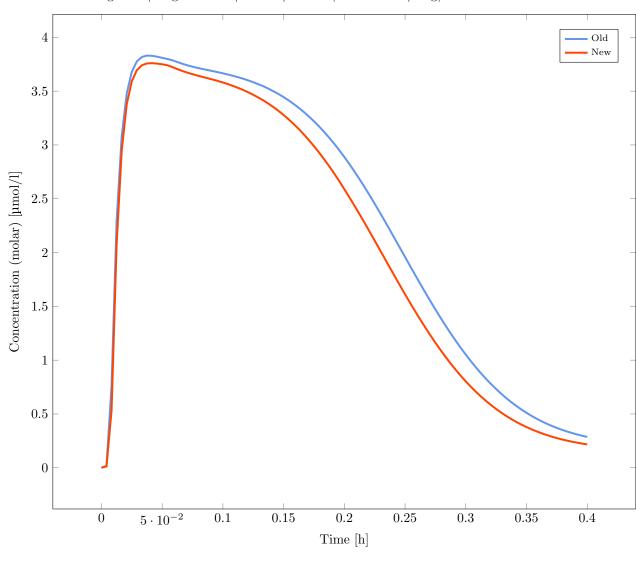


Figure 1.73



 $\cdot 10^{-3}\ \mathrm{Organism} | \mathrm{LargeIntestine} | \mathrm{Mucosa} | \mathrm{Caecum} | \mathrm{Intracellular} | \mathrm{drug} | \mathrm{Concentration\ in\ container}$ 

Figure 1.74

## $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism | Small Intestine | Mucosa | Lower I leum | Intracellular | drug | Concentration in container' is 32.88% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower Ileum | Intracellular | drug | Concentration \ in \ container$

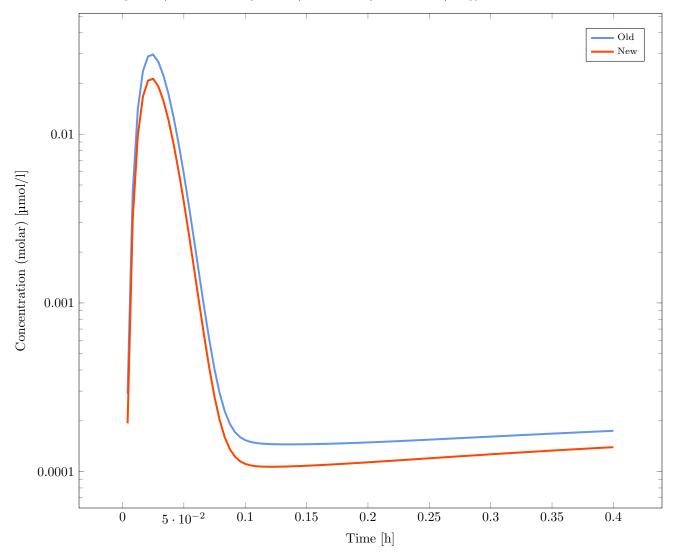
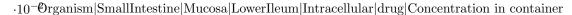
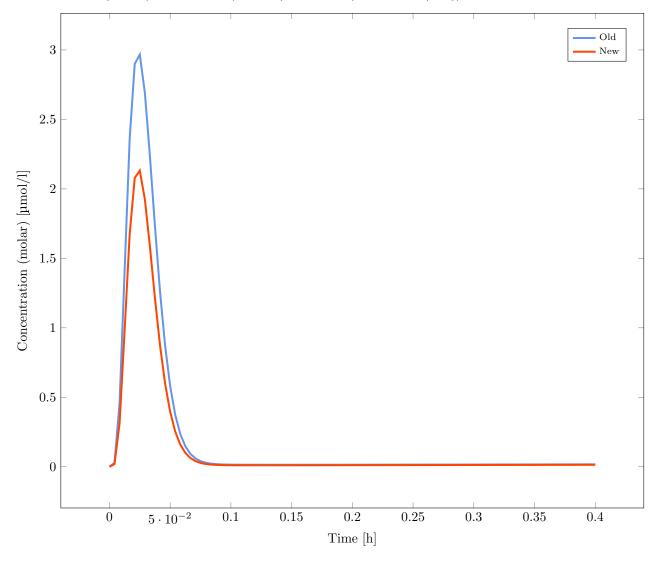


Figure 1.75





**Figure 1.76** 

### $Output\ Path:\ Organism | Small Intestine | Mucosa | Lower I leum | Interstitial | drug | Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerIleum|Interstitial|drug|Concentration in container' is 32.80% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower I leum | Interstitial | drug | Concentration \ in \ container$

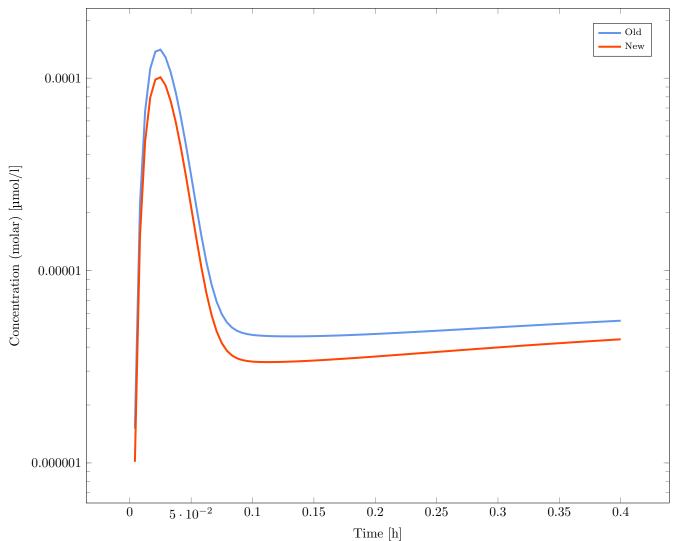
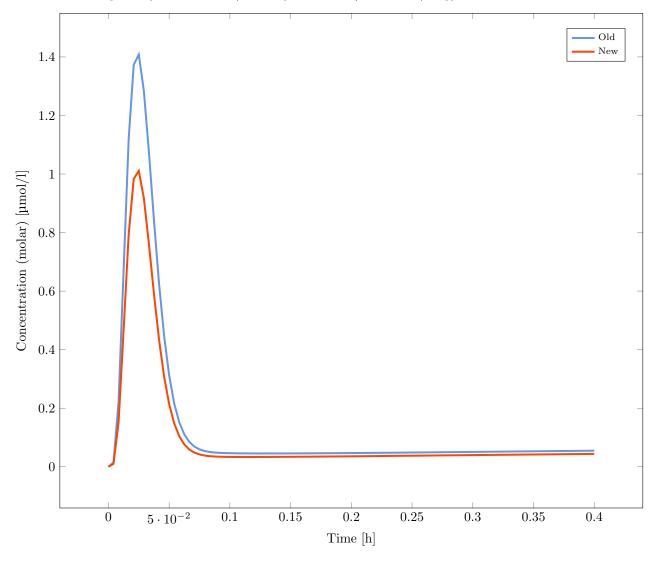


Figure 1.77



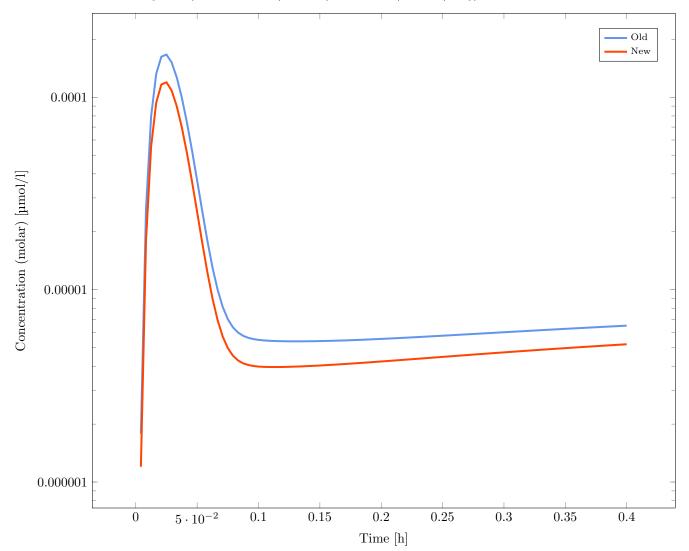


**Figure 1.78** 

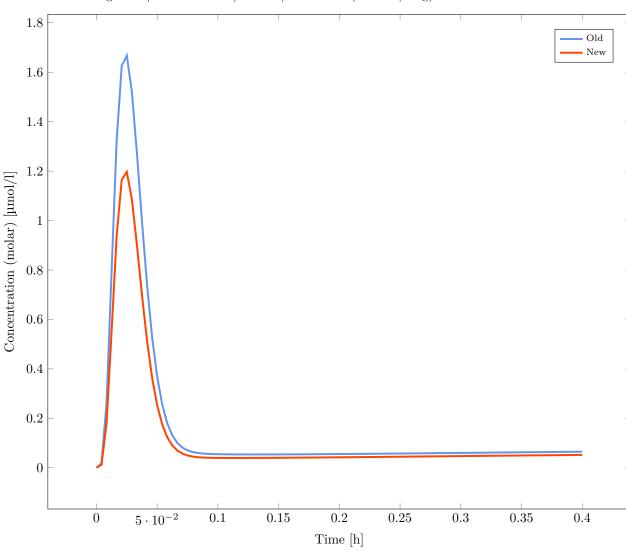
### $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration in container' is 32.80% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower Ileum | Plasma | drug | Concentration \ in \ container$



