

PBPK modeling to inform drug exposure in breastfeeding infants

Shinya Ito, MD

Hospital for Sick Children, Toronto,
CANADA

Disclosure

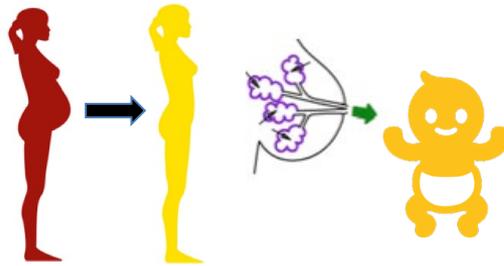
- Industry
 - AbbVie: Education material development
 - UCB: Education project grant
- Funding agency (Grant/Contract)
 - Canadian Institutes of Health Research
 - NIH

Highlights

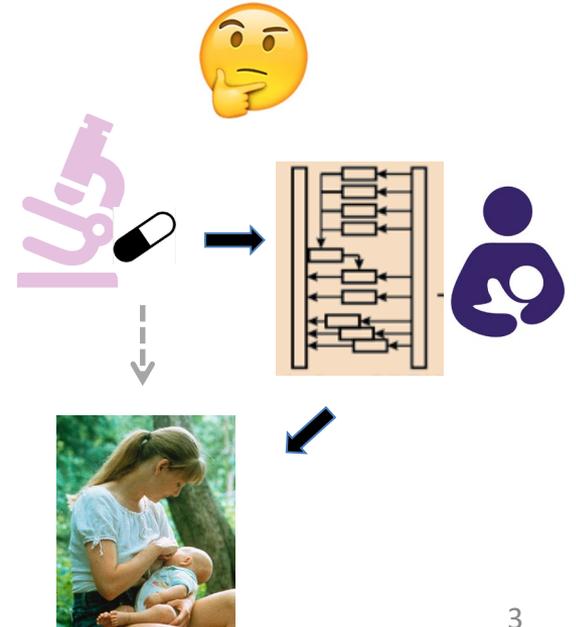
- Target population



- Issues prime for PBPK modeling



- Why PBPK may be the best?



Exclusive Breastfeeding is important
(even if the mother receives
medications).

BREASTFEEDING IS THE STANDARD

Cognitive function

Kramer et al. Arch Gen Psy 2008

Belfort et al. J Ped 2016



Cancer risks

Stuebe et al. Arch Int Med 2009

Infection risks

AAP. Pediatrics 2012

Gorlanova et al. J Ped 2016

Exclusive Breastfeeding

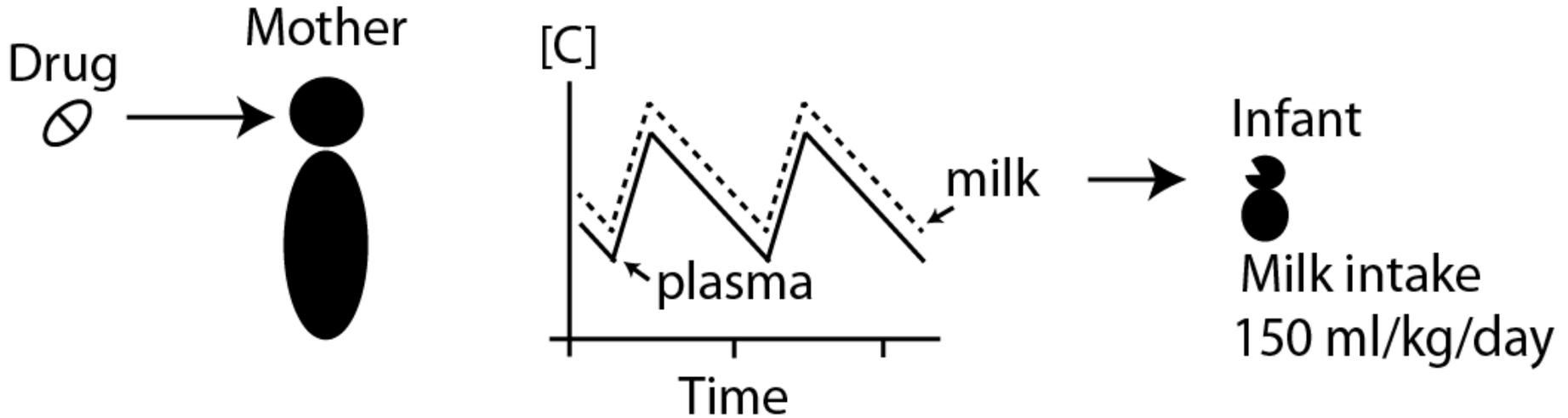
Many professional organizations recommend **exclusive breastfeeding for about 6 months**, with continuation of breastfeeding for 1 year or longer as mutually desired by mother and infant, a recommendation concurred to by the WHO and the Institute of Medicine.

