

Day 5 Exercise 1

Conducting a safety assessment for Retinoic Acid using a PBPK model

A Course on Physiologically Based Pharmacokinetic (PBPK) Modeling in Drug Development and Evaluation

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*Center for Human Health Assessment
Center for Drug Safety Sciences*



All-trans Retinoic Acid

Background

- Essential nutrient (vitamin A)
 - Prescribed during pregnancy to assure proper development
- Chemotherapeutic
 - Treatment of acute promyelocytic leukemia
- Skin cream
 - Treatment of wrinkles
- Teratogenic
 - Produces skeletal deformations in rodents
 - 13-cis isomer teratogenic in humans

All-trans Retinoic Acid Safety Assessment

- New proposed use as a topical skin treatment
- FDA concern: Potential human teratogenicity
 - ATRA teratogenic in animal studies
 - 13-cis isomer: known human teratogen
- FDA suggestion (Carl Peck): Use PBPK model to provide assurance of safety for intended use
- Approach: Compare fetal doses resulting from maternal dermal use with teratogenic doses in animal studies to estimate margins of safety

All-trans Retinoic Acid

PBPK Model

- Compartments: liver, fat, gut, intestinal lumen, skin, richly perfused, slowly perfused tissues
- Two metabolic pathways
 - Oxidation
 - Glucuronidation
- Three routes of exposure
 - IV
 - Oral
 - Skin

Species specific metabolic parameters

	RODENT	PRIMATE
hsc	0.001	0.001
hsk	0.03	0.03
Pfsc	9	9
Pscsk	6	6
Dsci	8.00E-09	8.00E-09
Dski	7.30E-06	7.30E-06
rpf	1	2.5
ff	5	5
kbc	0.01	0.01
kfc	0.1	0.12
Kmg	1.5	0.05
Vmaxgc	0.25	1
Kmo	0.8	6
Vmaxoc	1.2	6
krc	3	3
A	10	600
AT	10	12800

Physiological parameters

	MOUSE		RAT		MONKEY		HUMAN	
QCC	10		10		10		8	
QRC	0.52		0.47		0.46		0.45	
QLC	0.035		0.03		0.065		0.07	
QGC	0.165		0.18		0.185		0.19	
QSC	0.18		0.18		0.18		0.18	
QFC	0.03		0.06		0.05		0.05	
QSKC	0.07		0.08		0.06		0.06	
BW	0.02		0.3		4		70	
VBC	0.65		0.65		0.65		0.65	
VPC	0.04		0.04		0.04		0.04	
VRC	0.049		0.031		0.039		0.039	
VLC	0.046		0.037		0.027		0.023	
VGC	0.031		0.033		0.045		0.045	
VIC	0.054		0.058		0.053		0.053	
VSC	0.34		0.36		0.48		0.37	
VFC	0.1		0.07		0.05		0.16	
VSKC	0.17		0.195		0.11		0.11	
PR	2.25		2.25		2.25		2.25	
PL	3.8		3.8		3.8		3.8	
PG	1.45		1.45		1.45		1.45	
PS	0.67		0.67		0.67		0.67	
PF	3.35		3.35		3.35		3.35	
PSK	0.67		1.2		1.2		0.67	

Performing a safety assessment using a PBPK model

What we are going to do is calculate metrics of exposure to all-trans retinoic acid (ATRA) for minimally teratogenic doses in animals. We will then calculate the same metrics in humans for several potential human exposures to ATRA.

The purpose of performing these calculations is to calculate a Margin of Safety (MoS) for the clinical use of ATRA.

