

Modeling Motherhood II: An approach to modeling drug exposure during lactation

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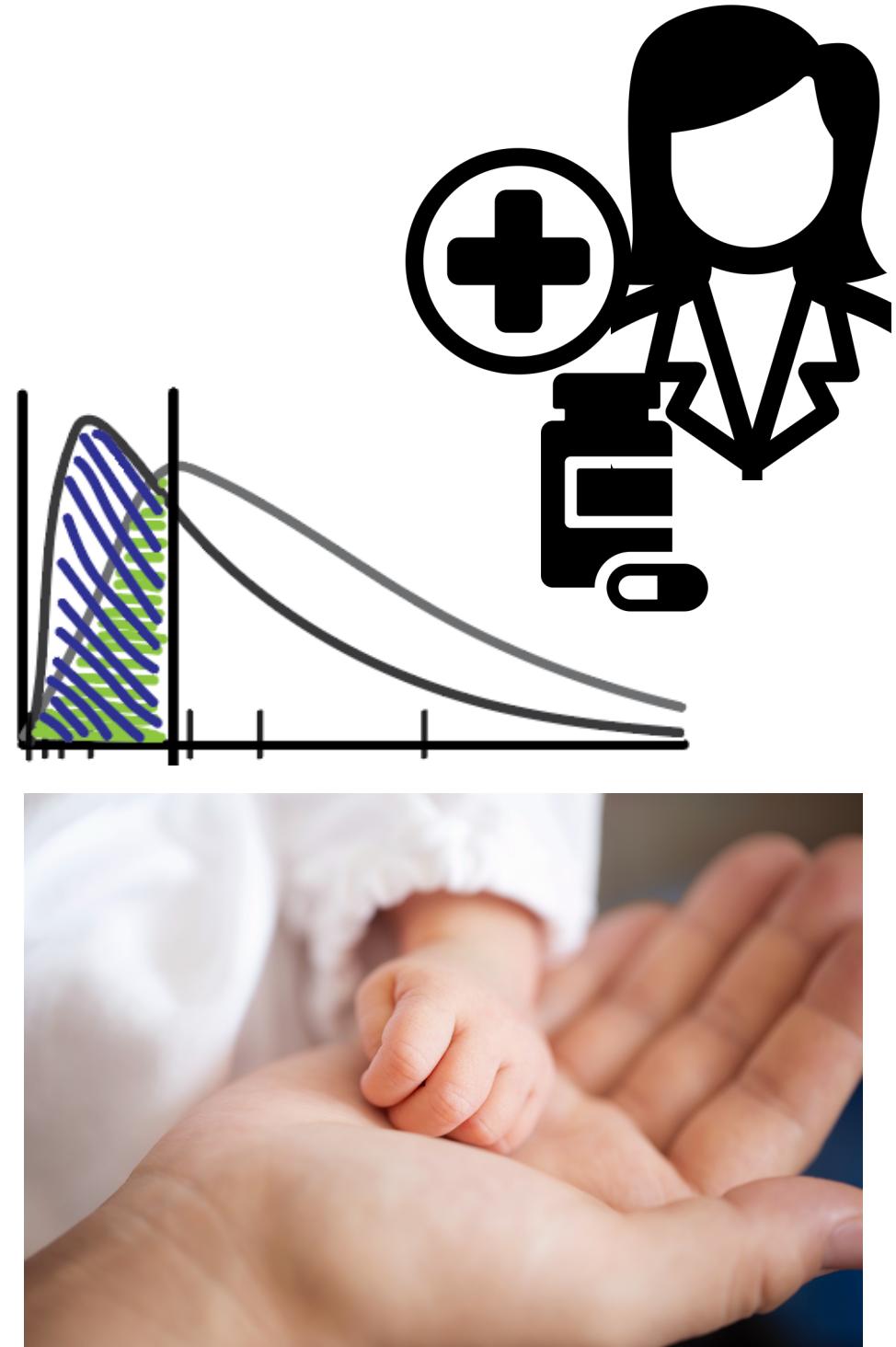