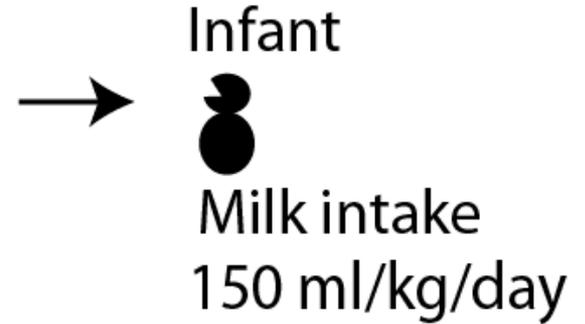
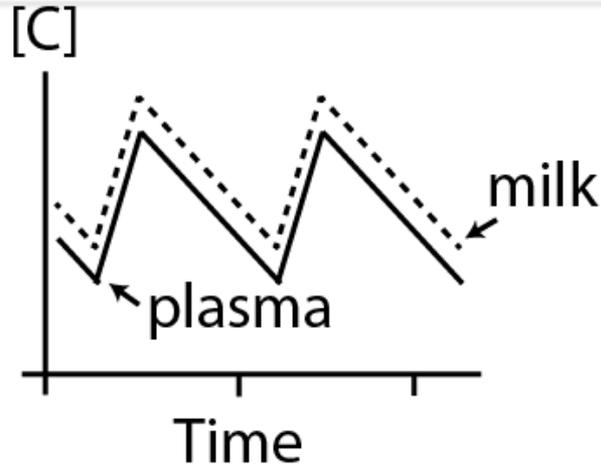
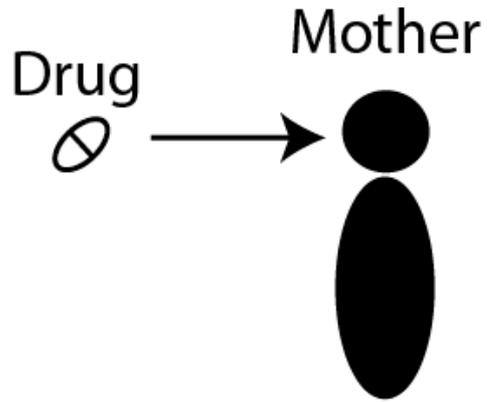
Policy statement: Breastfeeding and the use of human milk. Pediatrics 2012;129:e827–e841

Infant drug exposure through breast milk is relatively low in most cases.

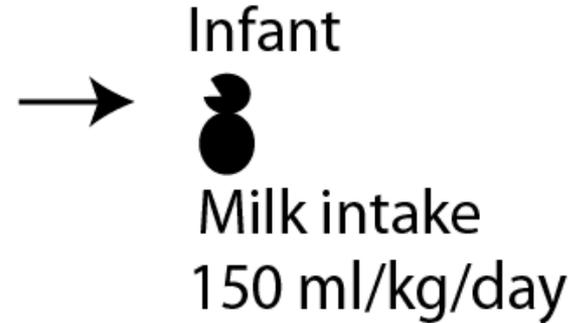
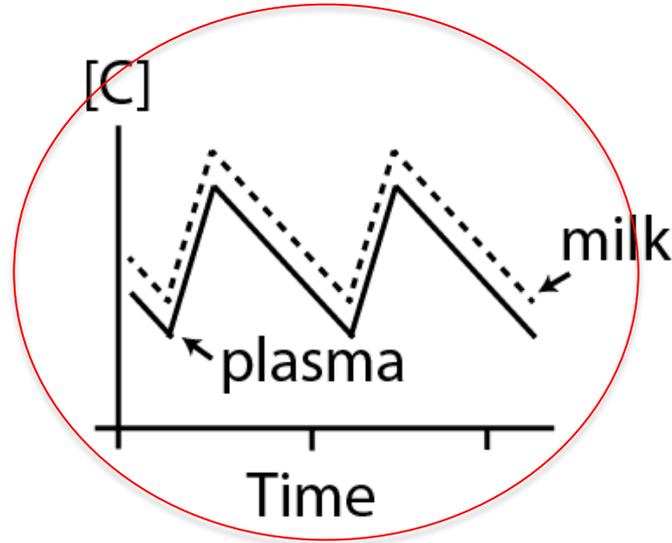
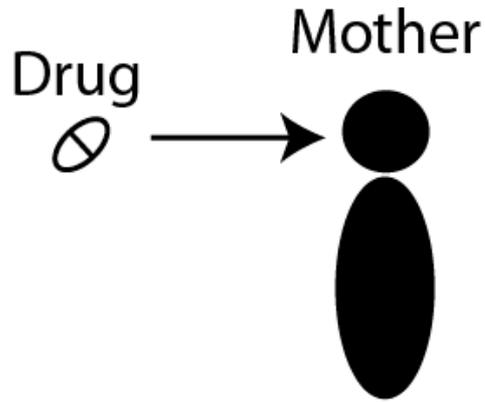
DRUG EXPOSURE OF BREASTFEEDING INFANTS