The dose metrics are:

C_{MAX} for ATRA in plasma: Visually Assess

AUC for ATRA in plasma: ACPT

(hint: use the crosshair cursor or table view)

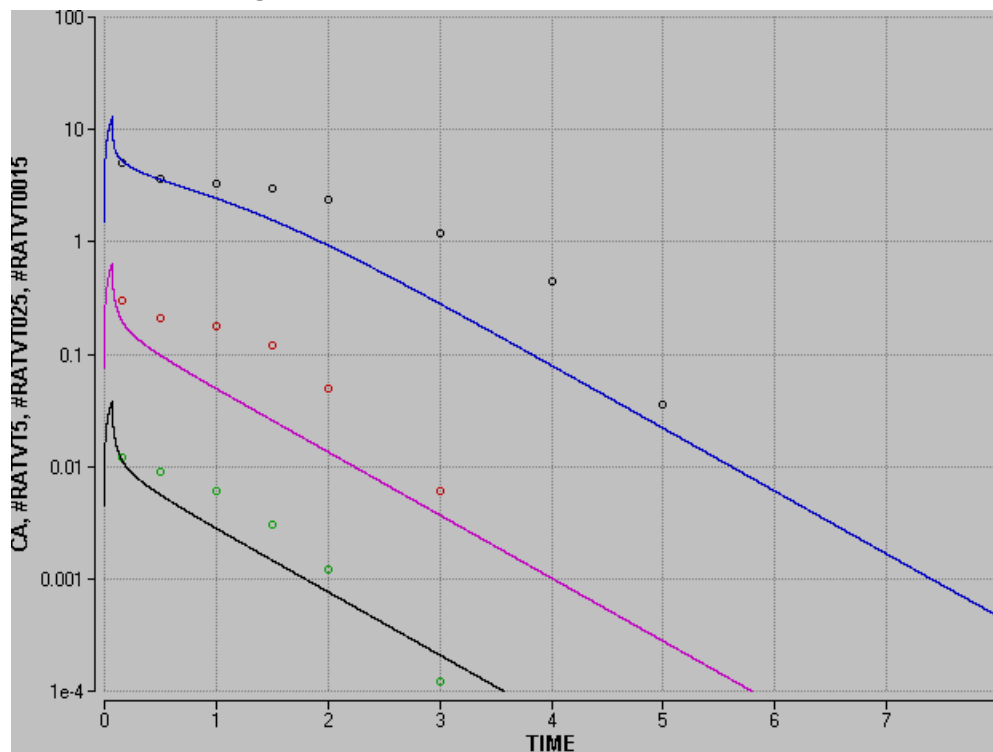
Follow the script and write dose metric results:

Metabolism	Rodent	Physiology	Rat
hsc	0.001	QCC	10.0
hsk	0.03	QRC	0.47
Pfsc	9.0	QLC	0.03
Pscsk	6.0	QGC	0.18
Dsci	8.00E-09	QSC	0.18
Dski	7.30E-06	QFC	0.06
rpf	1.0	QSKC	0.08
ff	5.0	BW	0.3
kbc	0.01	VBC	0.65
kfc	0.1	VPC	0.04
Kmg	1.5	VRC	0.031
Vmaxgc	0.25	VLC	0.037
Kmo	0.8	VGC	0.033
Vmaxoc	1.2	VIC	0.058
krc	3.0	VSC	0.36
A	10.0	VFC	0.07
AT	10.0	VSKC	0.195
		PR	2.25
		PL	3.8
		PG	1.45
		PS	0.67
		PF	3.35
		PSK	1.2

	Rat IV
STOPTIME	8.0
DT	0.0001
CFORM	0.0
DOC	0.0

- set rodent metabolism parameters
- set rat physiological parameters
- run rat intravenous exposures
- Run IV doses (DVC) of 5.0, 0.25, 0.015 mg/kg
(Overlay runs on Graph Page 1)

Figure should look similar to this:



Rat

dvc=0.0, doc=2.5 (set minimal teratogenic dose in rat)

STOPTIME =24.0 (long enough to capture exposure)

Run (run simulation)