I have nothing to disclose

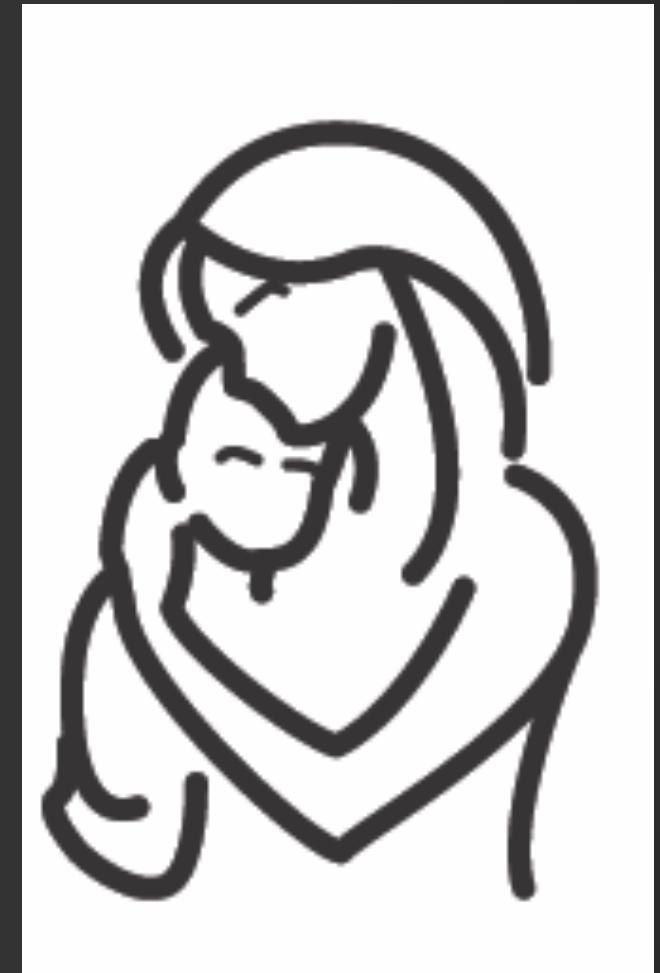


Presentation outline

1. Why look at drug transfer in moms?
2. How do we study drug transfer in moms?
3. Example



**Why do we care about
medications given to moms?**



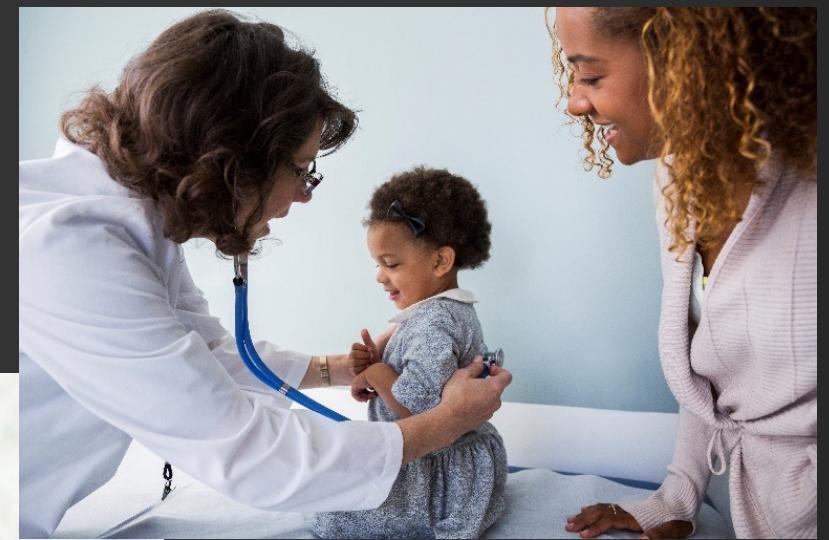
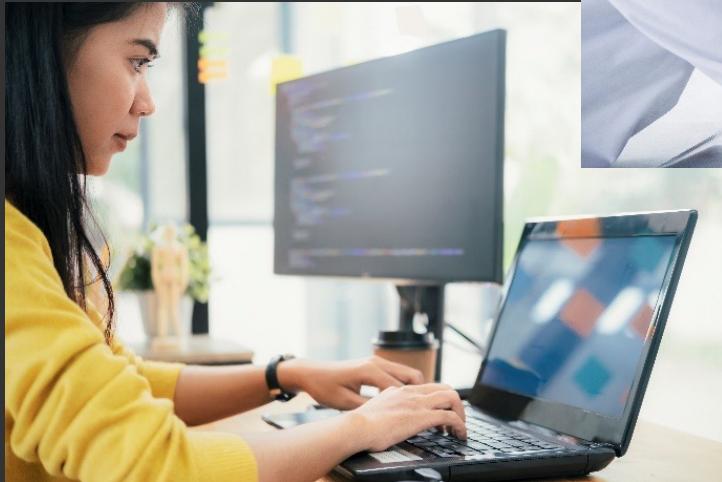
Most people take medications



Most of the medications lack appropriate labeling information for pregnant women and lactating women.

Ren. Drug development research in pregnant and lactating women. Am J Obstet Gynecol 2021.

How can we study these medications?



Opportunistic PK Studies

1. Enrolls participants already on a drug of interest
2. Collects samples as “add-ons” to standard of care procedures
3. Minimal/no added risk to participants



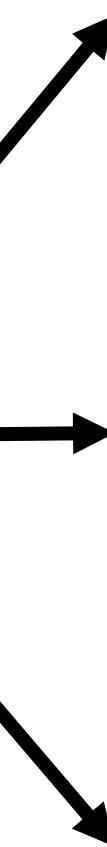
Example: Lactation



Commonly Used Drugs During Lactation and infant Exposure (CUDDLE) Study



Drug taken by mother



Maternal breastmilk sample



Maternal plasma/whole blood sample



Infant plasma/whole blood sample



Eunice Kennedy Shriver National Institute
of Child Health and Human Development

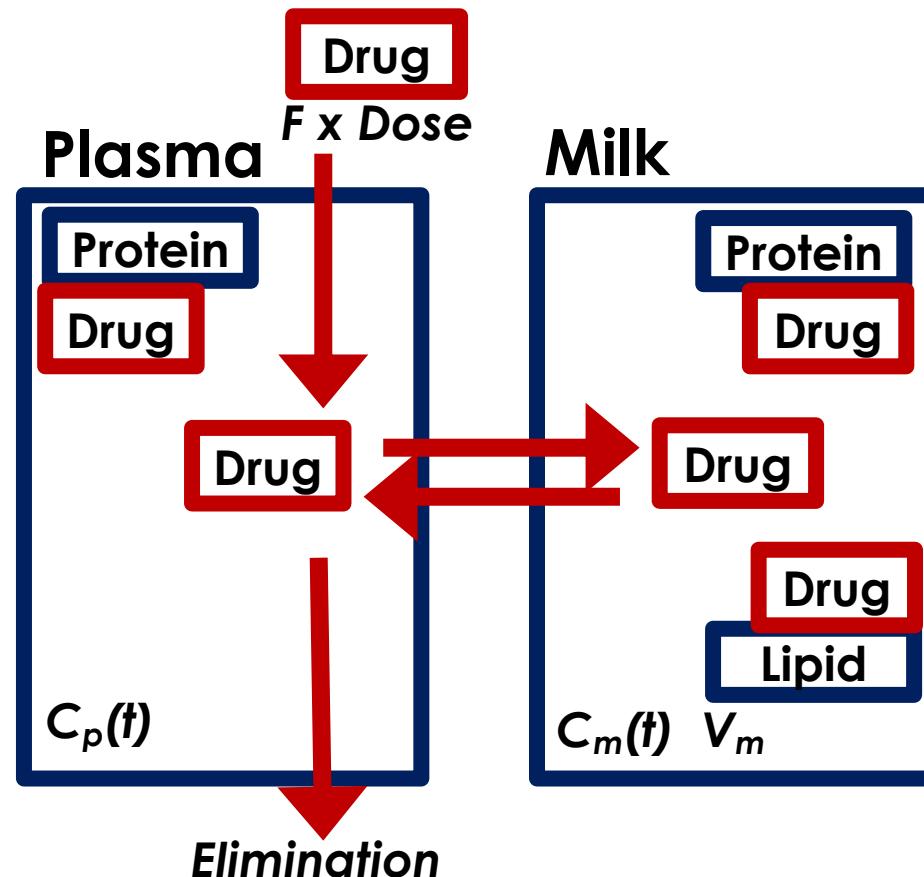
A project of the Best Pharmaceuticals for Children Act



PEDIATRIC
TRIALS NETWORK
Making drugs safer & more effective
for use in the youngest patients

Measures of infant exposure

Milk : Plasma Ratio



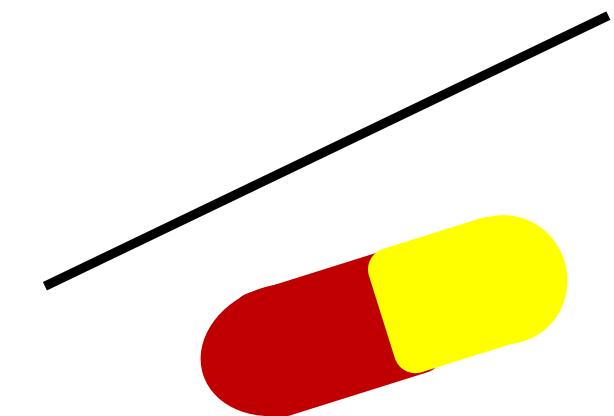
- >1 → concentrates in milk
- 1 → equal concentration
- <1 → less transfer to milk

Daily Infant Dose



Milk Concentration x Volume
(Assumes 150 mL/kg/d)