**Figure 1.79** 



 $\cdot 10^{-4}$  Organism|SmallIntestine|Mucosa|LowerIleum|Plasma|drug|Concentration in container

Figure 1.80

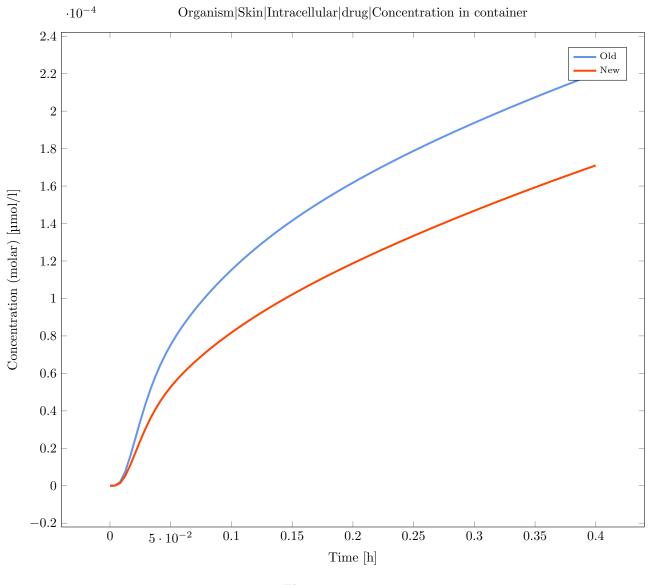
### $Output\ Path:\ Organism|Skin|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism|Skin|Intracellular|drug|Concentration in container' is 32.57% and is greater than the allowed max. tolerance of 3.00%

# $Organism | Skin | Intracellular | drug | Concentration \ in \ container$ Old New $10^{-4}$ Concentration (molar) $[\mu]$ $10^{-5}$ $10^{-6}$ $10^{-7}$ $5 \cdot 10^{-2}$ 0 0.1 0.15 0.2 0.25 0.3 0.35 0.4

Figure 1.81

Time [h]



**Figure 1.82** 

 $Simulation: \ Human\_SingleORAL\_Weibull-Human\_SingleORAL\_Weibull\_MW\_200\_fu\_0.2\_LogP\_5$ 

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

## $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerJejunum|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerJejunum|Intracellular|drug|Concentration in container' is 3.89% and is greater than the allowed max. tolerance of 3.00%

#### $Organism | Small Intestine | Mucosa | Lower Jejunum | Intracellular | drug | Concentration \ in \ container$

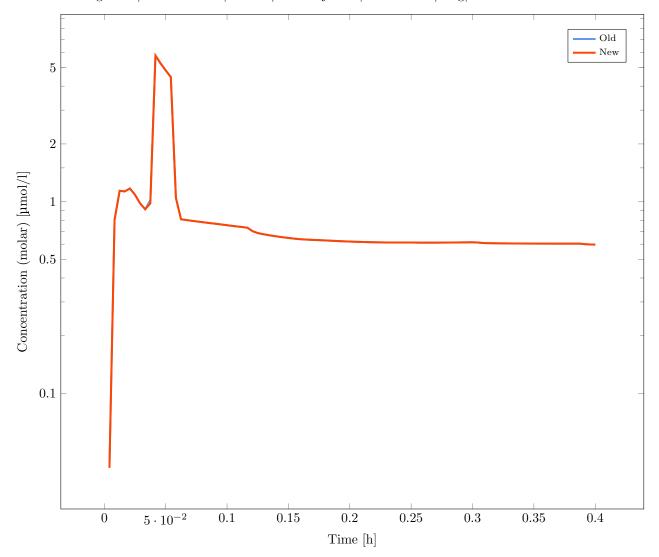


Figure 1.83

### Old6 New 5.5 5 4.5Concentration (molar) [µmol/l] 4 3.5 3 2.5 2 1.5 1 0.5 0 -0.50 0.15 0.2 0.3 0.35 $5\cdot 10^{-2}$ 0.1 0.25 0.4 Time [h]

#### $Organism | Small Intestine | Mucosa | Lower Jejunum | Intracellular | drug | Concentration \ in \ container$

Figure 1.84

### $Output\ Path:\ Organism | Small Intestine | Mucosa | Lower Jejunum | Interstitial | drug | Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerJejunum|Interstitial|drug|Concentration in container' is 3.40% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Lower Jejunum | Interstitial | drug | Concentration \ in \ container$

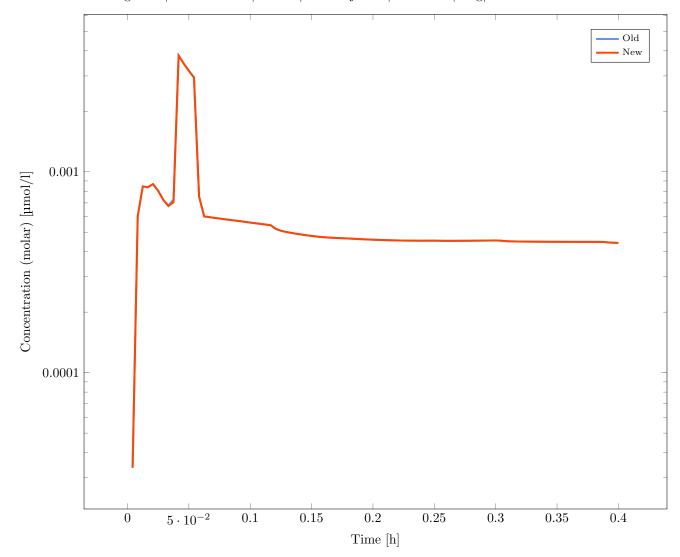


Figure 1.85

3.5 - 3 - [[\frac{1}{\text{New}}]] (2.5 - 2.5 -

 $\cdot 10\, \Im \text{Grganism} | \text{SmallIntestine} | \text{Mucosa} | \text{LowerJejunum} | \text{Interstitial} | \text{drug} | \text{Concentration in container} | \text{Concentration} | \text{Concentrat$ 

Figure 1.86

0.2

Time [h]

0.25

0.3

0.35

0.4

0.15

0.1

### $Output\ Path:\ Organism | Small Intestine | Mucosa | Lower Jejunum | Plasma | drug | Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerJejunum|Plasma|drug|Concentration in container' is 3.01% and is greater than the allowed max. tolerance of 3.00%