Drug Exposure of Breastfed Infants



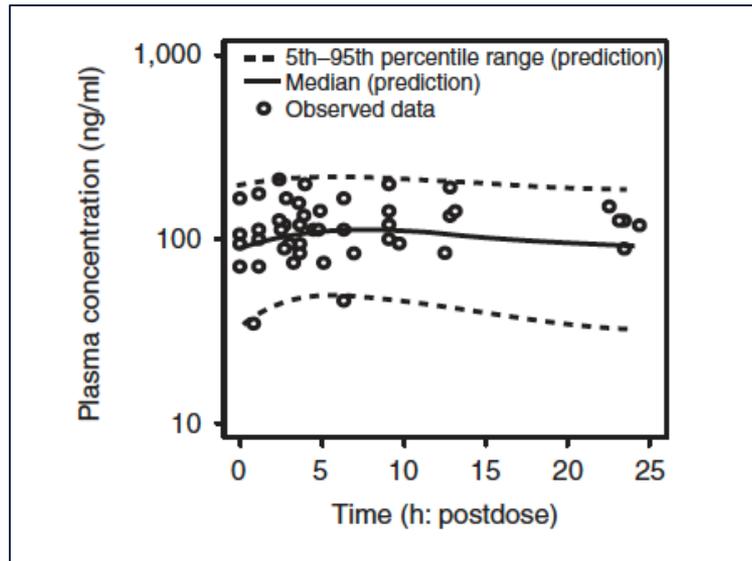


Drug Exposure of Breastfed Infants

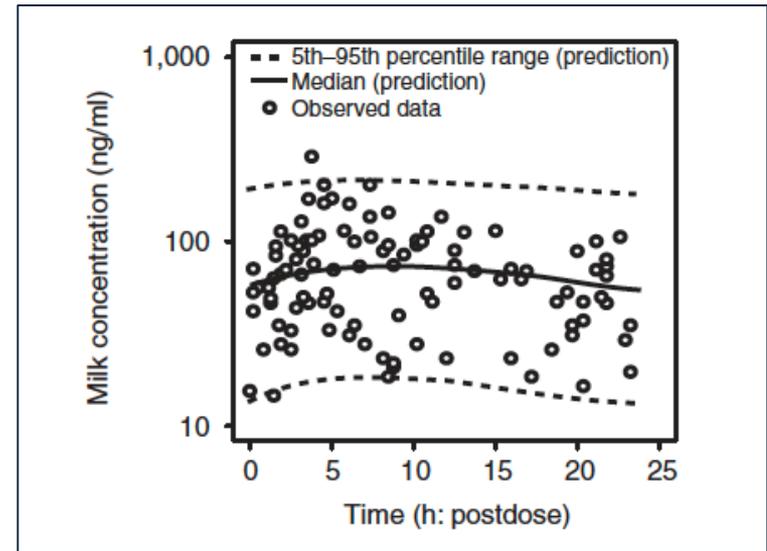


Plasma [C] vs. Milk [C]

Plasma fluoxetine

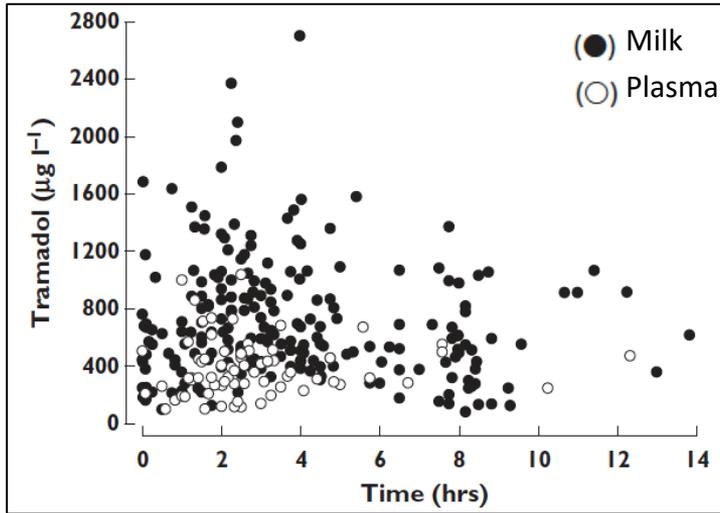


Milk fluoxetine



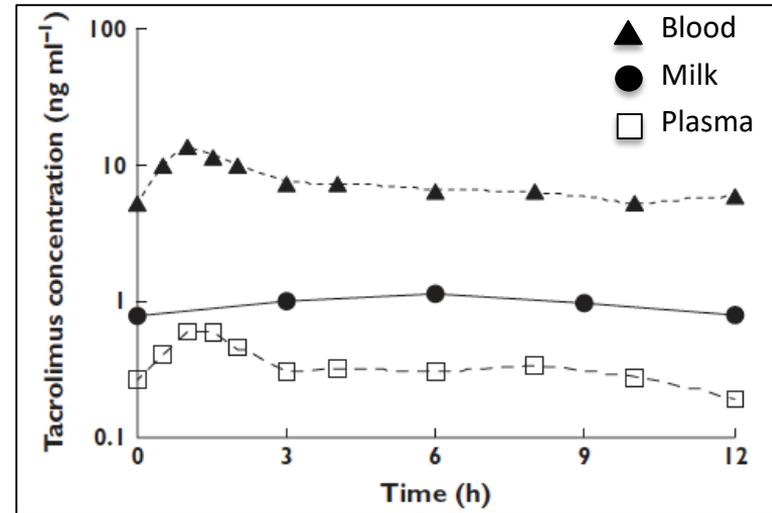
Plasma [C] vs. Milk [C]