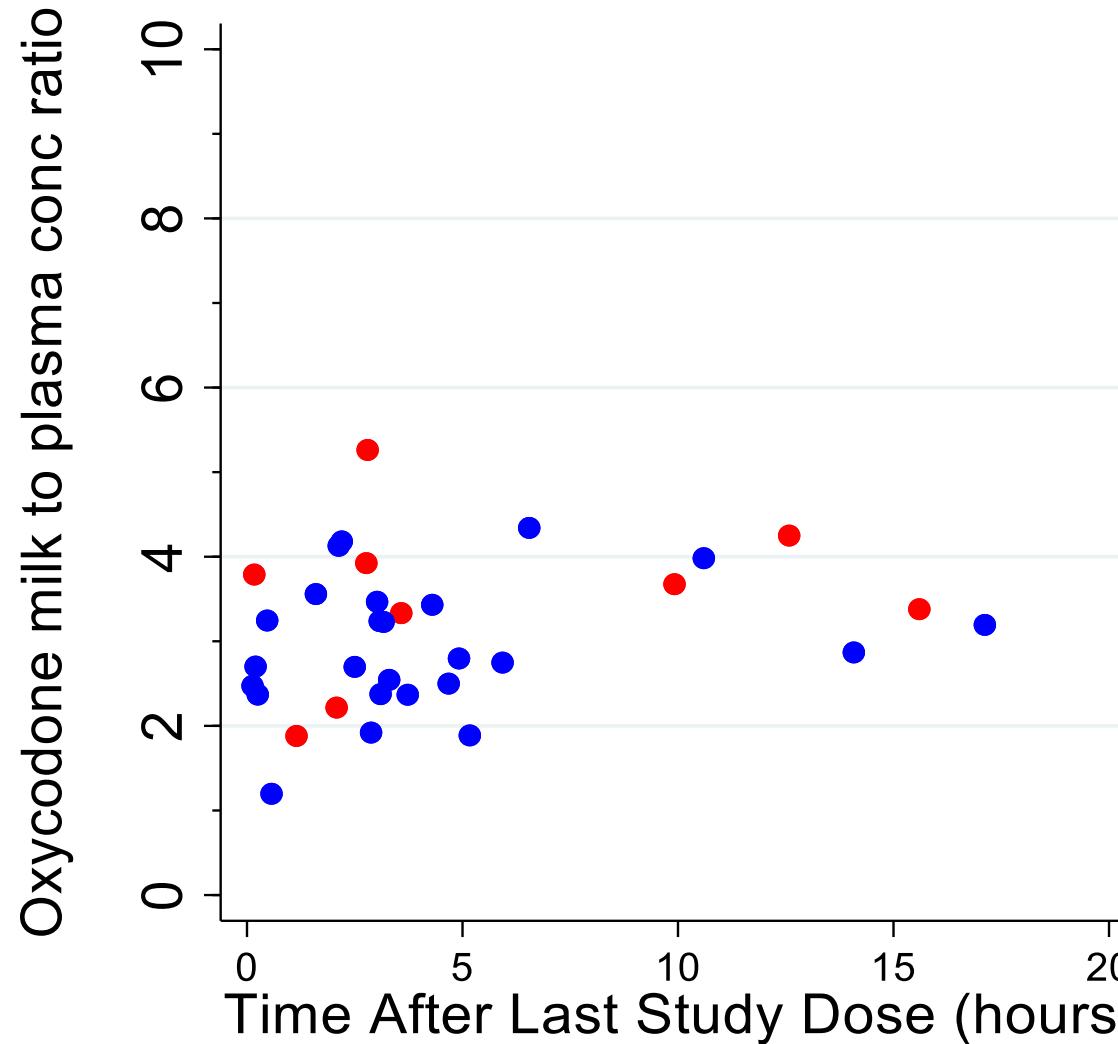
Relative Infant Dose (RID)



0.1 mg/kg/dose

Oxycodone exposure in breastmilk

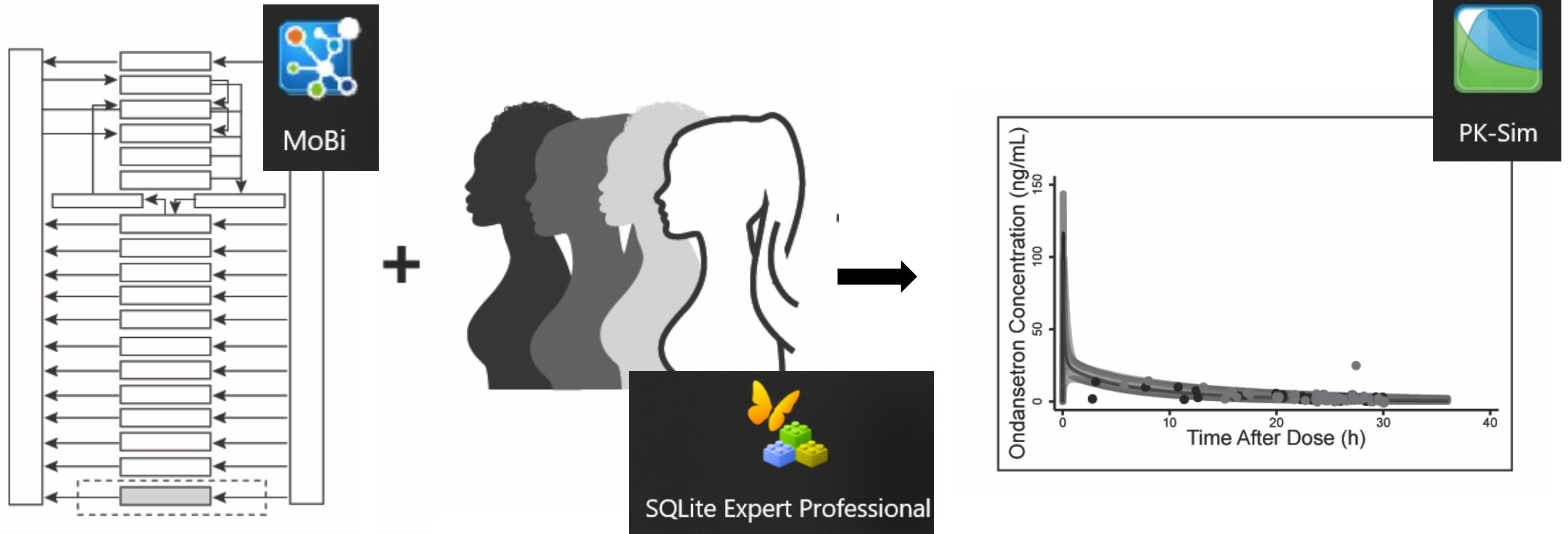
Oxycodone **concentrates** in milk



Time (h)	Milk conc (ng/mL)	Daily infant dose (mg/kg/day)	RID _{I:I} (%)
0-3	50.8	0.01	2.5
>3-6	55.4	0.01	2.8
Average 24 h	30.3	0.006	1.5
Max over 24 h	121	0.02	6.1