Deviation: 0.03

0

0

 $5\cdot 10^{-2}$ 

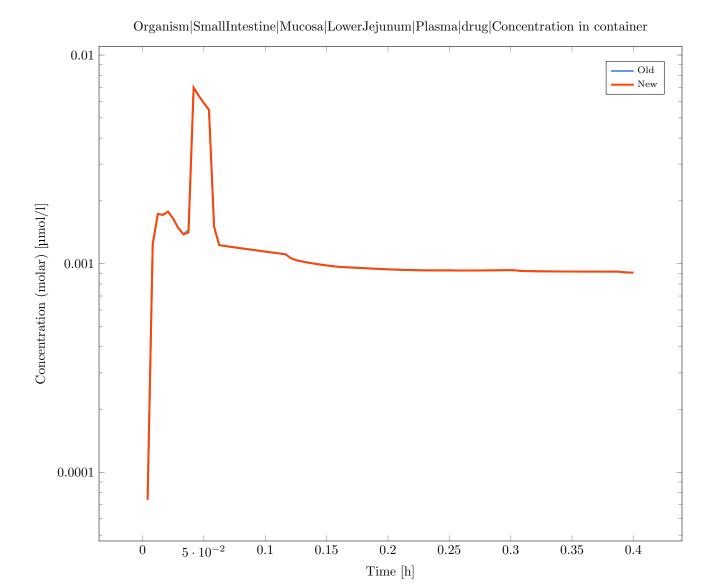
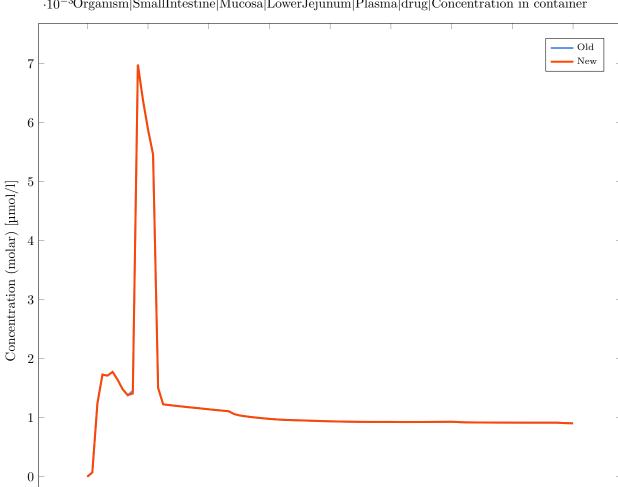


Figure 1.87



 $\cdot 10^{-3}$ Organism|SmallIntestine|Mucosa|LowerJejunum|Plasma|drug|Concentration in container

Figure 1.88

0.2

Time [h]

0.25

0.3

0.35

0.4

 $Simulation: Rat\_MultiORAL\_6\_6\_12\_Dissolved-Rat\_MultiORAL\_6\_6\_12\_Dissolved$ 

0.15

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

0

 $5\cdot 10^{-2}$ 

0.1

#### $Output\ Path:\ Organism | Small Intestine | Mucosa | Upper I leum | Intracellular | drug | Concentration\ in$ container

 $Deviation \ for \ 'Organism | Small Intestine | Mucosa | Upper I leum | Intracellular | drug | Concentration \ in \ container' \ is$ 4.86% and is greater than the allowed max. tolerance of 3.00%

#### $Organism | Small Intestine | Mucosa | Upper I leum | Intracellular | drug | Concentration \ in \ container$

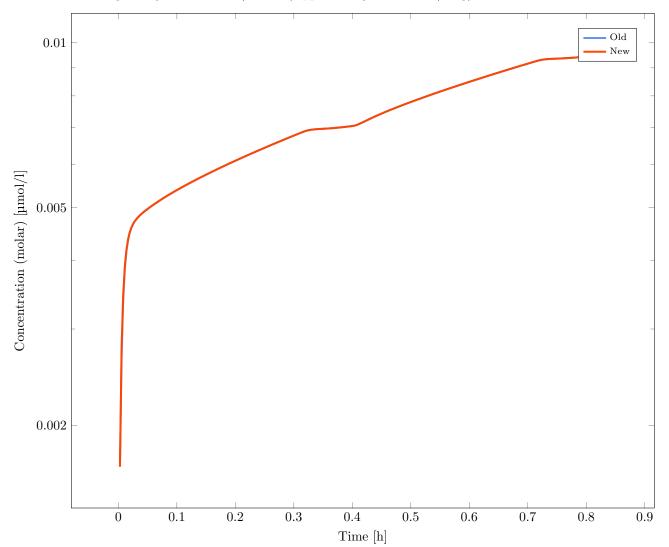
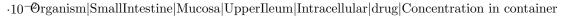


Figure 1.89



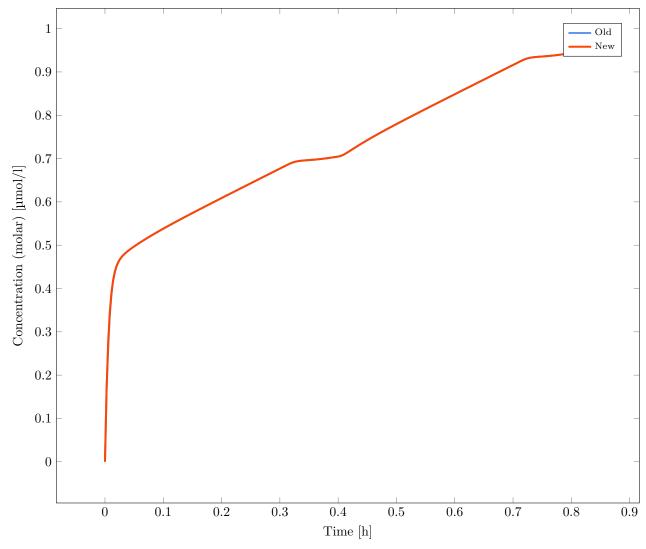


Figure 1.90

# $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration in container' is 4.77% and is greater than the allowed max. tolerance of 3.00%

#### $Organism | Small Intestine | Mucosa | Lower Ileum | Intracellular | drug | Concentration \ in \ container$

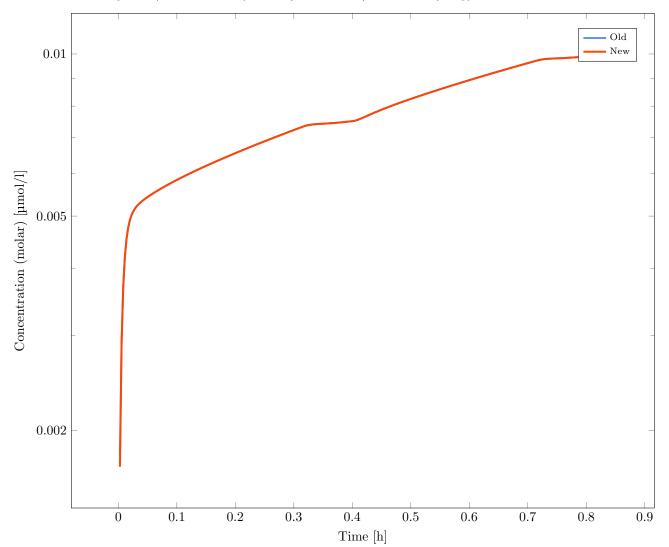


Figure 1.91



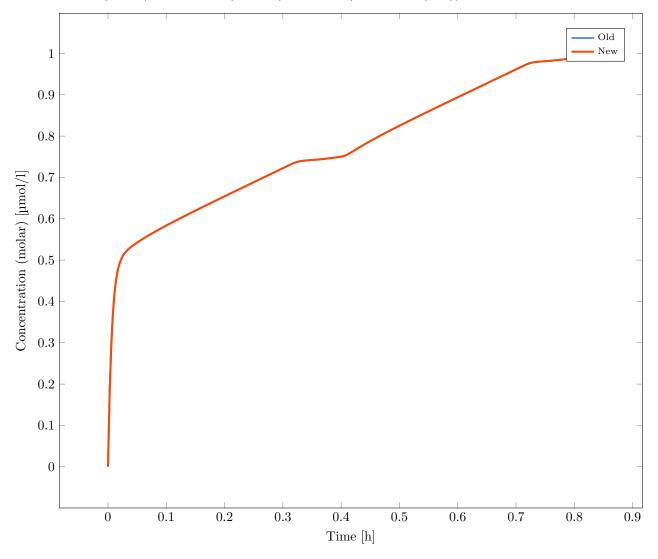


Figure 1.92

# $Output\ Path:\ Organism | Large Intestine | Mucosa | Colon Descendens | Intracellular | drug | Concentration in container$

Deviation for 'Organism | Large Intestine | Mucosa | Colon Descendens | Intracellular | drug | Concentration in container' is 3.84% and is greater than the allowed max. tolerance of 3.00%

Figure 1.93

0.4

Time [h]