Tramadol



Ilett et al. Br J Clin Pharmacol 2008

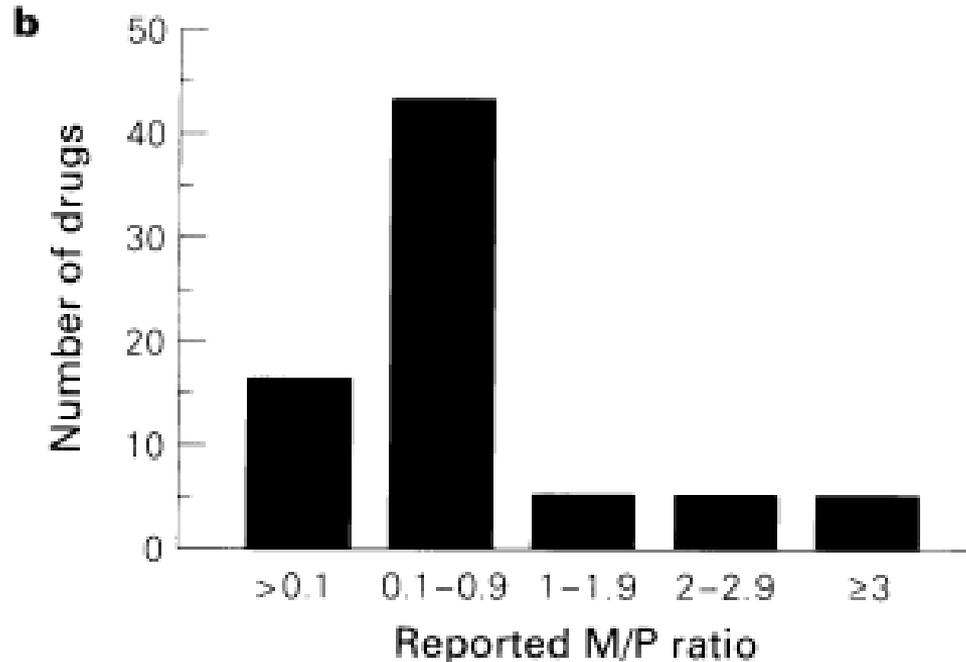
Tacrolimus



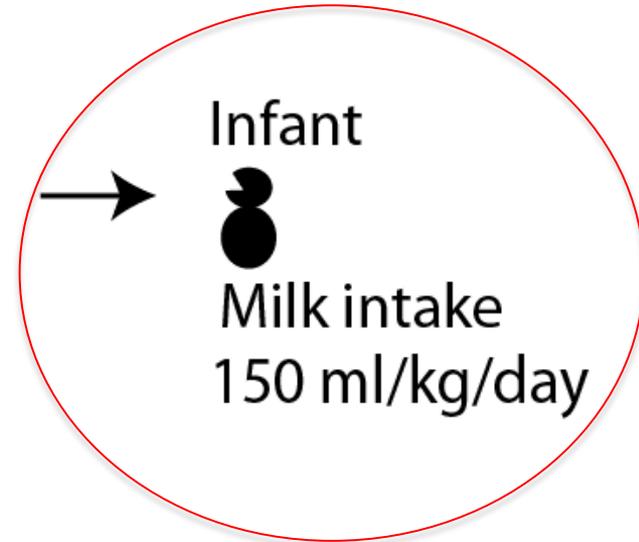
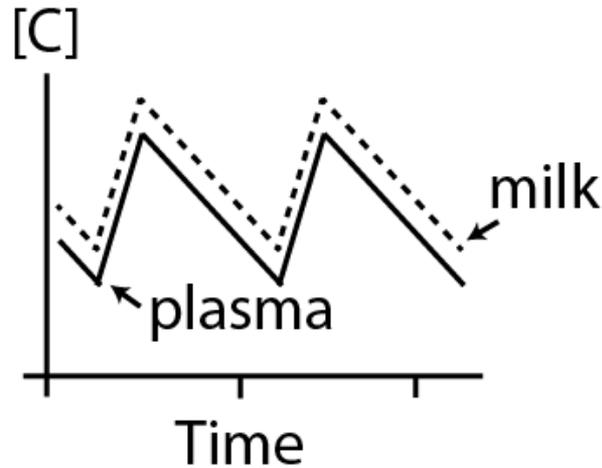
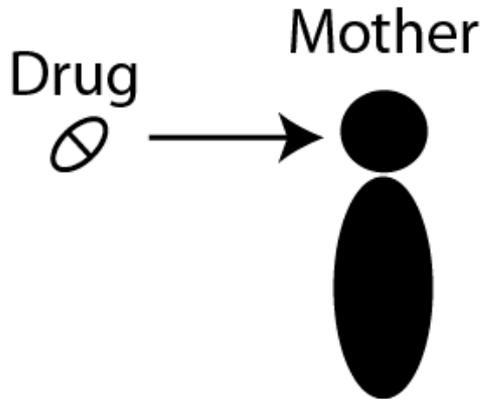
Zheng et al. Br J Clin Pharmacol 2013

