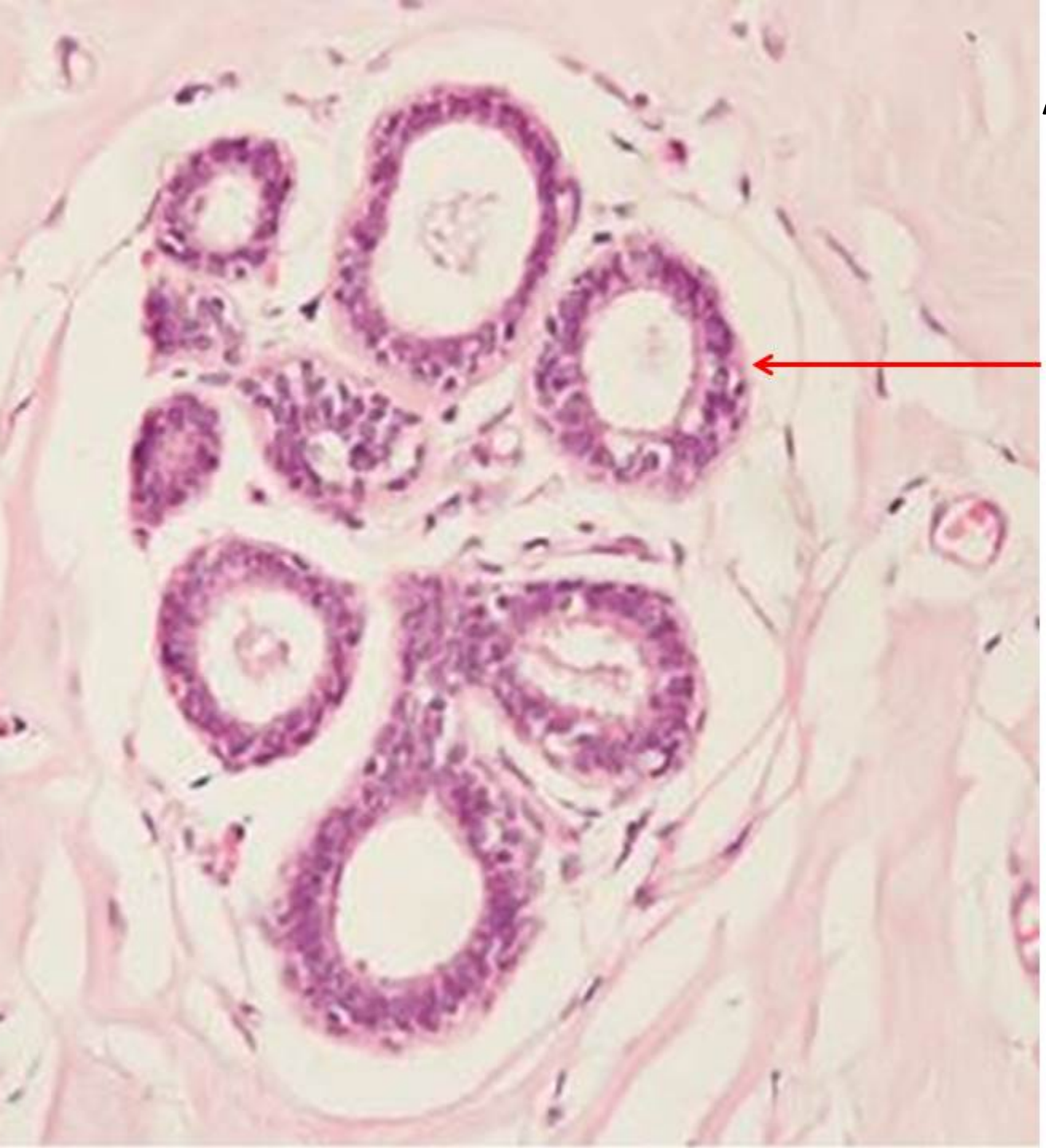
Modeling Drug Passage into Breastmilk

Philip O. Anderson, PharmD, FASHP
Health Sciences Clinical Professor
University of California San Diego
Skaggs School of Pharmacy & Pharmaceutical Sciences