- Infant dose is low
- Typical infant dose = 0.1 mg/kg q4-6h

Build the structural model and population

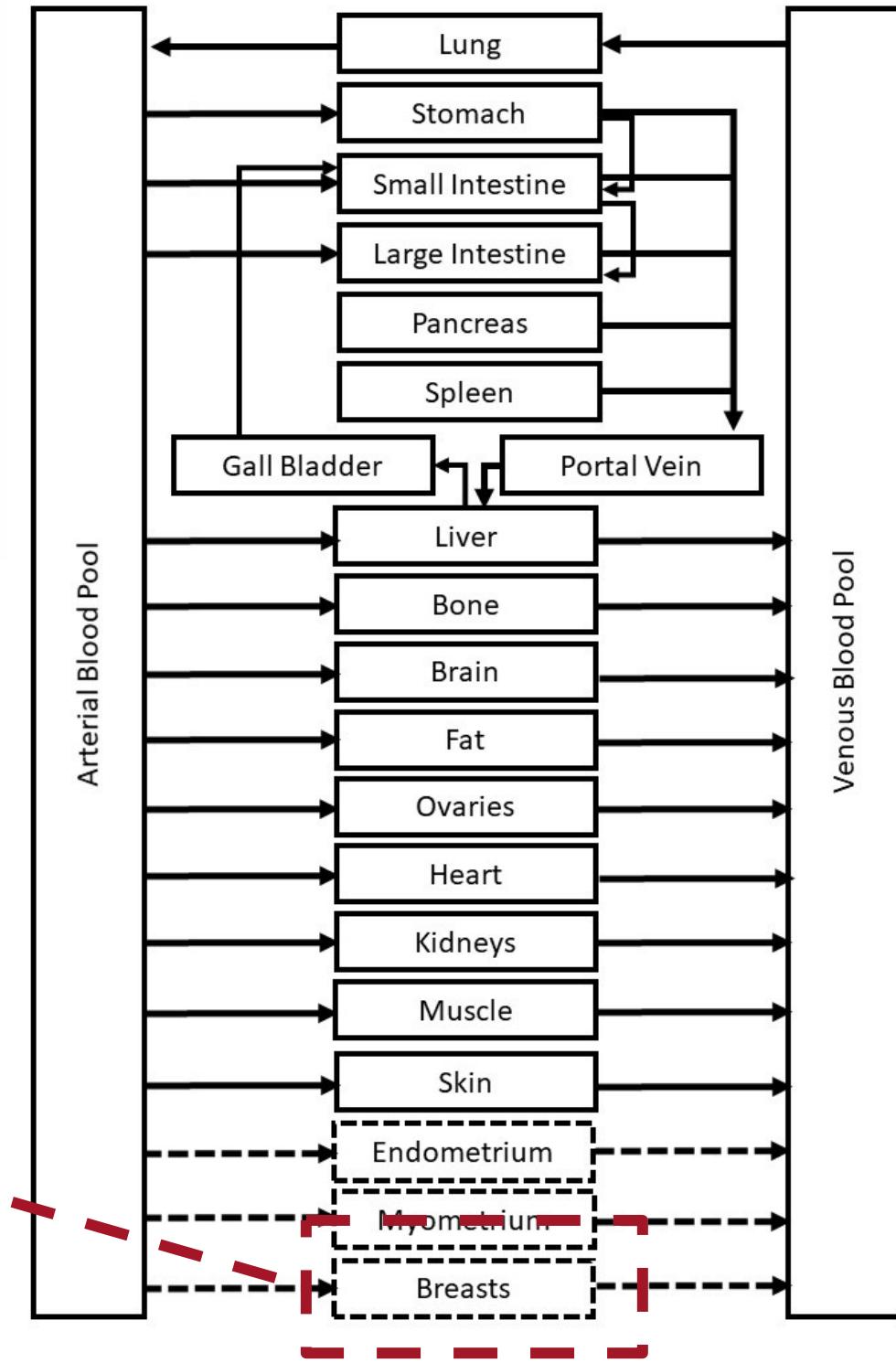
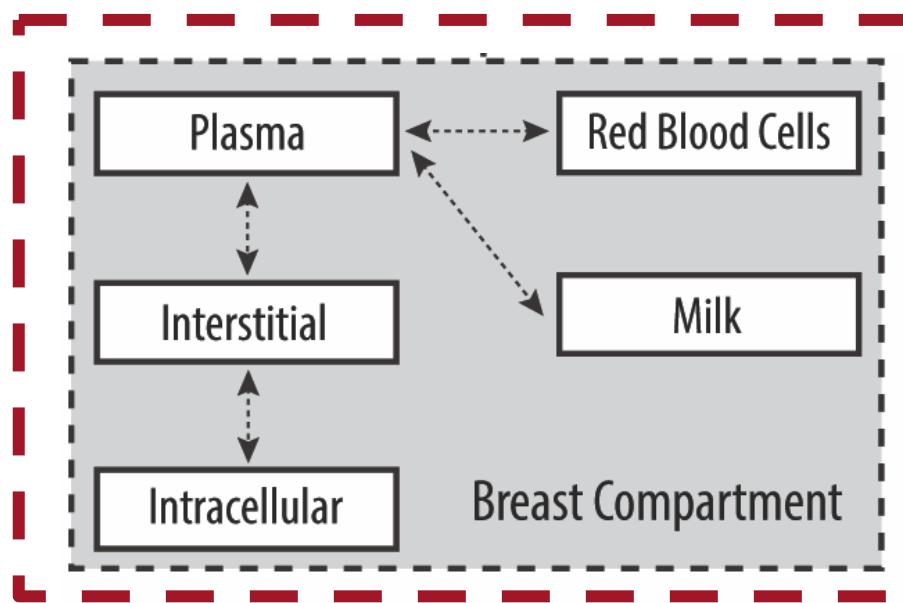


Develop lactation model for prediction



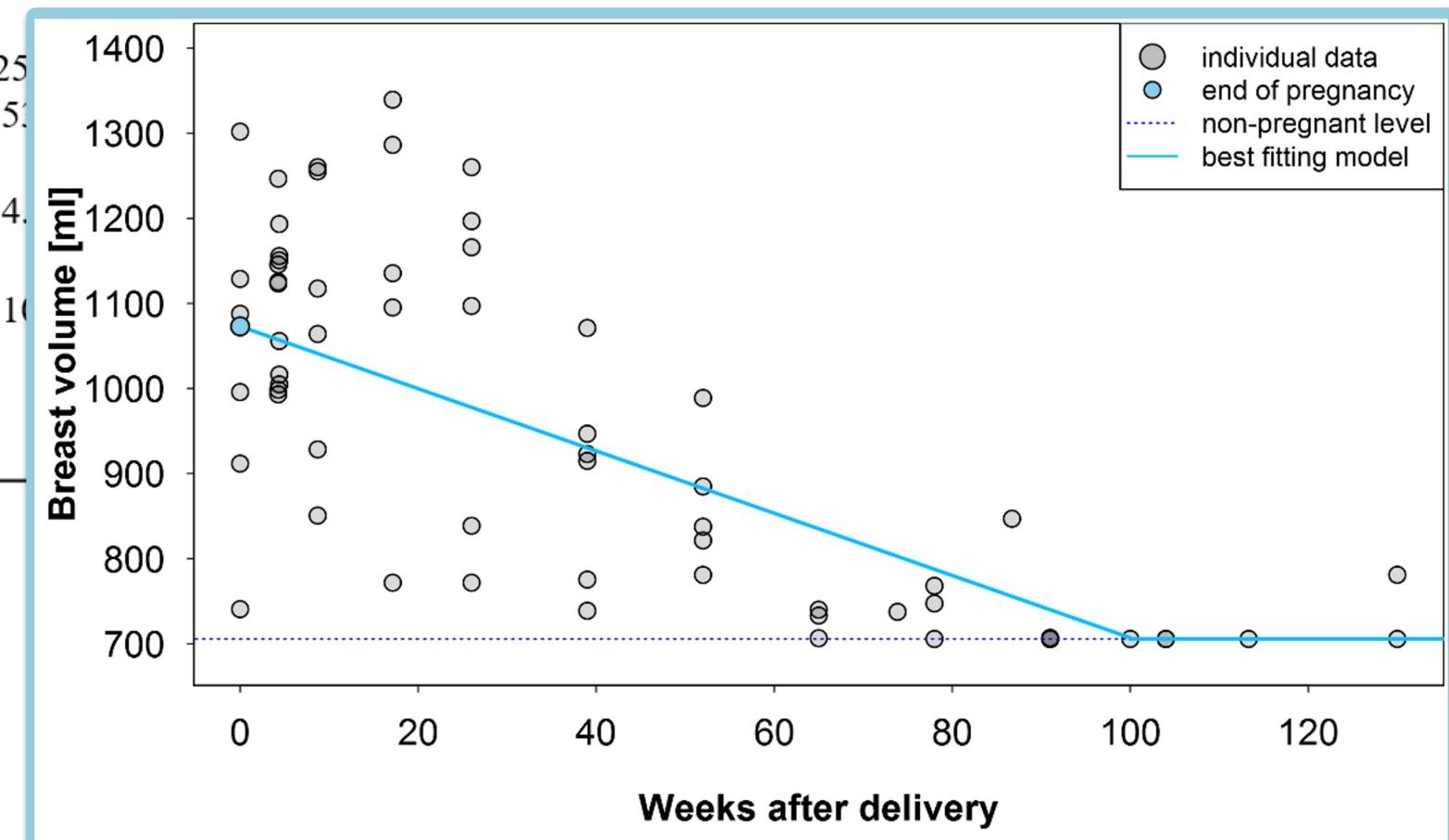
$$\frac{dN_{milk}}{dt} = P_{plasma \rightarrow milk} \cdot SA_{plasma, milk} \cdot f_u \cdot C_{plasma}$$

$$- P_{milk \rightarrow plasma} \cdot SA_{plasma, milk} \cdot f_u \cdot \frac{C_{milk}}{K_{milk: plasma}}$$