MP (milk-to-plasma) ratio

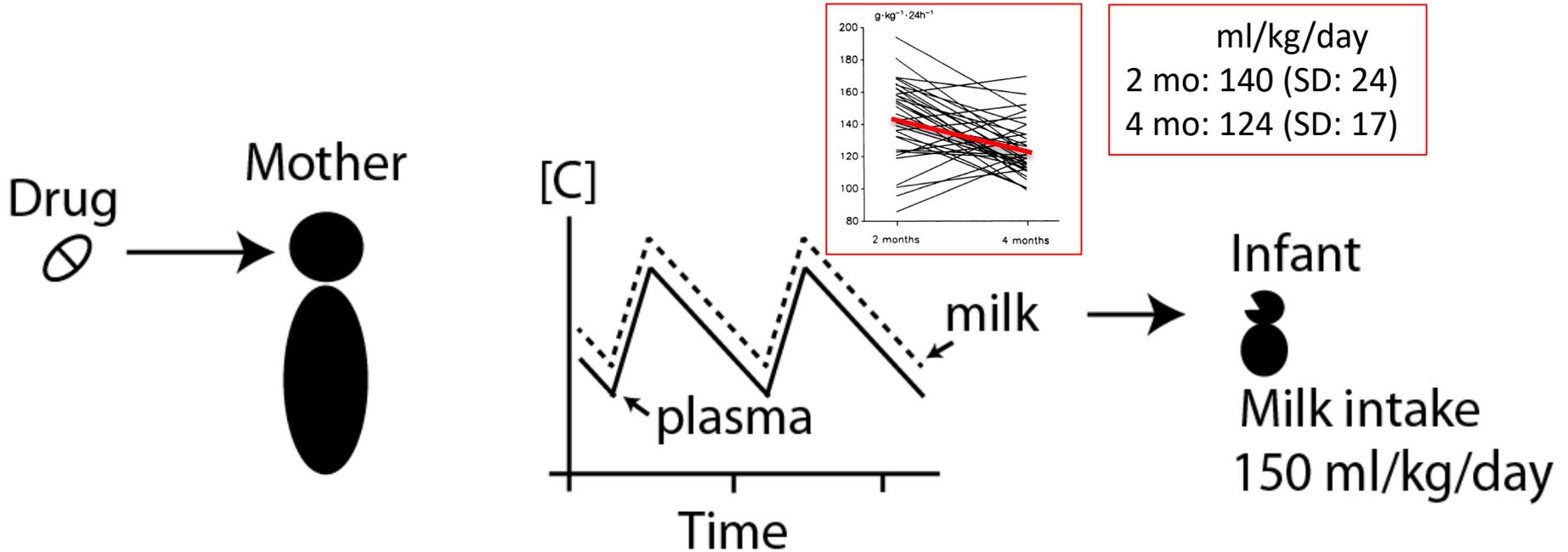
MP ratio of drugs is mostly 1 or lower



Drug Exposure of Breastfed Infants



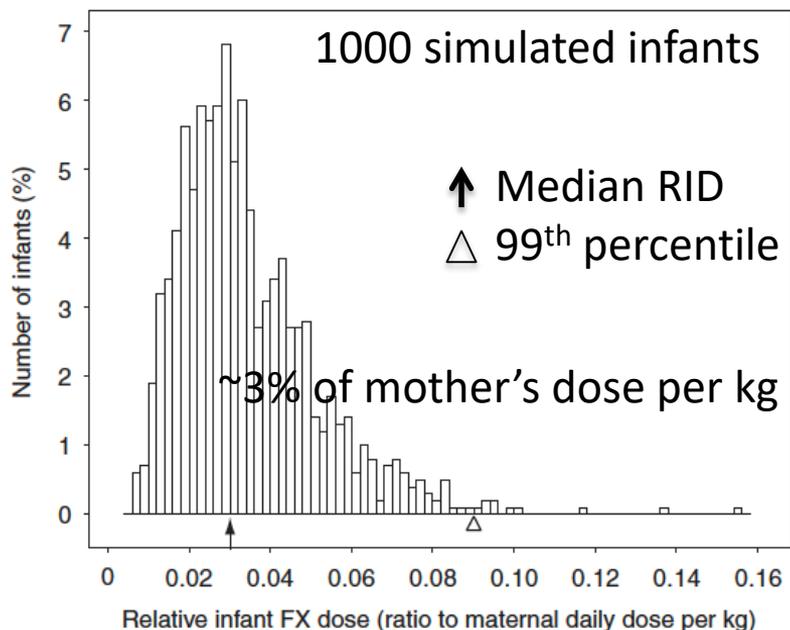
Drug Exposure of Breastfed Infants



Michaelsen et al. Am J Clin Nutr 1994

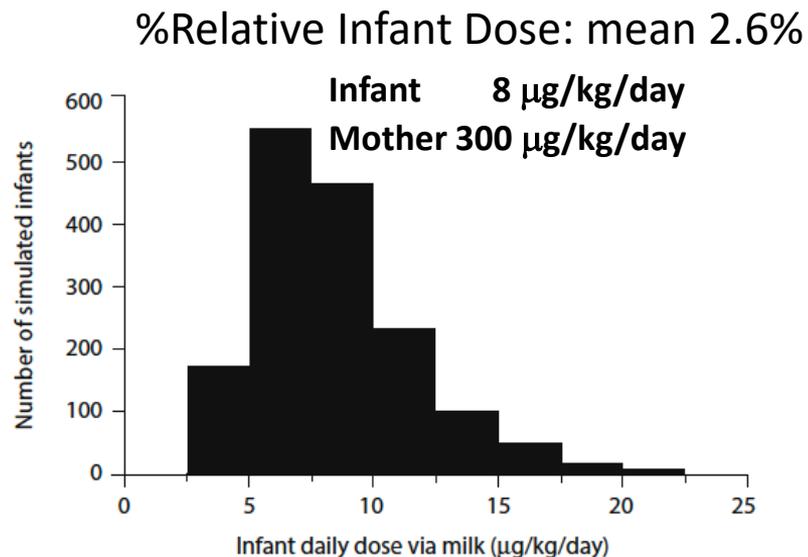
Infant Daily Dose via Milk

Fluoxetine



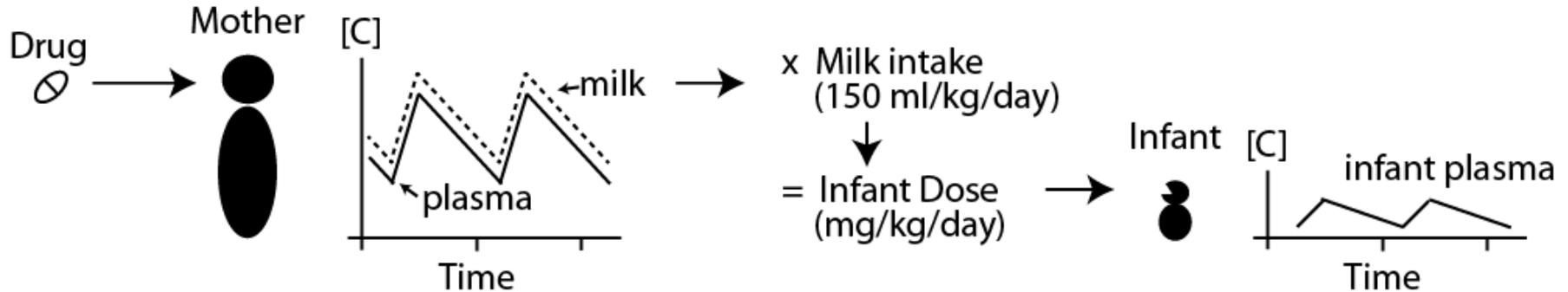
Panchaud et al. Clin Pharmacol Ther 2011