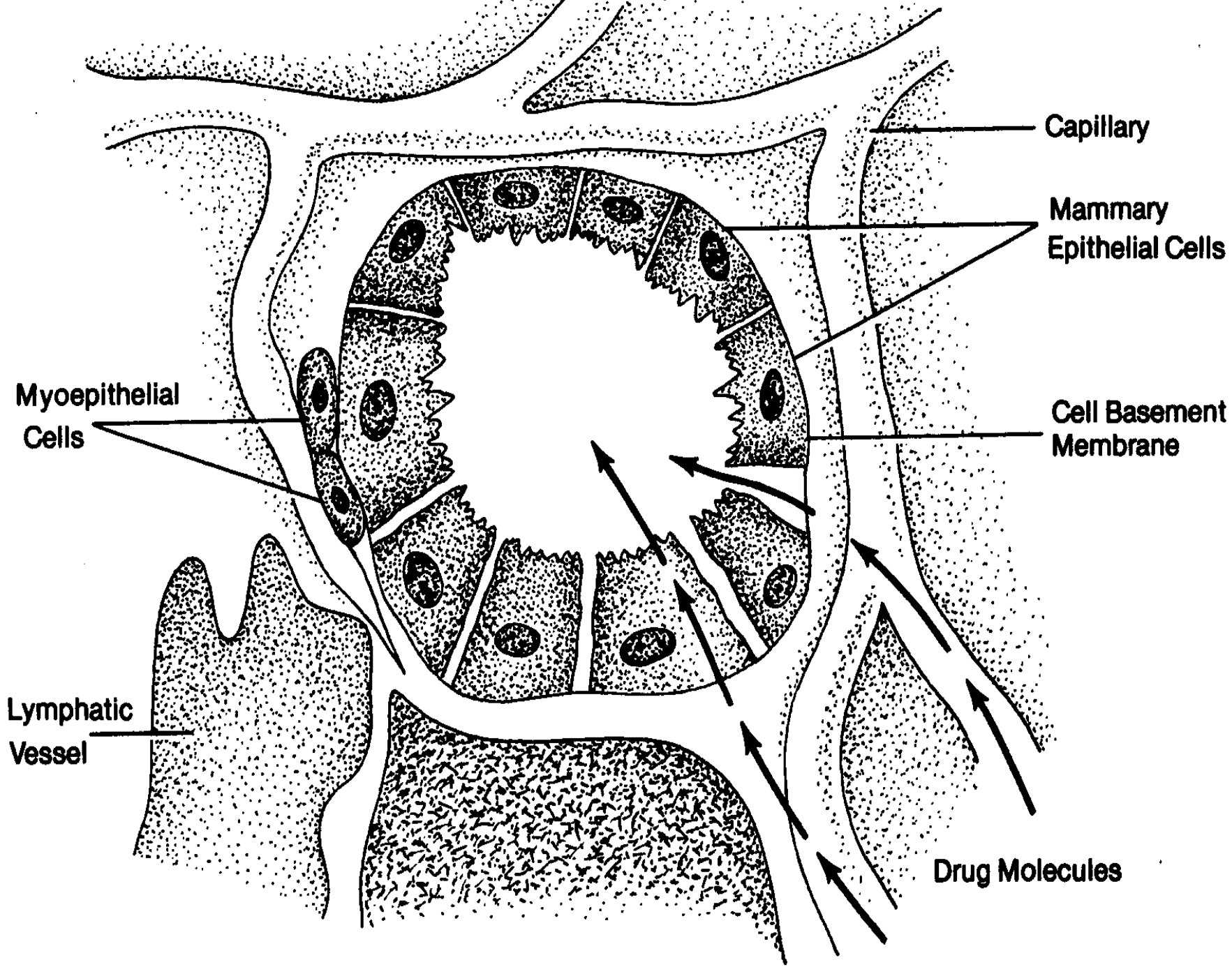
Based on Anderson PO, Sauberan JB. Modeling drug passage into human milk. Clin Pharmacol Ther July 2016: (in press)

The authors declare that they have no conflicts of interest.