0.5

0.6

0.7

0.3

0.000001

0

0.1

0.2

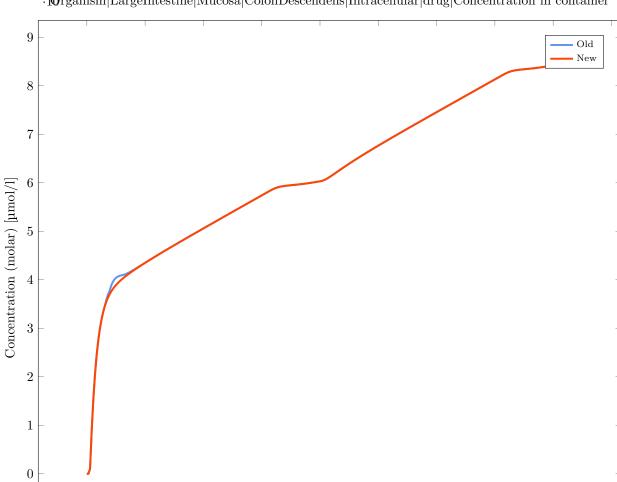
0.8

0.9

0.7

0.8

0.9



#### $\cdot 10$ rganism|LargeIntestine|Mucosa|ColonDescendens|Intracellular|drug|Concentration in container

Figure 1.94

0.4

Time [h]

0.5

0.6

0.3

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

0

0.1

0.2

## $Output\ Path:\ Organism|SmallIntestine|Mucosa|UpperIleum|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|UpperIleum|Intracellular|drug|Concentration in container' is 4.86% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Upper I leum | Intracellular | drug | Concentration \ in \ container$

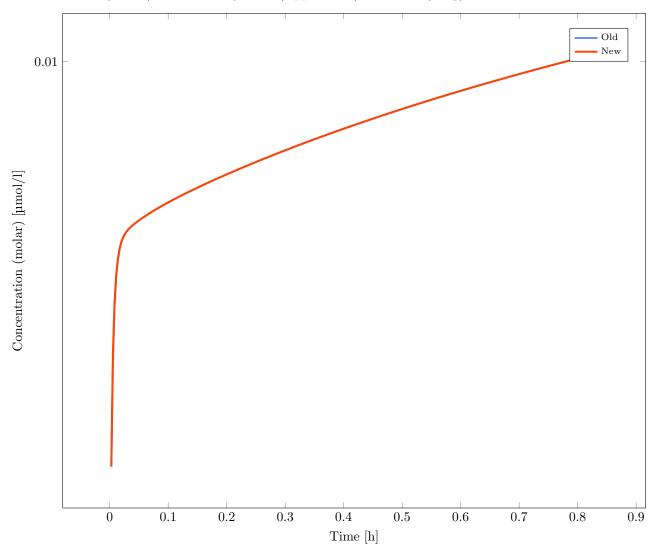
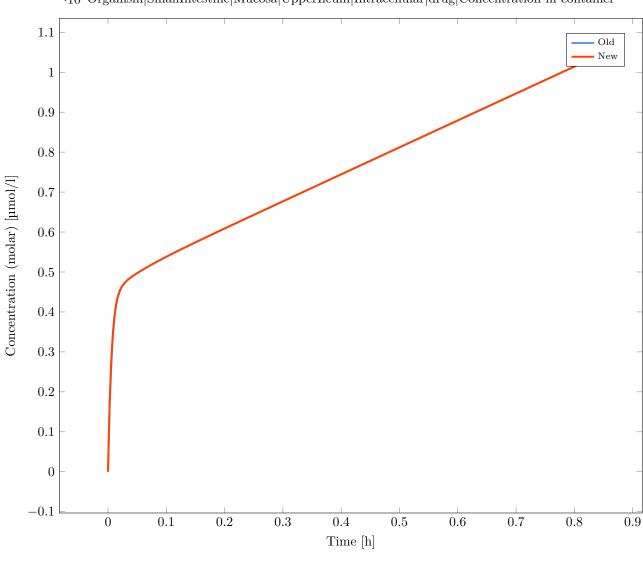


Figure 1.95



 $\cdot 10^{-\Theta}$ rganism|SmallIntestine|Mucosa|UpperIleum|Intracellular|drug|Concentration in container

Figure 1.96

# $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration in container' is 4.77% and is greater than the allowed max. tolerance of 3.00%

#### $Organism | Small Intestine | Mucosa | Lower Ileum | Intracellular | drug | Concentration \ in \ container$

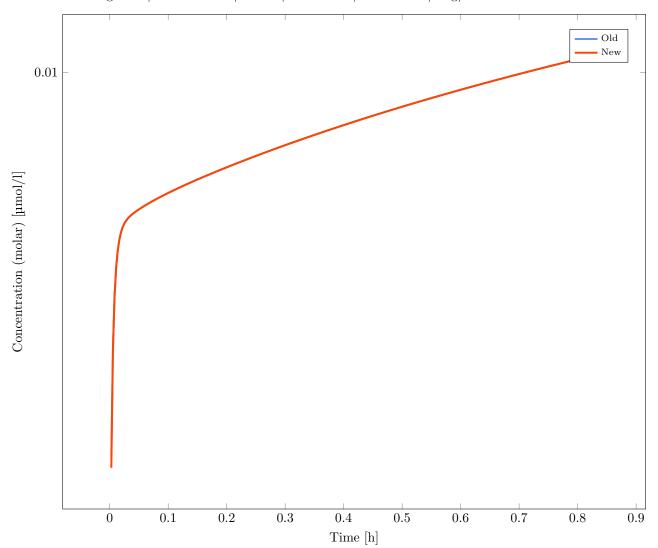
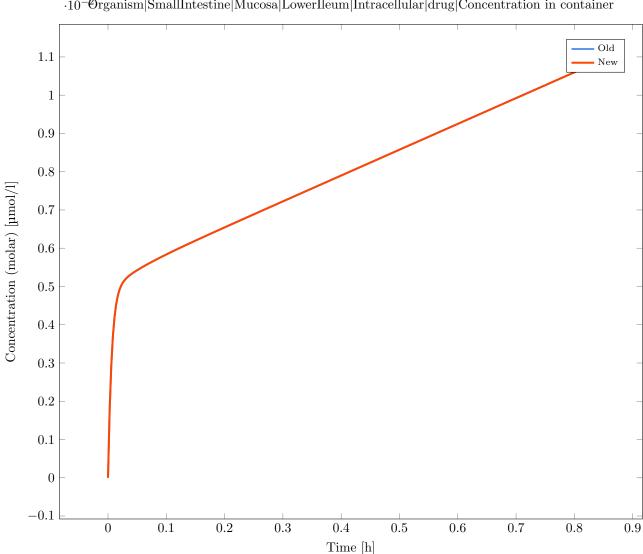


Figure 1.97



 $\cdot 10^{-} \Theta rganism | Small Intestine | Mucosa | Lower Ileum | Intracellular | drug | Concentration in container$ 

Figure 1.98

#### $Output\ Path:\ Organism | Large Intestine | Mucosa | Colon Descendens | Intracellular | drug | Concentration$ in container

 $Deviation \ for \ 'Organism | Large Intestine | Mucosa | Colon Descendens | Intracellular | drug | Concentration \ in \ container' | Concent$ is 3.84% and is greater than the allowed max. tolerance of 3.00%

 $Organism | Large Intestine | Mucosa | Colon Descendens | Intracellular | drug | Concentration \ in \ container$ 

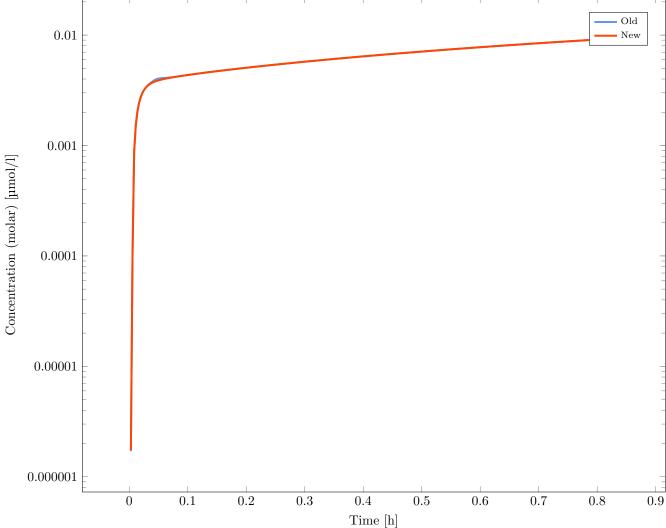
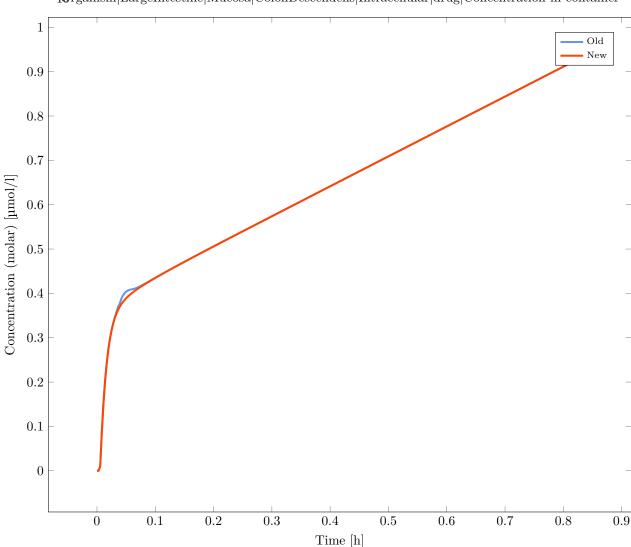