Escitalopram

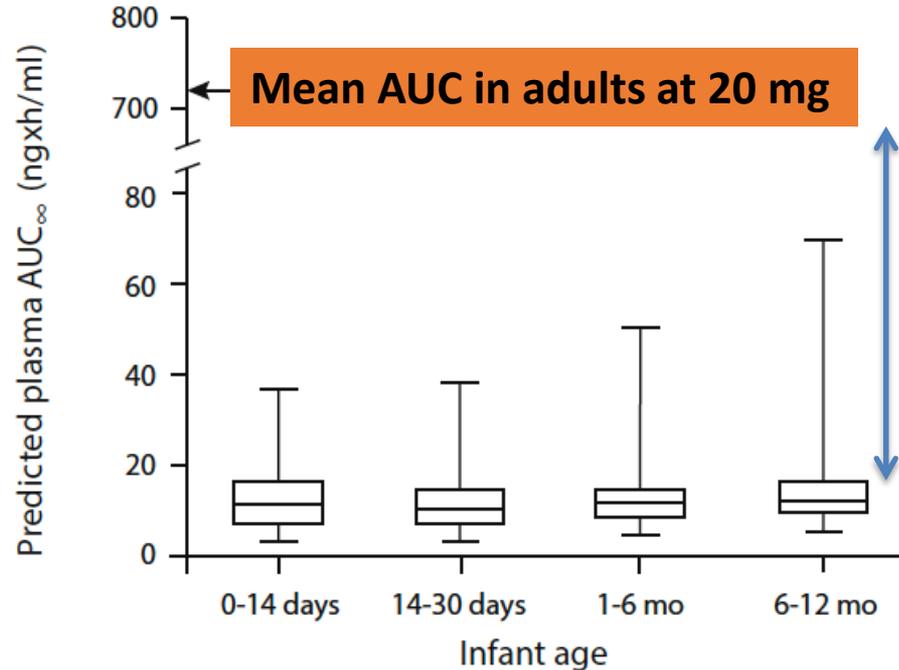


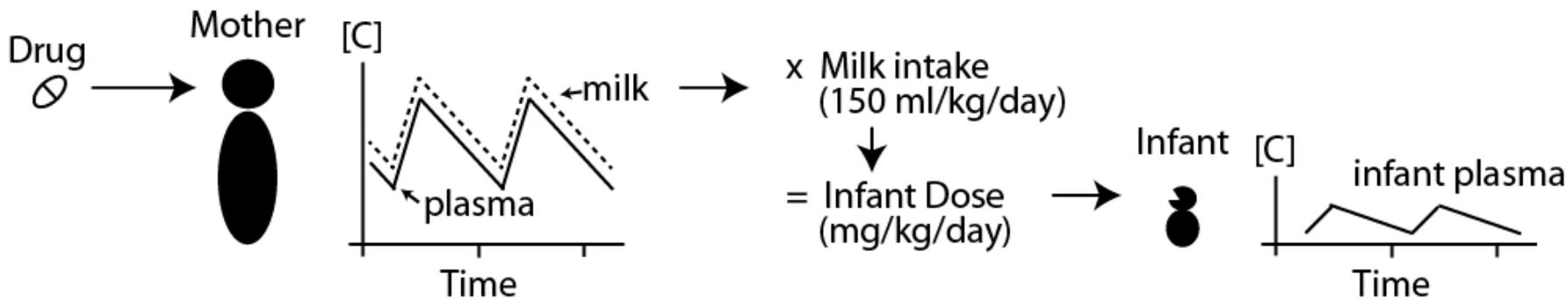
Delaney et al. Clin Pharmacokinetics 2018

Drug Exposure of Breastfed Infants



Infant Exposure: escitalopram





Milk/infant PK prediction must address “outliers”.

TOXICITY CASE: A STORY OF OUTLIERS

Toxicity case

- Mother: Tylenol #3 (codeine 30 mg + acetaminophen 500 mg) for 2 weeks postpartum.
 - 2 tabs Q12H: 1 tab Q12H from Day 2 on.
 - Somnolence and constipation
- A term healthy baby: breastfed
 - Poor feeding and lethargy Day 7 on
 - Dead at Day 13

Toxicity case: *cont'd*

- Stored milk samples: morphine 86 ng/ml
 - Typical milk morphine levels after repeated codeine (60 mg Q6H): 2-20 ng/ml

150 ml/kg/day x 100 ng/ml = 15 microgram/kg/day

(Neonate IV maintenance dose: 100 microgr/kg/day)

Toxicity case *cont'd*

- Stored milk samples: morphine 86 ng/ml
 - Typical mother treated with codeine (60 mg Q6H): 2-20 ng/ml

Mother: CYP2D6 UM

150 ml/kg/day \times 100 ng/ml = 15 microgram/kg/day

Infant: low CL?

(Neonate IV morphine dose: 200 microgr/kg/day)

Multiple study approaches exist.