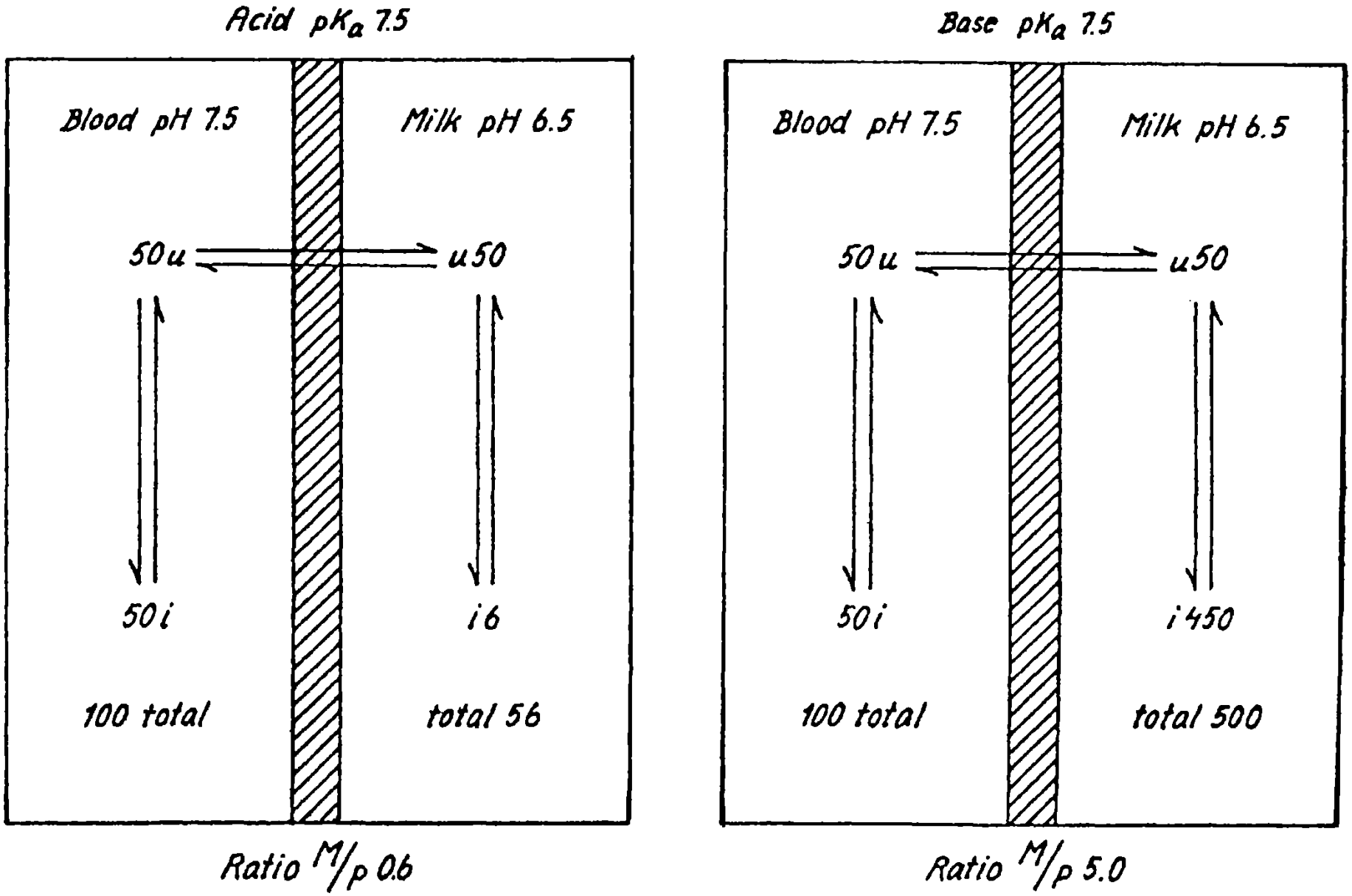
Alveoli in the Breast



Hassiotou F, Geddes D.
Clin Anat 2013;26:29-48.


Capillary
Mammary
Epithelial Cells
Myoepithelial
Cells
Cell Basement
Membrane
Lymphatic
Vessel
Drug Molecules