Figure 1.99



 $\cdot 10 \text{F}_{2}^{2}$ anism|LargeIntestine|Mucosa|ColonDescendens|Intracellular|drug|Concentration in container

**Figure 1.100** 

 $Simulation: \ Rat\_MultiORAL\_8\_8\_8\_Dissolved-Rat\_MultiORAL\_8\_8\_8\_Dissolved$ 

Result of the validation: Invalid Absolute Tolerance: 1.00E-10 Relative Tolerance: 1.00E-5

## $Output\ Path:\ Organism|SmallIntestine|Mucosa|UpperIleum|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|UpperIleum|Intracellular|drug|Concentration in container' is 4.86% and is greater than the allowed max. tolerance of 3.00%

### $Organism | Small Intestine | Mucosa | Upper I leum | Intracellular | drug | Concentration \ in \ container$

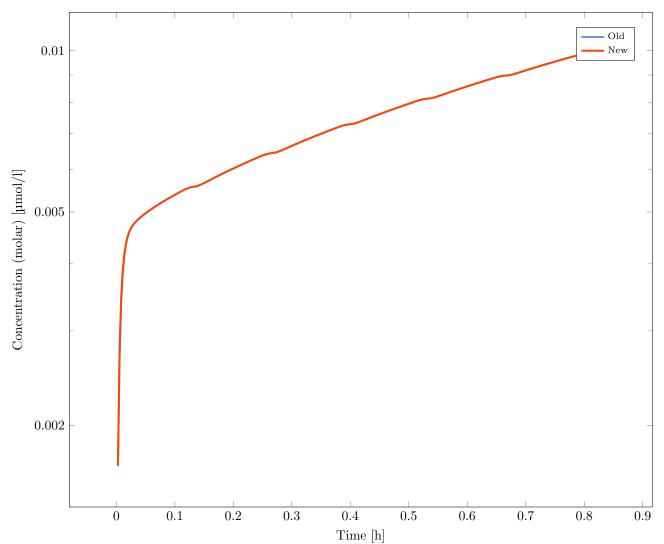
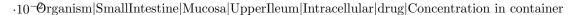


Figure 1.101



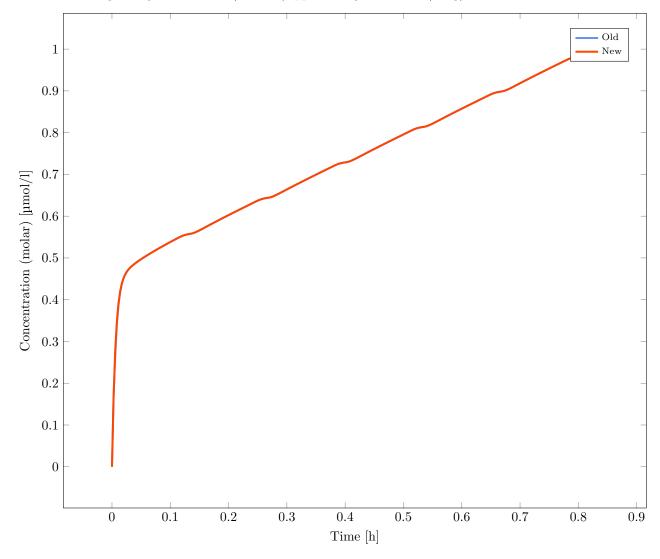


Figure 1.102

# $Output\ Path:\ Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration\ in\ container$

Deviation for 'Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration in container' is 4.77% and is greater than the allowed max. tolerance of 3.00%

#### $Organism | Small Intestine | Mucosa | Lower Ileum | Intracellular | drug | Concentration \ in \ container$

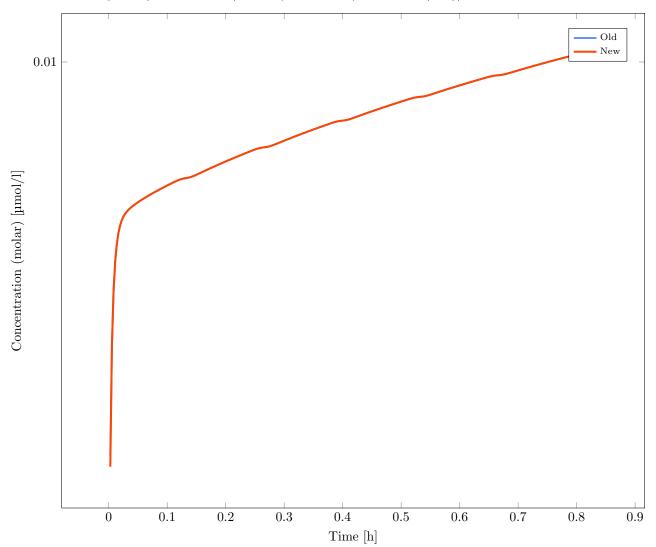
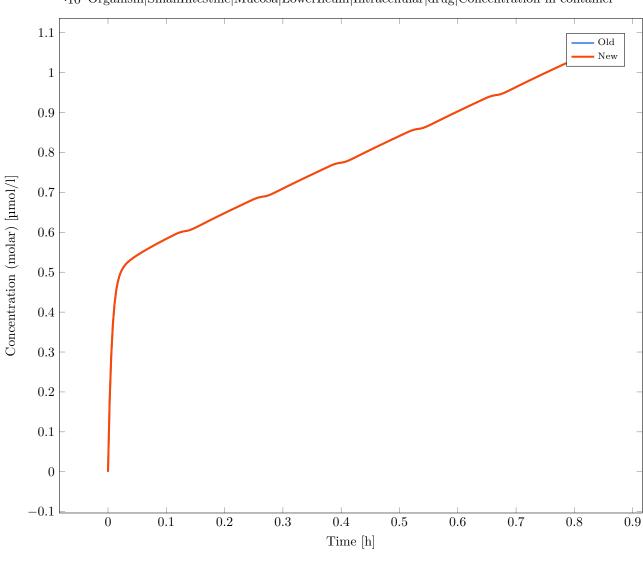


Figure 1.103



 $\cdot 10^{-}$ Organism|SmallIntestine|Mucosa|LowerIleum|Intracellular|drug|Concentration in container

**Figure 1.104** 

# $Output\ Path:\ Organism | Large Intestine | Mucosa | Colon Descendens | Intracellular | drug | Concentration in container$

Deviation for 'Organism | Large Intestine | Mucosa | Colon Descendens | Intracellular | drug | Concentration in container' is 3.84% and is greater than the allowed max. tolerance of 3.00%

0.001 [molar] [molar] 0.0001 [molar] 0.00001 [

 $Organism | Large Intestine | Mucosa | Colon Descendens | Intracellular | drug | Concentration \ in \ container$ 

 ${\bf Figure~1.105}$ 

0.4

Time [h]

0.5

0.6

0.7

0.8

0.9

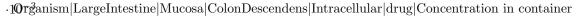
0.3

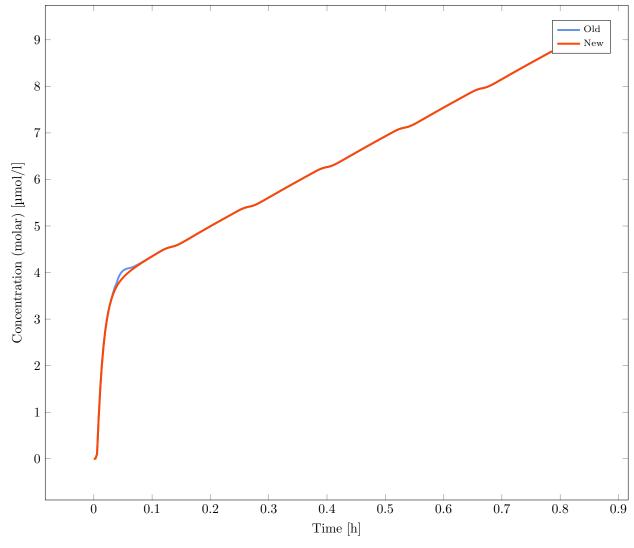
0.000001

0

0.1

0.2





**Figure 1.106** 

## 1.1.2 Valid Simulations (142/155)

Simulation: Beagle\_SingleORAL\_Dissolved-Beagle\_SingleORAL\_Dissolved

Result of the validation: Valid

 $Simulation: Beagle\_SingleORAL\_Dissolved\_Beagle\_SingleORAL\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_5$ 