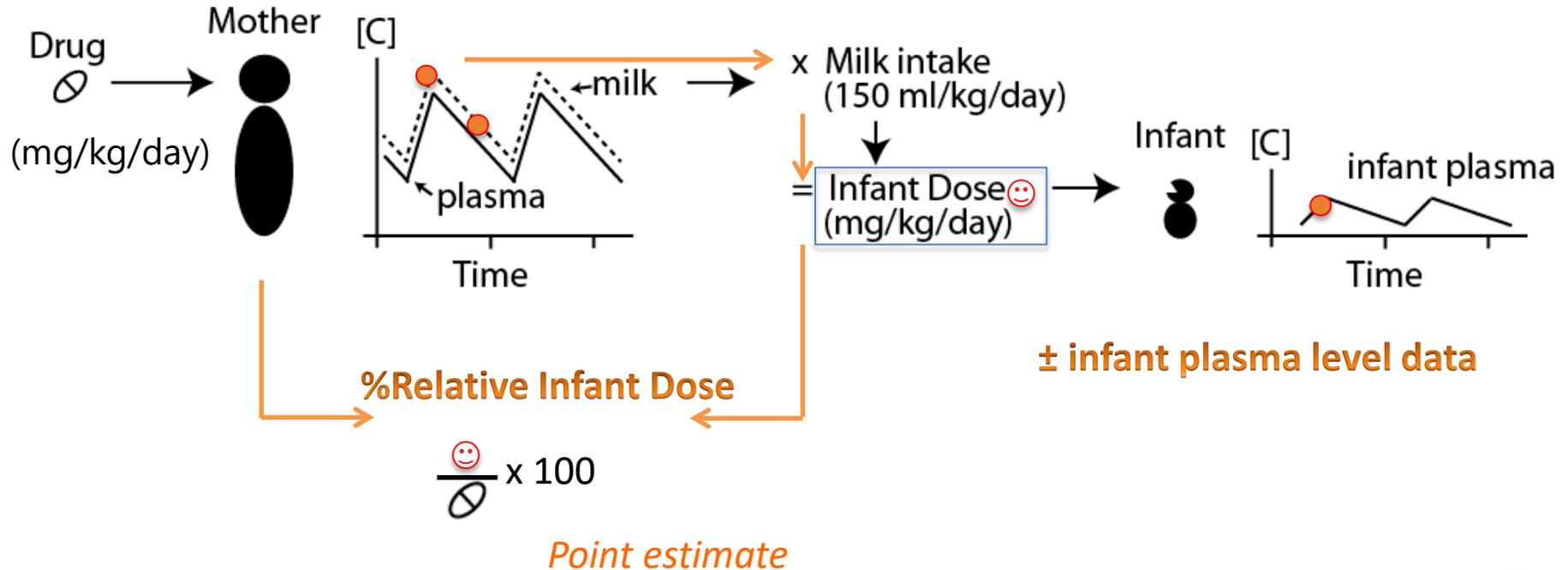
STUDY APPROACH

What information do we need?

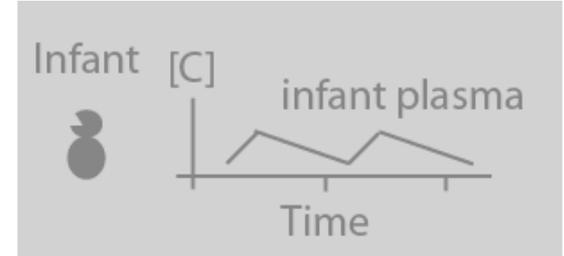
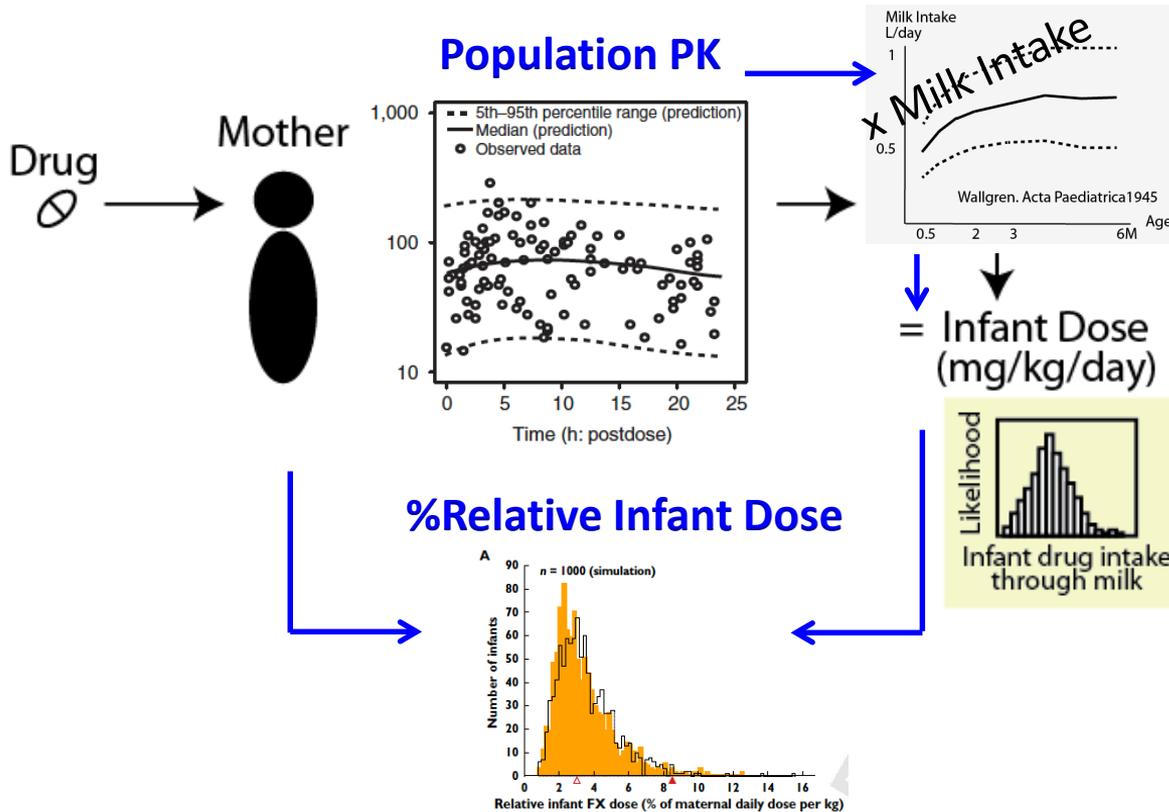
- Estimate of ***Infant Plasma [C]***: neonates
 - Its variation and probability (frequency)
- Toxicity risk factors
- For both
 - *marketed drugs*; and
 - *drugs under development*