Create postpartum population

Parameters [Unit]	0 weeks	0.5 weeks	1 weeks	4 weeks
Volume [L]				
Breasts	1.07 +/- 1.74	1.07 +/- 1.74	1.07 +/- 1.74	1.06 +/- 1.74
Fat	24.4 +/- 1.5	24.1 +/- 1.5	23.7 +/- 1.5	22.1 +/- 1.5
Kidney	0.40 +/- 0.10	0.39 +/- 0.10	0.38 +/- 0.10	0.32 +/- 0.10
Arterial Blood Plasma	0.33 +/- 0.02	0.32 +/- 0.02	0.32 +/- 0.02	0.29 +/- 0.02
Venous Blood Plasma	1.00 +/- 0.04	0.98 +/- 0.04	0.96 +/- 0.04	0.86 +/- 0.04
Organ Blood Flows [L/min]				
Breasts	0.23 +/- 0.004	0.24 +/- 0.004	0.25	
Kidney	2.55 +/- 0.14	2.54 +/- 0.14	2.51	
Other Parameters				
Mean Body Weight [kg]	66.2 +/- 3.0	65.4 +/- 3.0	64.4	
GFR [mL/min]	0.11 +/- 0.03	0.11 +/- 0.03	0.10	
Protein Binding		0.99		
Scaling	1.00			
Hematocrit [%]	0.36	0.36		



Update SQL database

Screenshot of the SQLite Expert Professional 5.2 interface showing the 'tab_populations' table.

The left sidebar lists various tables, with 'VIEW_PARAMETER_DISTRIBUTIONS' highlighted in yellow.

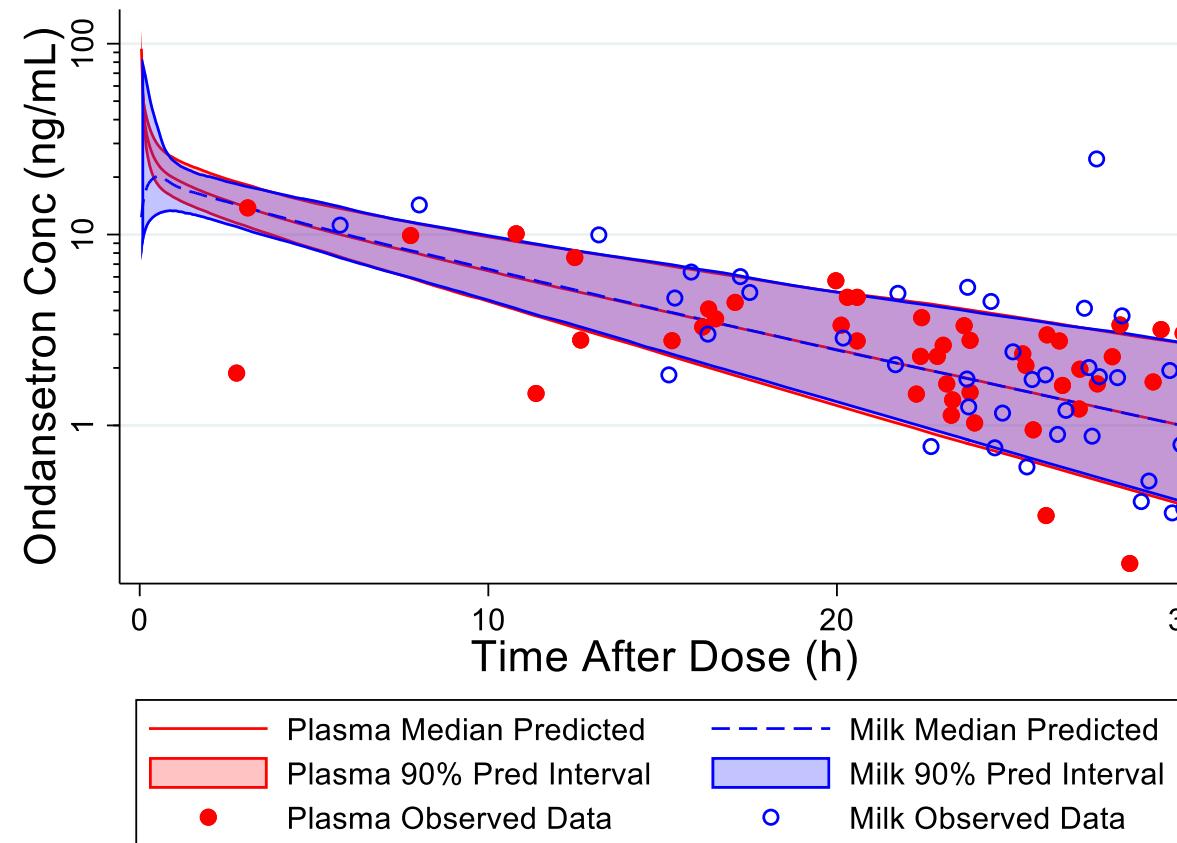
The main window displays the 'tab_populations' table data:

rowid	population	race_index	species	display_name
1	Asian_Tanaka_1996	4	Human	Asian (Tanaka, 1996)
2	Beagle	20	Beagle	Beagle
3	BlackAmerican_NHANES_1997	2	Human	Black American (NHANES, 1997)
4	Dog	23	Dog	Dog
5	European_ICRP_2002	0	Human	European (ICRP, 2002)
6	Japanese_Population	6	Human	Japanese (2015)
7	MexicanAmericanWhite_NHANES_1997	3	Human	Mexican American - White (NHANES, 1997)
8	Minipig	24	Minipig	Minipig
9	Monkey	25	Monkey	Monkey
10	Mouse	26	Mouse	Mouse
11	Pregnant	7	Human	Pregnant (Dallmann et al. 2017)
12	Preterm	5	Human	Preterm
13	Rabbit	28	Rabbit	Rabbit
14	Rat	27	Rat	Rat
15	WhiteAmerican_NHANES_1997	1	Human	White American (NHANES, 1997)
16	Postpartum	8	Human	Postpartum (Job et al. 2021)

Below the main table, a smaller preview table shows the first 16 rows of data.