Result of the validation: Valid

 $Simulation: Beagle\_SingleORAL\_Dissolved\_Beagle\_SingleORAL\_Dissolved\_MW\_800\_fu\_0.6\_LogP\_-5$ 

 $Simulation: \ DDI\_Multiple Combinations-01\_MM\_Competitive\_Competitive$ 

Result of the validation: Valid

Simulation: DDI\_MultipleCombinations-02\_MM\_Uncompetitive\_Uncompetitive

Result of the validation: Valid

Simulation: DDI\_MultipleCombinations-03\_MM\_Noncompetitive\_Noncompetitive

Result of the validation: Valid

Simulation: DDI\_MultipleCombinations-04\_MM\_Mixed\_Mixed

Result of the validation: Valid

 $Simulation: \ DDI\_MultipleCombinations-05\_MM\_Mechanism based\_Mechanism based$ 

Result of the validation: Valid

 $Simulation: \ DDI\_Multiple Combinations-06\_MM\_Induction\_Induction$ 

Result of the validation: Valid

 $Simulation: \ DDI\_Multiple Combinations - 07\_MM\_Competitive\_Competitive\_Mechanism based\_Mechanism based\_Mech$ 

Result of the validation: Valid

 $Simulation: \ DDI\_Multiple Combinations - 08\_MM\_Uncompetitive\_Uncompetitive\_Mechanism based\_Incompetitive\_Mechanism based\_Incompetitive\_Mechanism based\_Incompetitive\_Mechanism based\_Incompetitive\_Incompetitive\_Mechanism based\_Incompetitive\_Incompetitive\_Mechanism based\_Incompetitive\_Incompetitive\_Mechanism based\_Incompetitive\_Incompetitive\_Mechanism based\_Incompetitive\_Incompetitive\_Mechanism based\_Incompetitive\_Incompetitive\_Mechanism based\_Incompetitive\_Incompetitive\_Mechanism based\_Incompetitive\_$ 

 ${\bf Mechanism based}$ 

Result of the validation: Valid

 $Simulation: \ DDI\_Multiple Combinations - 09\_MM\_Noncompetitive\_Noncompetitive\_Mechanism based\_-like and the property of the$ 

Mechanismbased

Result of the validation: Valid

 $Simulation: DDI\_MultipleCombinations-10\_MM\_Mixed\_Mechanismbased\_Mechanismbased$ 

Result of the validation: Valid

 $Simulation: DDI\_Multiple Combinations - 11\_MM\_Mechanism based\_Mechanism based\_Induction\_-linear and the combination of the co$ 

Induction

Result of the validation: Valid

 $Simulation: \ DDI\_Multiple Combinations - 12\_MM\_All\_DDI\_Types$ 

Result of the validation: Valid

Simulation: DDI\_MultipleCombinations-23\_1st\_Noncompetitive\_Noncompetitive

Simulation: DDI\_MultipleCombinations-24\_1st\_Mixed\_Mixed

Result of the validation: Valid

 $Simulation: \ DDI\_MultipleCombinations-25\_1st\_Mechanism based\_Mechanism based$ 

Result of the validation: Valid

Simulation: DDI\_MultipleCombinations-26\_1st\_Induction\_Induction

Result of the validation: Valid

Simulation: DDI\_MultipleCombinations-27\_1st\_Competitive\_Competitive\_Mechanismbased\_Mechanismbased

Result of the validation: Valid

 $Simulation: \ DDI\_Multiple Combinations - 28\_1 st\_Uncompetitive\_Uncompetitive\_Mechanism based\_-line - 28\_1 st\_Uncompetitive\_Uncompetitive\_Mechanism based\_-line - 28\_1 st\_Uncompetitive\_Uncompetitiv$ 

Mechanismbased

Result of the validation: Valid

 $Simulation: \ DDI\_Multiple Combinations - 29\_1st\_Noncompetitive\_Noncompetitive\_Mechanism based\_-1st\_Noncompetitive\_Noncompetitive\_Mechanism based\_-1st\_Noncompetitive\_Non$ 

Mechanismbased

Result of the validation: Valid

Simulation: DDI\_MultipleCombinations-30\_1st\_Mixed\_Mixed\_Mechanismbased\_Mechanismbased

Result of the validation: Valid

Simulation: DDI\_MultipleCombinations-31\_1st\_Mechanismbased\_Mechanismbased\_Induction\_Induction

Result of the validation: Valid

 $Simulation: \ DDI\_Multiple Combinations \textbf{-32\_1st\_All\_DDI\_Types}$ 

Result of the validation: Valid

 $Simulation: \ Dog\_MultiORAL\_12\_12\_Dissolved-Dog\_MultiORAL\_12\_12\_Dissolved-Dog\_MultiORAL\_12\_12\_Dissolved-Dog\_MultiORAL\_12\_12\_Dissolved-Dog\_MultiORAL\_12\_12\_Dissolved-Dog\_MultiORAL\_12\_12\_Dissolved-Dog\_MultiORAL\_12\_12\_Dissolved-Dog\_MultiORAL\_12\_12\_Dissolved-Dog\_MultiORAL\_12\_12\_Dissolved-Dog\_MultiORAL\_12\_12\_Dissolved-Dog\_MultiORAL\_12\_Dissolved-Do$ 

Result of the validation: Valid

 $Simulation: \ Dog\_MultiORAL\_24\_Dissolved-Dog\_MultiORAL\_24\_Dissolved$ 

Result of the validation: Valid

 $Simulation: European\_SingleORAL\_Age\_0\_CYP3A4-European\_SingleORAL_Age\_0\_CYP3A4-European\_SingleORAL_Age\_0\_CYP3A4-European\_SingleORAL_Age\_0\_CYP3A4-European\_SingleORAL_Age\_0\_CYP3A4-European\_SingleORAL_Age\_0\_CYP3A4-European\_SingleORAL$ 

Result of the validation: Valid

 $Simulation: \ European\_SingleORAL\_Age\_0\_GFR-European\_SingleORAL\_Age\_0\_GFR$ 

 $Simulation: European\_SingleORAL\_Age\_1\_CYP3A4-European\_SingleORAL\_AGe\_1\_CYP3A4-European\_SingleORAL$ 

Result of the validation: Valid

 $Simulation: European\_SingleORAL\_Age\_1\_GFR-European\_SingleORAL\_Age\_1\_GFR$ 

Result of the validation: Valid

Simulation: Human\_CompetitiveInhibition-Human\_CompetitiveInhibition

Result of the validation: Valid

Simulation: Human\_ICRP\_AGP-01\_ICRP\_0y\_Male

Result of the validation: Valid

Simulation: Human  $ICRP\_AGP-02\_ICRP\_0.05y\_Female$ 

Result of the validation: Valid

Simulation: Human\_ICRP\_AGP-03\_ICRP\_0.18y\_Male

Result of the validation: Valid

Simulation: Human\_ICRP\_AGP-04\_ICRP\_1y\_Female

Result of the validation: Valid

 $Simulation: \ Human\_ICRP\_AGP-05\_ICRP\_12y\_Male$ 

Result of the validation: Valid

Simulation: Human\_ICRP\_AGP-06\_ICRP\_30y\_Female

Result of the validation: Valid

 $Simulation: \ Human\_ICRP\_AGP-07\_ICRP\_100y\_Male$ 

Result of the validation: Valid

Simulation: Human\_IrreversibleInhibition-Human\_IrreversibleInhibition

Result of the validation: Valid

 ${\bf Simulation: \ Human\_MixedInhibition-Human\_MixedInhibition}$ 

Result of the validation: Valid

 $Simulation: \ Human\_MultiIV\_6\_6\_12-Human\_MultiIV\_6\_6\_12$ 

Result of the validation: Valid

 $Simulation: \ Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_Dissolved-Human\_MultiORAL\_6\_12\_Dissolved-Human\_MultiORAL\_6\_Dissolved-Human\_Dissolved-Human\_MultiORAL\_6\_Dissolved-Human\_$ 