C_{\max} _____

ACPT _____

Metabolism	Rodent	MOUSE		Mouse Oral	
hsc	0.001	QCC	10	STOPTIME	8.0
hsk	0.03	QRC	0.52	DT	0.0001
Pfsc	9.0	QLC	0.035	CFORM	0.0
Pscsk	6.0	QGC	0.165	DVC	0.0
Dsci	8.00E-09	QSC	0.18		
Dski	7.30E-06	QFC	0.03		
rpf	1.0	QSKC	0.07		
ff	5.0	BW	0.02		
kbc	0.01	VBC	0.65		
kfc	0.1	VPC	0.04		
Kmg	1.5	VRC	0.049		
Vmaxgc	0.25	VLC	0.046		
Kmo	0.8	VGC	0.031		
Vmaxoc	1.2	VIC	0.054		
krc	3.0	VSC	0.34		
A	10.0	VFC	0.1		
AT	10.0	VSKC	0.17		
		PR	2.25		
		PL	3.8		
		PG	1.45		
		PS	0.67		
		PF	3.35		
		PSK	0.67		

Mouse (set mouse physiology parameters)

doc=4.0 (set minimal teratogenic dose in mouse)

Run (run simulation)

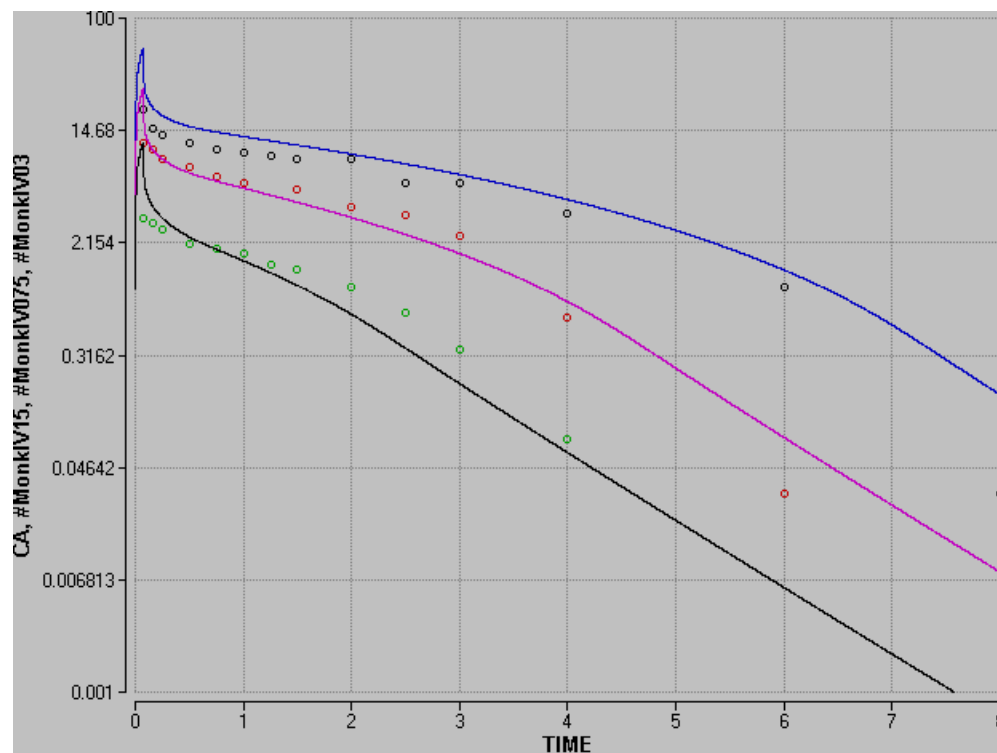
C_{max} _____

ACPT _____

Monkey Intravenous Exposures

Metabolism	Primate	Physiology	Monkey	Monkey IV
hsc	0.001	QCC	10.0	STOPTIME 8.0
hsk	0.03	QRC	0.46	DT 0.0001
Pfsc	9.0	QLC	0.065	CFORM 0.0
Pscsk	6.0	QGC	0.185	DOC 0.0
Dsci	8.00E-09	QSC	0.18	
Dski	7.30E-06	QFC	0.05	
rpf	2.5	QSKC	0.06	
ff	5.0	BW	7.5	
kbc	0.01	VBC	0.65	
kfc	0.12	VPC	0.04	
Kmg	0.05	VRC	0.039	
Vmaxgc	1.0	VLC	0.027	
Kmo	6.0	VGC	0.045	
Vmaxoc	6.0	VIC	0.053	
krc	3.0	VSC	0.48	
koc	0.7	VFC	0.05	
A	600	VSKC	0.11	
AT	12800	PR	2.25	
		PL	3.8	
		PG	1.45	
		PS	0.67	
		PF	3.35	
		PSK	1.2	