- VIEW_OBSERVERS
- VIEW_OBSERVER_DESCRIPTOR_CONDITIONS
- VIEW_ONTOGENIES
- VIEW_ORGAN_TYPES
- VIEW_PARAMETERS_IN_CONTAINERS
- VIEW_PARAMETER DISTRIBUTIONS
- VIEW_PARAMETER_RATES
- VIEW_PARAMETER_RHS
- VIEW_PARAMETER_VALUES
- VIEW_PARAMETER_VALUE VERSIONS
- VIEW_POPULATIONS
- VIEW_POPULATION AGE
- VIEW_POPULATION_CONTAINERS

Run simulations and evaluate Final model



Development of a Generic Physiologically-Based Pharmacokinetic Model for Lactation and Prediction of Maternal and Infant Exposure to Ondansetron via Breast Milk

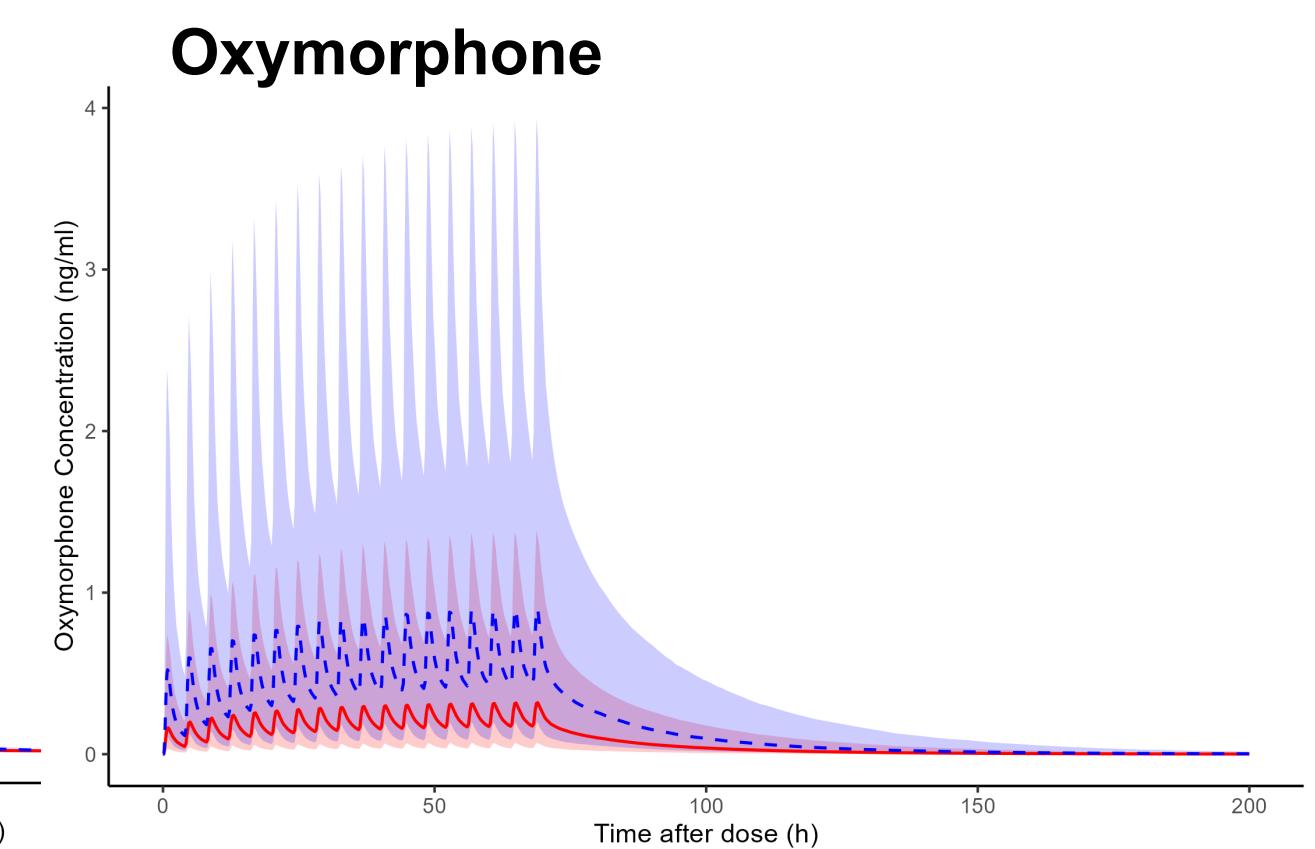
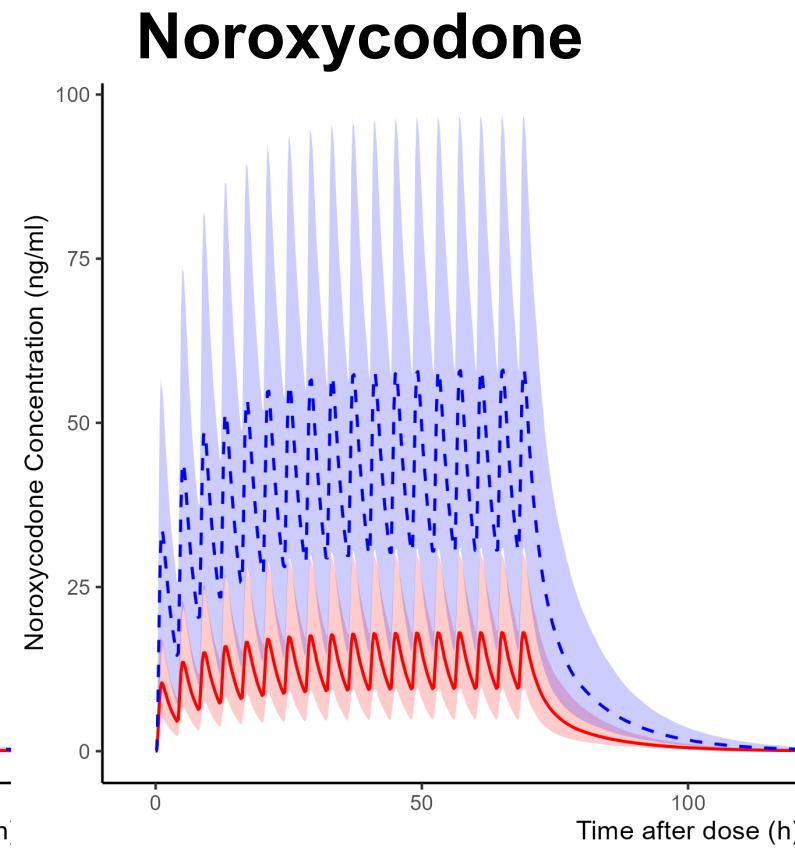
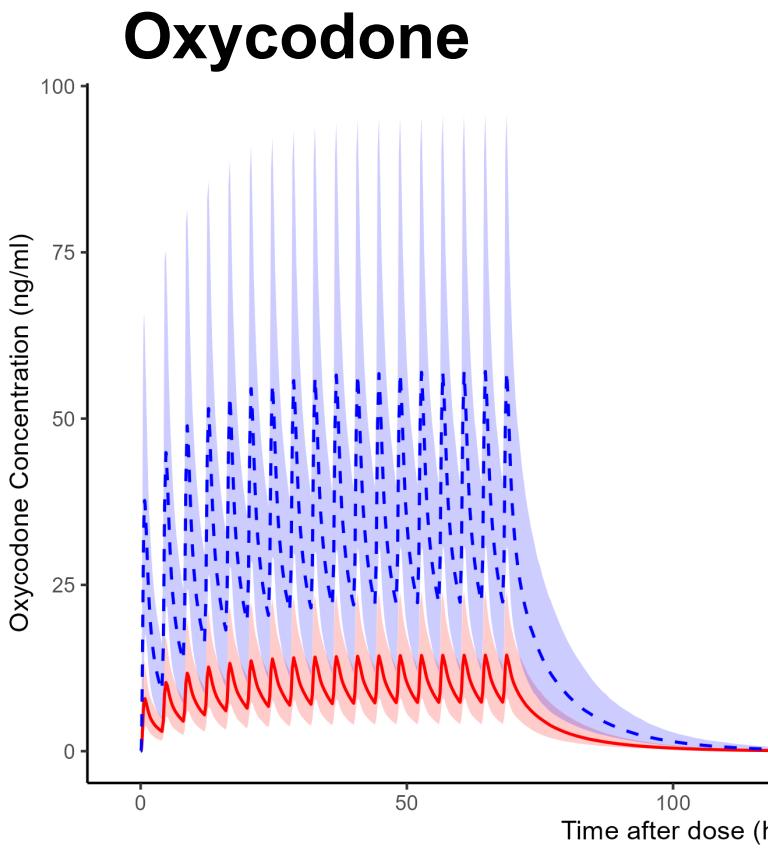
Kathleen M Job ¹, André Dallmann ², Samuel Parry ³, George Saade ⁴, David M Haas ⁵,
Brenna Hughes ⁶, Pamela Berens ⁷, Jia-Yu Chen ⁸, Christina Fu ⁸, Kelsey Humphrey ⁸,
Christoph Hornik ⁹, Stephen Balevic ⁹, Kanecia Zimmerman ⁹, Kevin Watt ¹