 $Simulation: Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved\_absorption\_sink\_conditions$ 

Result of the validation: Valid

 $Simulation: Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved\_EHC\_continuous\_fraction\_0.5$ 

Result of the validation: Valid

 $Simulation: \ Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved\_EHC\_-12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_Dissolved-Human\_MultiORAL\_6\_Dissolved-Human\_6\_Dissolve$ 

 $continuous\_fraction\_1$ 

Result of the validation: Valid

 $Simulation: \ Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved\_pKa-Dissolved\_pK$ 

dependent penalty factor

Result of the validation: Valid

 $Simulation: \ Human\_MultiORAL\_6\_12\_12\_Dissolved-Human\_MultiORAL\_6\_12\_12\_Dissolved\_solubility$ 

Result of the validation: Valid

Simulation: Human\_MultipleIV\_Binding-Human\_MultipleIV\_Binding

Result of the validation: Valid

 $Simulation: \ Human\_Multiple IV\_Efflux Basolateral-Human\_Multiple IV\_Efflux Basolateral$ 

Result of the validation: Valid

 $Simulation: \ Human\_MultipleIV\_Efflux-Human\_MultipleIV\_Efflux$ 

Result of the validation: Valid

 $Simulation: \ Human\_Multiple IV\_Influx Basolateral-Human\_Multiple IV\_Influx Basolat$ 

Result of the validation: Valid

 $Simulation: \ Human\_MultipleIV\_Influx-Human\_MultipleIV\_ActiveInflux$ 

Result of the validation: Valid

 $Simulation: \ Human\_Multiple IV\_Metabolizm Binding-Human\_Multiple IV\_Metabolizm Binding$ 

Result of the validation: Valid

Simulation: Human\_MultipleIV\_Metabolizm-Human\_MultipleIV\_Metabolizm

Result of the validation: Valid

Simulation: Human\_NonCompetitiveInhibition-Human\_NonCompetitiveInhibition

Simulation: Human\_Oral\_BiDaily\_TableFormulation-S1\_suspension

Result of the validation: Valid

Simulation: Human\_pH\_SolubilityTable-S1\_Table

Result of the validation: Valid

Simulation: Human\_pH\_SolubilityTable-S2\_Measurement

Result of the validation: Valid

Simulation: Human\_pH\_SolubilityTable-S3\_Table\_SolubilityChanged

Result of the validation: Valid

Simulation: Human\_pH\_SolubilityTable-S4\_Table\_SolubilityTableChanged

Result of the validation: Valid

Simulation: Human\_SingleIV\_Configuration-Human\_SingleIV\_Configuration

Result of the validation: Valid

Simulation: Human\_SingleIV-Human\_SingleIV

Result of the validation: Valid

 $Simulation: Human\_SingleIV\_Human\_SingleIV\_MW\_200\_fu\_0.2\_LogP\_5$ 

Result of the validation: Valid

Simulation: Human\_SingleIV-Human\_SingleIV\_MW\_800\_fu\_0.6\_LogP\_-5

Result of the validation: Valid

 $Simulation: Human\_SingleORAL\_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_Singl$ 

Result of the validation: Valid

 $Simulation: Human\_SingleORAL\_Dissolved\_PlasmaClearance-Human\_Singl$ 

 $MW\_200\_fu\_0.2\_LogP\_5$ 

Result of the validation: Valid

 $Simulation: \ Human\_SingleORAL\_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_SingleORAL_Dissolved\_PlasmaClearance-Human\_Sin$ 

 $MW_-800\_fu_-0.6\_LogP_--5$ 

Result of the validation: Valid

Simulation: Human\_SingleORAL\_Dissolved-Human\_SingleORAL\_Dissolved

 $Simulation: Human\_SingleORAL\_Dissolved\_Human\_SingleORAL\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Lo$ 

 $\mathbf{5}$ 

Result of the validation: Valid

 $Simulation: Human\_SingleORAL\_Dissolved\_Human\_SingleORAL\_Dissolved\_MW\_800\_fu\_0.6\_LogP\_-RAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-RAL_Dissolved\_MW_800\_fu\_0.6\_LogP\_-RAL_Dissolved\_MW_800\_fu\_0.6\_LogP\_-RAL_Dissolved\_MW_800\_fu\_0.6\_LogP\_-RAL_Dissolved\_MW_800\_fu\_0.6\_LogP\_-RAL_Dissolved\_MW_800\_fu\_0.6\_LogP\_-RAL_Dissolved\_MW_800\_fu\_0.6\_LogP\_-RAL_Dissolved\_MW_800$ 

-5

Result of the validation: Valid

Simulation: Human\_SingleORAL\_Lint80\_AsSuspention-Human\_SingleORAL\_Lint80\_AsSuspention

Result of the validation: Valid

Simulation: Human\_SingleORAL\_Lint80-Human\_SingleORAL\_Lint80

Result of the validation: Valid

 $Simulation: Human\_SingleORAL\_Weibull\_AsSuspention-Human\_SingleORAL\_Weibull\_AsSuspention$ 

Result of the validation: Valid

 $Simulation: Human\_SingleORAL\_Weibull\_AsSuspention-Human\_SingleORAL\_Weibull\_AsSuspention\_-Incomplete the property of the prop$ 

 $MW\_200\_fu\_0.2\_LogP\_5$ 

Result of the validation: Valid

 $Simulation: Human\_SingleORAL\_Weibull\_AsSuspention-Human\_SingleORAL\_Weibull\_AsSuspention\_-Incomplete the control of the contr$ 

 $MW_-800\_fu_-0.6\_LogP_--5$ 

Result of the validation: Valid

 $Simulation: \ Human\_SingleORAL\_Weibull-Human\_SingleORAL\_Weibull$ 

Result of the validation: Valid

 $Simulation: \ \ Human\_SingleORAL\_Weibull-Human\_SingleORAL\_Weibull\_MW\_800\_fu\_0.6\_LogP\_-lo$ 

5

Result of the validation: Valid

 $Simulation: \ Human\_Uncompetitive Inhibition-Human\_Uncompetitive Inhibition$ 

Result of the validation: Valid

 $Simulation: \ Minipig\_SingleORAL\_Dissolved-Minipig\_SingleORAL\_Dissolved$ 

Result of the validation: Valid

 $Simulation: \ Minipig\_SingleORAL\_Dissolved\_Minipig\_SingleORAL\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-lo$ 

5

 $Simulation: Minipig\_SingleORAL\_Dissolved\_Minipig\_SingleORAL\_Dissolved\_MW\_800\_fu\_0.6\_LogP\_-LogP$ 

Result of the validation: Valid

Simulation: Monkey\_SingleORAL\_Dissolved-Monkey\_SingleORAL\_Dissolved

Result of the validation: Valid

 $Simulation: Monkey\_SingleORAL\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-togP$ 

5

Result of the validation: Valid

 $Simulation: Monkey\_SingleORAL\_Dissolved\_MORAL\_Dissolved\_MW\_800\_fu\_0.6\_LogP\_-Installation: Monkey\_SingleORAL\_Dissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORALDissolved\_MORA$ 

-5

Result of the validation: Valid

Simulation: Mouse\_SingleORAL\_Dissolved-Mouse\_SingleORAL\_Dissolved

Result of the validation: Valid

 $Simulation: Mouse\_SingleORAL\_Dissolved\_Mouse\_SingleORAL\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Included to the control of the control$ 

 $\mathbf{5}$ 

Result of the validation: Valid

 $Simulation: Mouse\_SingleORAL\_Dissolved\_Mouse\_SingleORAL\_Dissolved\_MW\_800\_fu\_0.6\_LogP\_-Incomplete the control of the control$ 

-5

Result of the validation: Valid

Result of the validation: Valid

Result of the validation: Valid

 $Simulation: Preterm\_SingleIV\_Age\_15\_GA\_32\_CYP3A4-Preterm\_SingleIV\_Age\_15\_CYP3A4-Prete$ 

Result of the validation: Valid

 $Simulation: \ Preterm\_SingleIV\_Age\_15\_GA\_32\_GFR-Preterm\_SingleIV\_Age\_15\_GA\_32\_GFR$ 