- *set monkey metabolism parameters
- *set monkey physiological parameters
- *run monkey intravenous exposures
- *Run IV doses of 15.0, 7.5, 3.0 mg/kg
(Overlay runs on Graphs Page 2)



Set dvc=0.0, doc=5.0

Stoptime=72.0

Run; result

(set minimal teratogenic dose)

(long enough to capture exposure)

C_{\max} _____

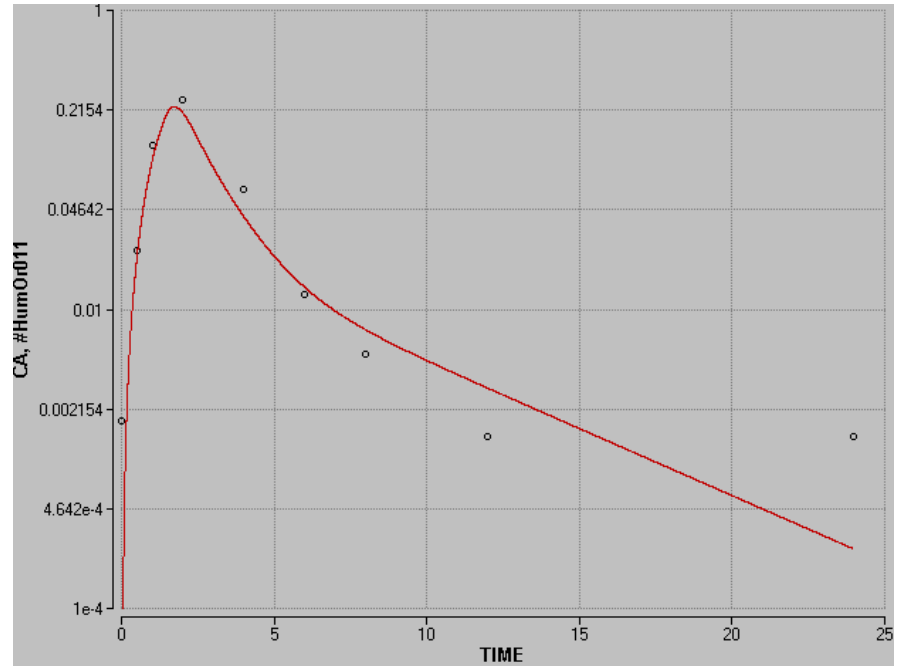
ACPT _____

Run Human Oral Exposure

Physiology	Human
QCC	8
QRC	0.45
QLC	0.07
QGC	0.19
QSC	0.18
QFC	0.05
QSKC	0.06
BW	70
VBC	0.65
VPC	0.04
VRC	0.039
VLC	0.023
VGC	0.045
VIC	0.053
VSC	0.37
VFC	0.16
VSKC	0.11
PR	2.25
PL	3.8
PG	1.45
PS	0.67
PF	3.35
PSK	0.67

	Human Oral
STOPTIME	24.0
DT	0.0001
CFORM	0.0
DVC	0.0

*set human physiological parameters
 *Run an oral dose of 1.1 mg/kg
 (View graph on Page 3)