Conventional study approach

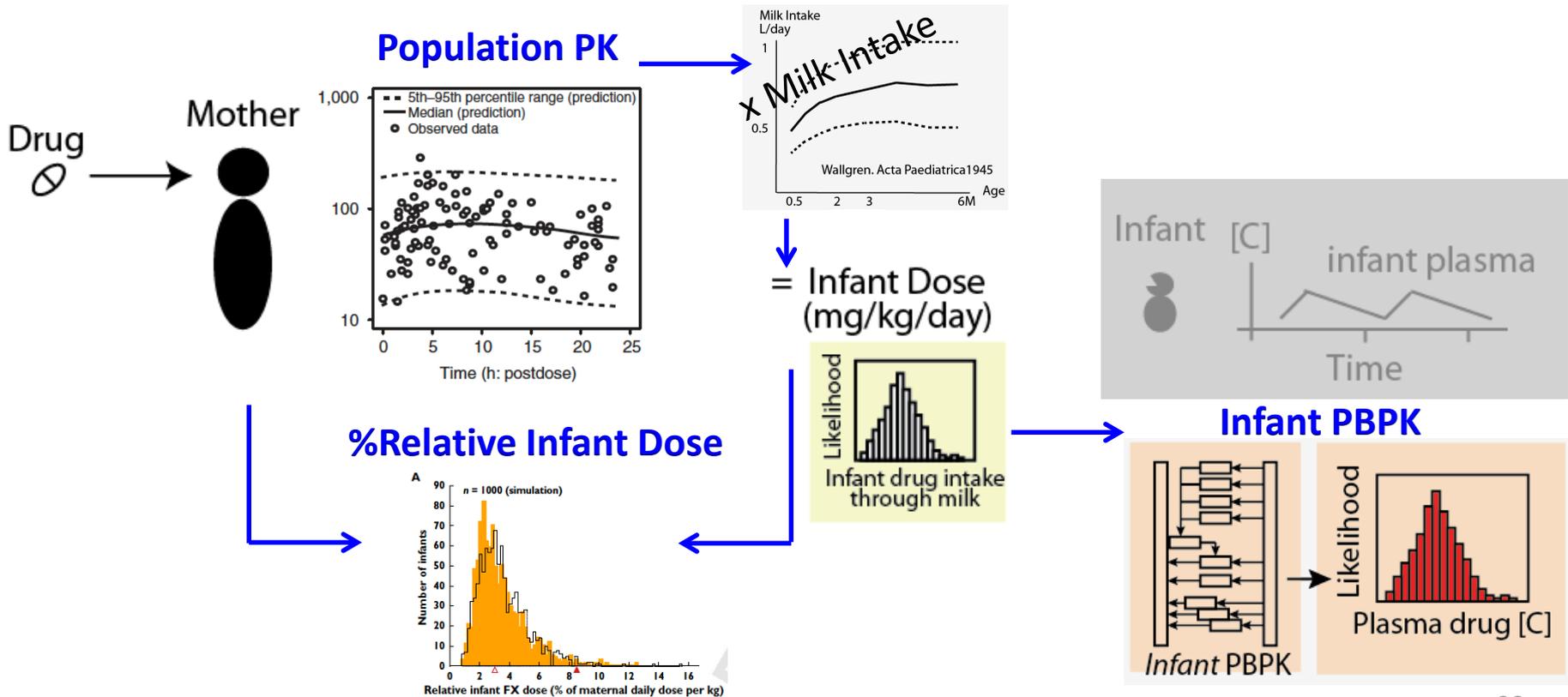
Case reports/series



1. Population PK modeling approach



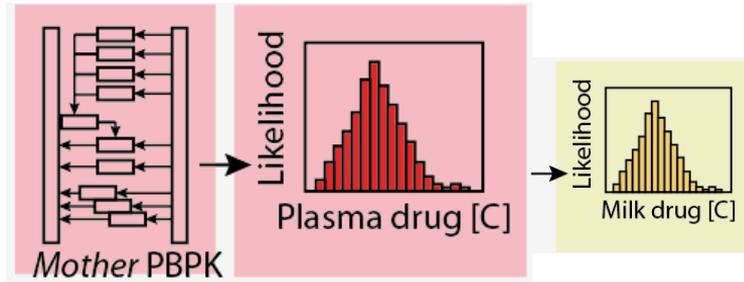
2. popPK – *inf* PBPK modeling approach



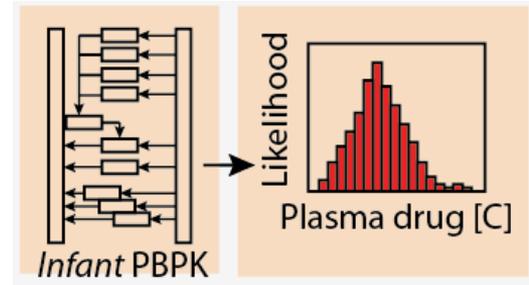
3. *MM-Infant* PBPK modeling approach



Mother-Milk PBPK



Infant PBPK

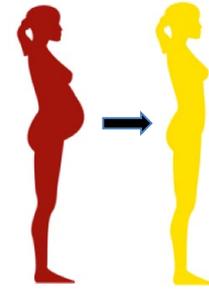


Challenges

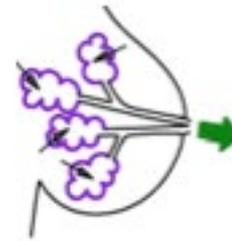
Mother-Milk PBPK

Pregnancy-Postpartum PK

Transition: ? *Time profiles*



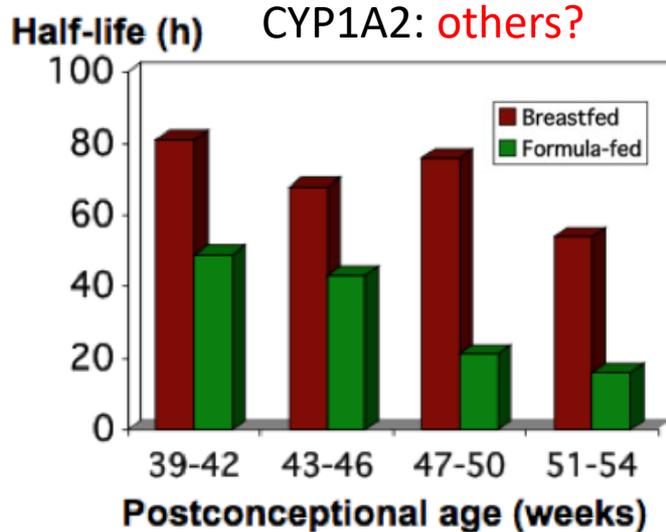
Plasma-milk drug transfer: ? *Drug transporters in the mammary gland*



Challenges

Infant PBPK

Feeding impact on PK



PGX profile development