Result of the validation: Valid

 $Simulation: \ Rabbit\_SingleORAL\_Dissolved-Rabbit\_SingleORAL\_Dissolved$ 

 $Simulation: Rabbit\_SingleORAL\_Dissolved\_Rabbit\_SingleORAL\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW\_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW_200\_fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW_200\_Fu\_0.2\_LogP\_-Rabbit\_Dissolved\_MW_200\_Fu\_0.2\_$ 

 $\mathbf{5}$ 

Result of the validation: Valid

 $Simulation: Rabbit\_SingleORAL\_Dissolved\_Rabbit\_SingleORAL\_Dissolved\_MW\_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL\_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL_Dissolved\_MW_800\_fu\_0.6\_LogP\_-Rabbit\_SingleORAL_Dissolved\_MW_800\_Fu\_0.6\_LogP\_-Rabbit\_SingleORAL_Dissolved\_MW_800\_F$ 

-5

Result of the validation: Valid

Simulation: SingleIV\_2Pores\_Human-SingleIV\_2Pores\_Human

Result of the validation: Valid

 $Simulation: Single IV\_2 Pores\_Human\_Single IV\_2 Pores\_Human\_Simulation C$ 

Result of the validation: Valid

 $Simulation: Single IV\_2 Pores\_Human\_Single IV\_2 Pores\_Human\_Simulation D$ 

Result of the validation: Valid

Simulation: SingleIV\_2Pores\_Human\_SingleIV\_2Pores\_Human\_SimulationF

Result of the validation: Valid

Simulation: SingleIV\_2Pores\_Monkey-SingleIV\_2Pores\_Monkey

Result of the validation: Valid

Simulation: SingleIV\_2Pores\_Monkey\_SingleIV\_2Pores\_Monkey\_SimulationG

Result of the validation: Valid

 $Simulation: Single IV\_2 Pores\_Monkey\_Single IV\_2 Pores\_Monkey\_Simulation H$ 

Result of the validation: Valid

 $Simulation: Single IV\_2 Pores\_Mouse-Single IV\_2 Pores\_Mouse$ 

Result of the validation: Valid

 $Simulation: Single IV\_2 Pores\_Mouse\_Single IV\_2 Pores\_Mouse\_Simulation A$ 

Result of the validation: Valid

 $Simulation: Single IV\_2 Pores\_Mouse\_Single IV\_2 Pores\_Mouse\_Simulation B$ 

Result of the validation: Valid

 $Simulation: Single IV\_2 Pores\_Mouse\_Single IV\_2 Pores\_Mouse\_Simulation E$ 

 $Simulation: Single IV\_C1\_4 Comp\_standard\_stand$ 

Result of the validation: Valid

 $Simulation: Single IV\_C2\_4 Comp\_PT\_standard\_st$ 

Result of the validation: Valid

 $Simulation: Single IV\_C2\_4 Comp\_RR\_standard\_st$ 

Result of the validation: Valid

 $Simulation: Single IV\_C2\_4 Comp\_standard\_schmitt\_standard\_Single IV\_C2\_4 Comp\_standard\_schmitt\_schmitt\_standard\_schmitt_schmitt_sch$ 

standard

Result of the validation: Valid

 $Simulation: Single IV\_C3\_4 Comp\_RR\_schmitt\_standard-Single IV\_C3\_standard-Single IV\_C3\_sta$ 

Result of the validation: Valid

 $Simulation: Single IV\_C3\_4 Comp\_standard\_schmittnorm lized\_standard\_Single IV\_C3\_4 Comp\_standard\_schmittnorm lized\_standard\_schmittnorm lized\_schmittnorm lized\_sch$ 

 $schmittnormlized\_standard$ 

Result of the validation: Valid

 $Simulation: Single IV\_C4\_2 Pores\_RR\_standard\_standard\_Single IV\_C4\_2 Pores\_RR\_standard\_stan$ 

Result of the validation: Valid

 $Simulation: Single IV\_C4\_4 Comp\_Ber\_standard\_s$ 

Result of the validation: Valid

 $Simulation: Single IV\_C5\_2 Pores\_Ber\_standard\_$ 

Result of the validation: Valid

 $Simulation: Single IV\_C5\_2 Pores\_PT\_standard\_s$ 

Result of the validation: Valid

 $Simulation: Single IV\_C5\_2 Pores\_RR\_schmitt\_standard-Single IV\_C5\_2 Pores\_schmitt\_standard-Single IV\_C5\_2 Pores\_schmitt\_schmitt\_schmitt_schm$ 

Result of the validation: Valid

 $Simulation: Single IV\_C6\_2 Pores\_standard\_stan$ 

standard

Result of the validation: Valid

Simulation: SingleIV\_C7\_2Pores\_standard\_schmitt\_standard-SingleIV\_C7\_2Pores\_standard\_schmitt\_-

standard

 $Simulation: Single IV\_C7\_4 Comp\_schmitt\_standard\_standa$ 

Result of the validation: Valid

 $Simulation: Single IV\_C8\_2 Pores\_standard\_schmittnormalized\_standard\_Single IV\_C8\_2 Pores\_standard\_schmittnormalized\_schmittnormalized\_s$ 

Result of the validation: Valid

 $Simulation: Single IV\_C9\_2 Pores\_schmitt\_standard\_standard-Single IV\_C9\_2 Pores\_schmitt\_standard-Single IV\_C9\_2 Pores\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt\_schmitt$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C10\_4 Comp\_PT\_standard\_standard-Single ORAL\_C10\_4 Comp\_PT\_standard-Single ORAL\_C10\_4 Comp\_Single ORAL\_C10\_4 C00\_4 C00\_$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C11\_4 Comp\_schmitt\_standard\_sta$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C11\_4 Comp\_standard\_st$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C12\_4 Comp\_standard\_schmitt\_standard-Single ORAL\_C12\_4 Comp\_standard\_schmitt\_standard\\$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C13\_2 Pores\_schmitt\_standard\_standard\_Single ORAL\_C13\_2 Pores\_schmitt\_standard\_standa$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C13\_4 Comp\_standard\_schmittnormalized\_schmittnormalized\_sc$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C14\_2 Pores\_PT\_standard\_standard\_Single ORAL\_C14\_2 Pores\_PT\_standard\_standar$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C2\_2 Pores\_standard\_st$ 

 $Simulation: Single ORAL\_C3\_2 Pores\_standard\_schmitt\_standard-Single ORAL\_C3\_2 Pores\_standard\_schmitt\_standard\\$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C4\_2 Pores\_standard\_schmittnormalized\_standard\_Single ORAL\_C4\_2 Pores\_standard\_schmittnormalized\_standard$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C6\_4 Comp\_Ber\_standard\_standard\_Single ORAL\_C6\_4 Comp\_Ber\_standard\_$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C6\_4 Comp\_RR\_standard\_standard\_Single ORAL\_C6\_4 Comp\_RR\_standard\_st$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C7\_2 Pores\_Ber\_standard\_standard\_Single ORAL\_C7\_2 Pores\_Ber\_standard\_standar$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C7\_4 Comp\_RR\_schmitt\_standard-Single ORAL\_C7\_standard-Single ORAL\_C7\_standard-Sing$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C8\_2 Pores\_RR\_standard\_standard\_Single ORAL\_C8\_2 Pores\_RR\_standard\_$ 

Result of the validation: Valid

 $Simulation: Single ORAL\_C9\_2 Pores\_RR\_schmitt\_standard-Single ORAL\_c9\_2 Pores\_schmitt\_standard-Single ORAL\_c9\_2 Pores\_schmitt\_schmitt\_standard-Single ORAL\_c9\_2 Pores\_schmitt\_schmitt\_standard-Single ORAL\_c9\_2 Pores\_schmitt\_schmitt\_s$ 

Result of the validation: Valid

Simulation: Test  $18.1\_I1\_C1\_A1\_Config1$ -Test  $18.1\_I1\_C1\_A1\_Config1$ 

Result of the validation: Valid

 $Simulation: \ Test\ 18.1\_I2\_C1\_A1\_Config2-Test\ 18.1\_I2\_C1\_A1\_Config2$ 

Result of the validation: Valid

 $Simulation: \ Test\ 18.1\_I2\_C3\_A1\_Config2-Test\ 18.1\_I2\_C3\_A1\_Config2$ 

Result of the validation: Valid

 $Simulation: \ Test\ 18.1\_I3\_C3\_A3\_Config2-Test\ 18.1\_I3\_C3\_A3\_Config2$