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Lactation model and postpartum population available on GitHub

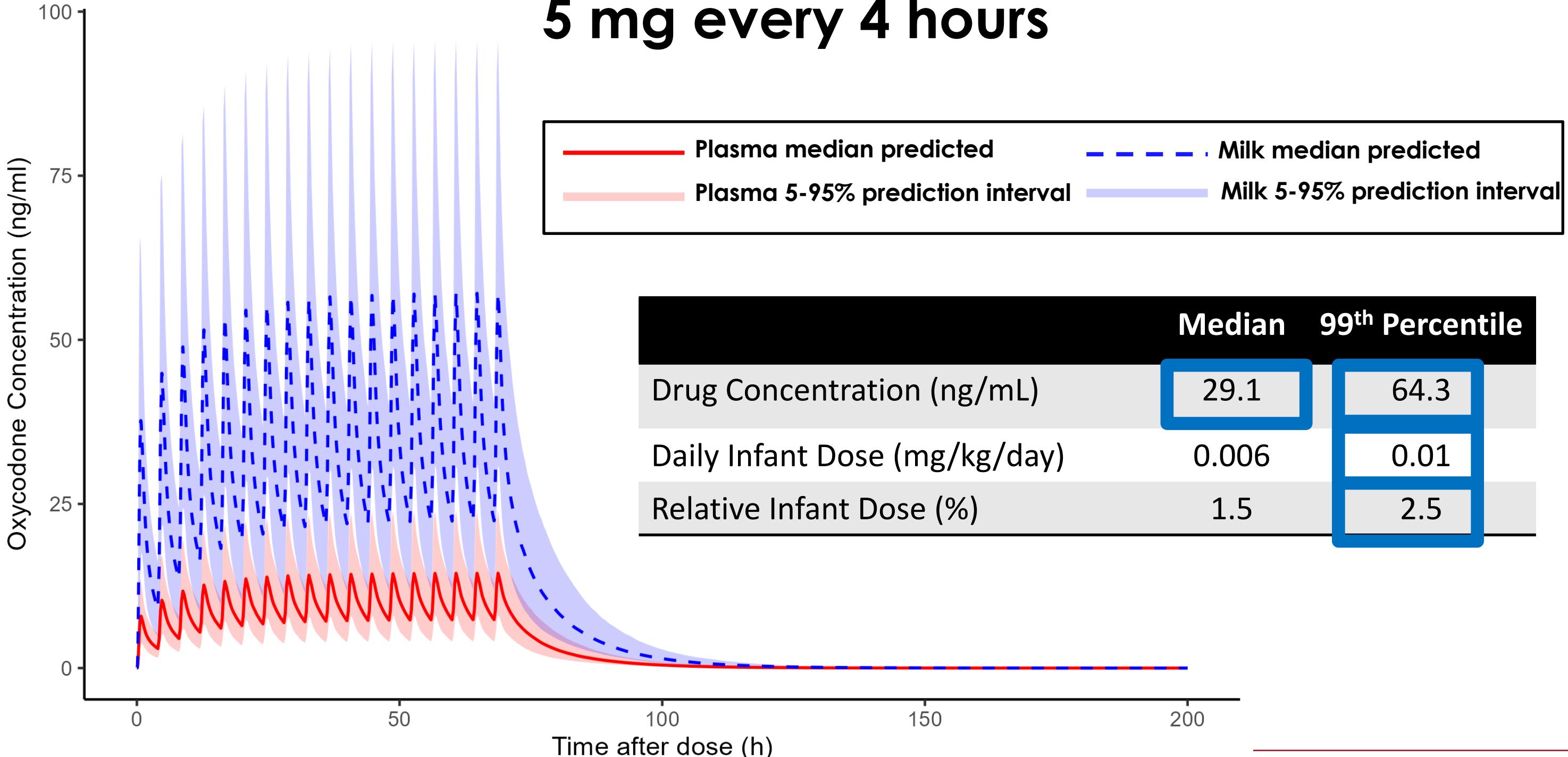
Oxycodone PBPK Model

Plasma median predicted **Milk median predicted**
Plasma 5-95% prediction interval **Milk 5-95% prediction interval**