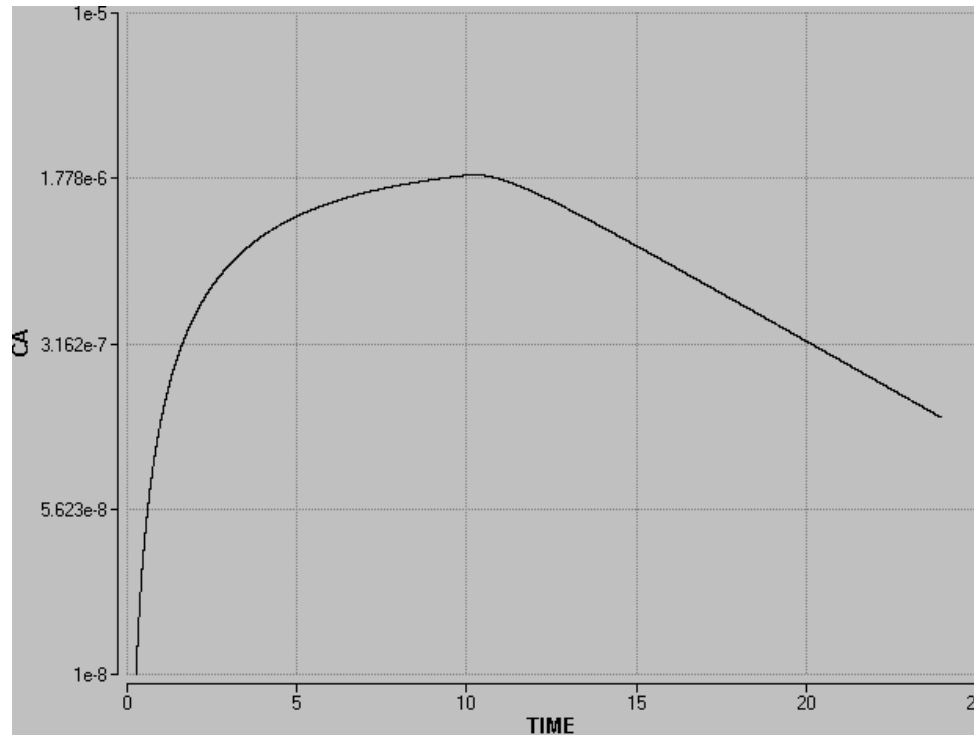
s tstop=168.0 (to capture exposure)
 start; result (oral cancer therapy)

C_{max} _____

ACPT _____

Human Dermal Exposure

SET Stoptime=24., Cform=500.0, Tsk=10.0, rpf=5.56
Dvc=0.0, Doc=0.0, A=50.0, AT=20000.0



Small woman

SET Stoptime=168, BW=40.0, VFC=0.16, VSC=0.37,
AT=12800.0, rpf=2.51

A=600 (face and hands)

Run Simulation (normal topical use-TSK=10.0)

C_{\max} _____

ACPT _____

SET A=2000 (face, hands, arms, and chest)

SET Tsk=24 (don't wash off)

Run Simulation (abuse)

C_{\max} _____

ACPT _____

Comparison of dose surrogates for Retinoic Acid teratogenicity

Fill out this table with your dose metric results.

Species	Route	Dose (mg/kg)	Cmax (ng/mL)	AUC (ng*hr/mL)
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Minimal Teratogenic Doses

Mouse	Oral	4.0		
Rat	Oral	2.5		
Monkey	Oral	5.0		

Clinical Doses

Human	Oral	1.1		
Human	Topical	Therapy ^a		
Human	Topical	Abuse ^b		

^a 0.05% formulation; face only; wash after 10 hours.

^b 0.05% formulation; face, arms, chest; wash after 24 hours.

Now calculate the Margin of Safety for each Use

$$MoS = \frac{\textit{Metric Associated with Teratogenicity}}{\textit{Metric Associated with Human Exposure}}$$

MoS

oral:

topical:

abusive topical:

Would you approve ATRA for:

- oral use in cancer therapy?
- for topical use as a wrinkle cream?
- what would you want on the label?

What did FDA decide?

- FDA CDER evaluation:
 - “Internal exposure calculations are relatively insensitive to changes in the PBPK model which preserve correspondence with the experimental data”
- Result: Resolved FDA concern regarding topical abuse
 - moved forward to labeling discussions