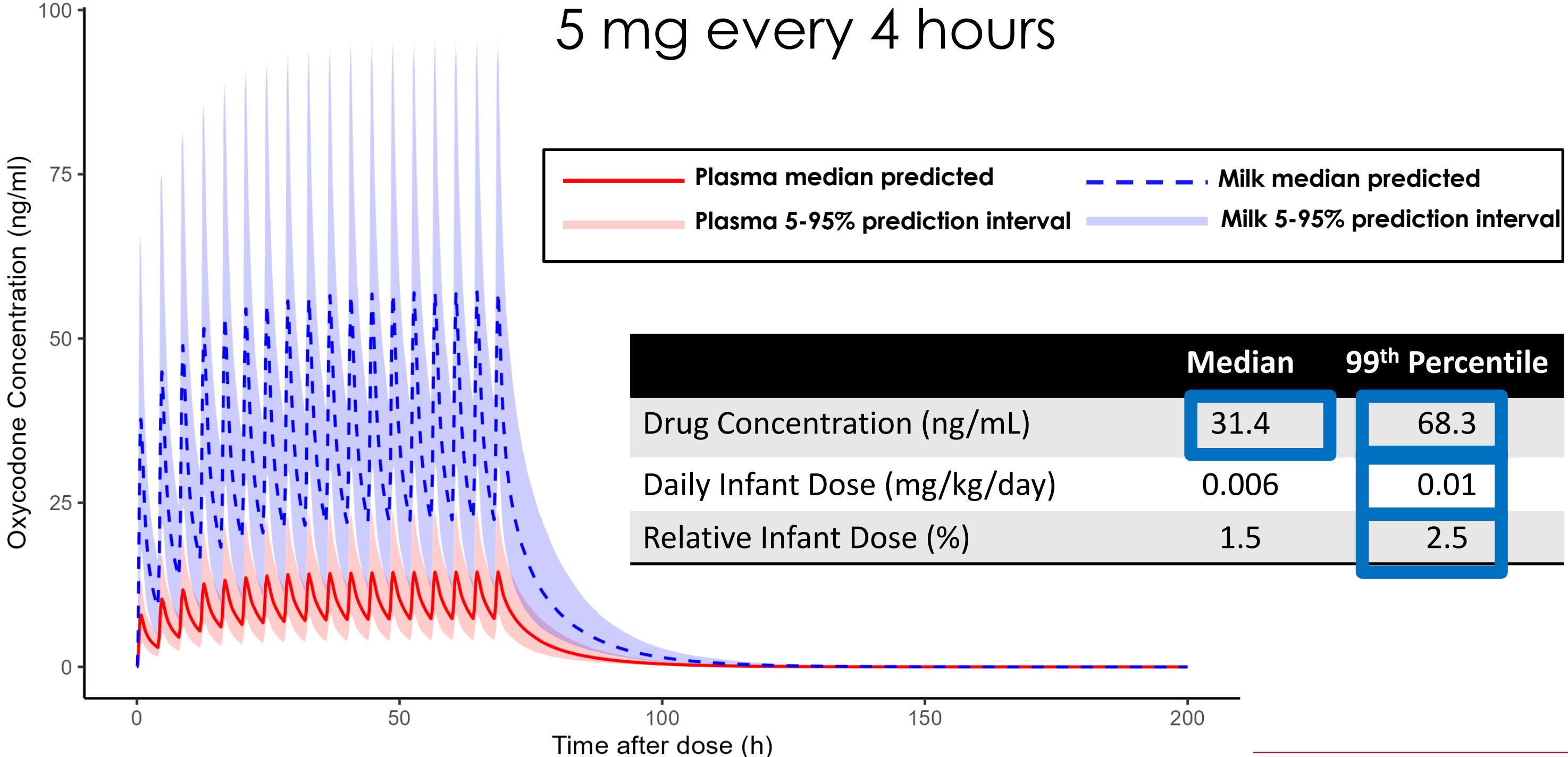
Oxycodone Exposure

5 mg every 4 hours



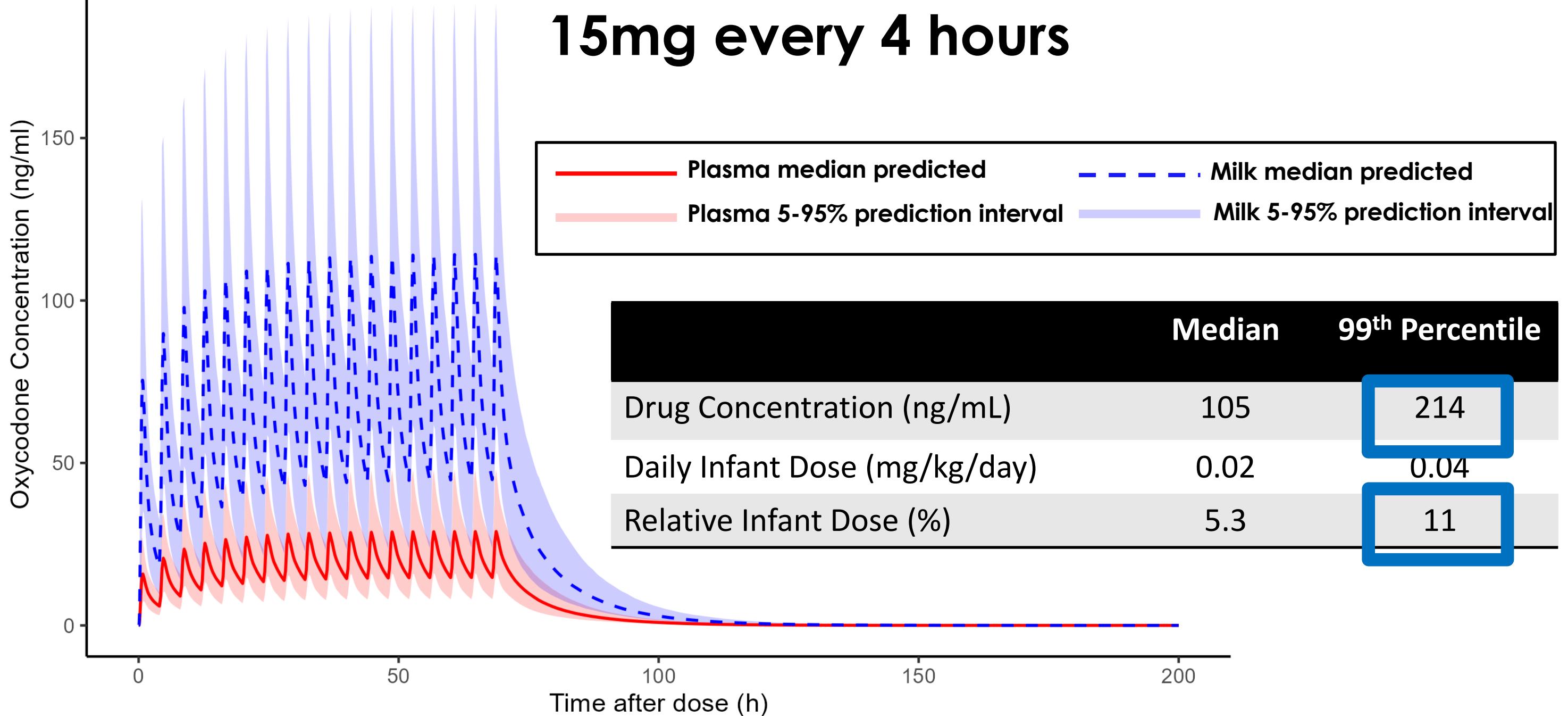
Oxycodone Exposure in Poor Metabolizer

5 mg every 4 hours



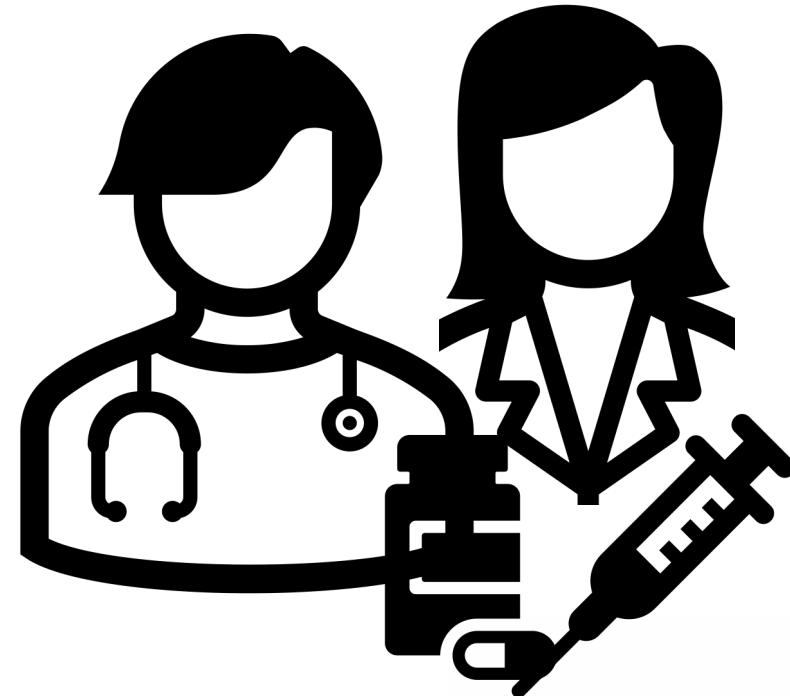
Oxycodone Exposure

15mg every 4 hours



Summary

1. There is a critical need to understand the extent of drug transfer to the fetus during pregnancy and baby during lactation
2. Quantifying exposure in pregnant and lactating populations is challenging, but creativity and flexible tools can help support drug decisions and labeling



Thank you to...

OSP Orga Committee

Pediatric Trials Network

Division of Clinical Pharmacology

- Kevin Watt, MD, PhD
- Rachel Hudson, PhD

...and many others!

Questions, Comments, Discussion