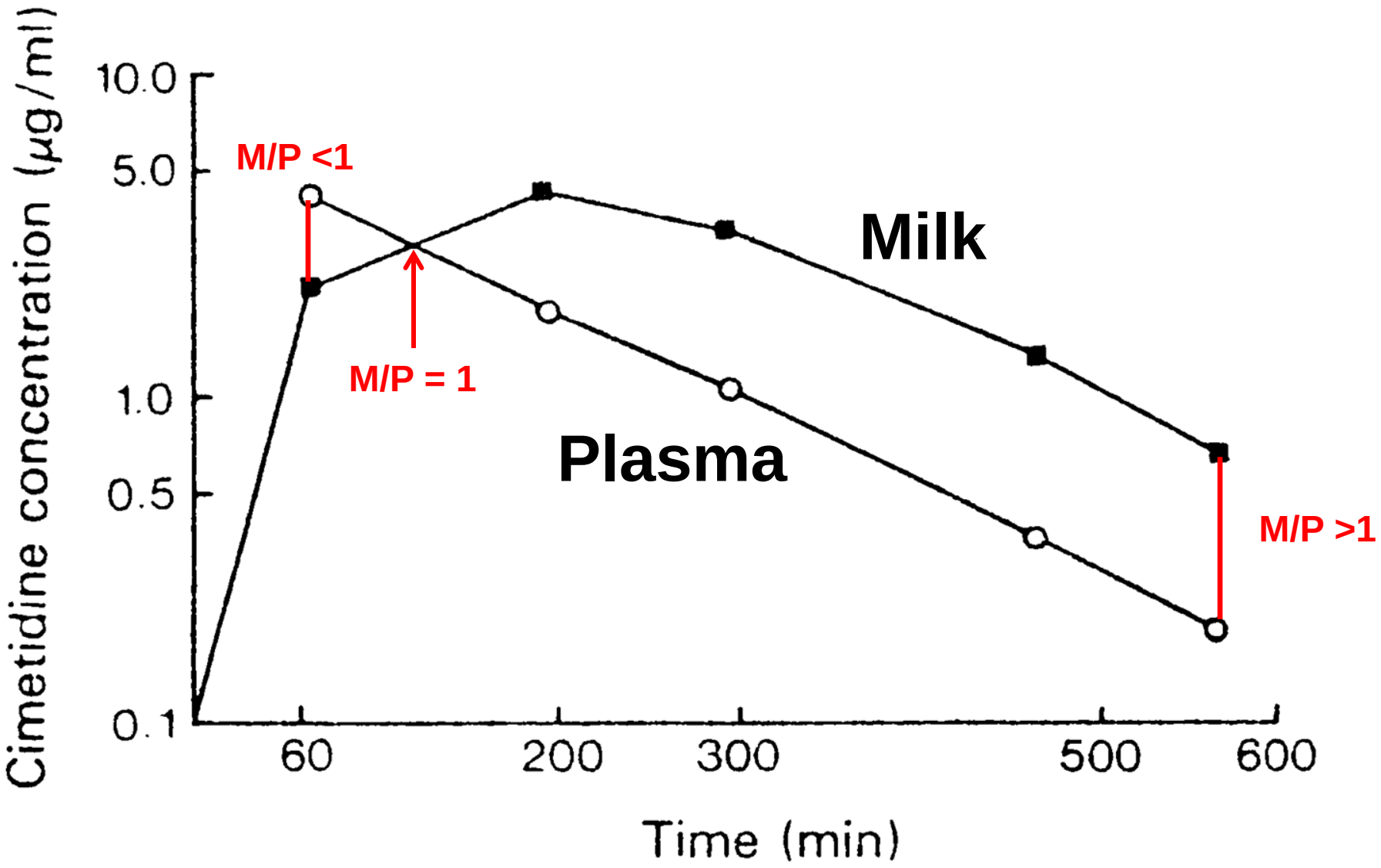
Ion Trapping



Rasmussen F. In, Brodie BB, Gillette JR, eds. Concepts in biochemical pharmacology. New York: Springer-Verlag 1971:390-402.

The Milk to Plasma (M/P) Ratio and Relative Infant Dose (RID)

Cimetidine 400 mg Orally



Somogyi A, Gugler R. Br J Clin Pharmacol 1979;7:627-9.

Dosage Calculation

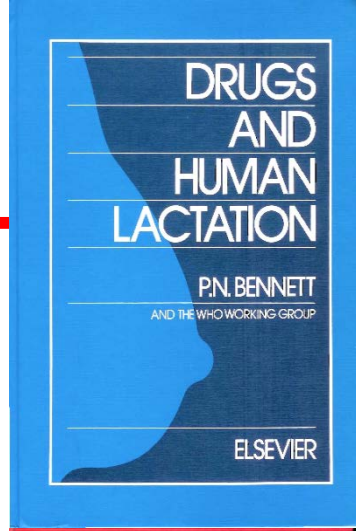
Infant's Daily Dosage = M/P x Maternal Serum Concentration x Milk Volume

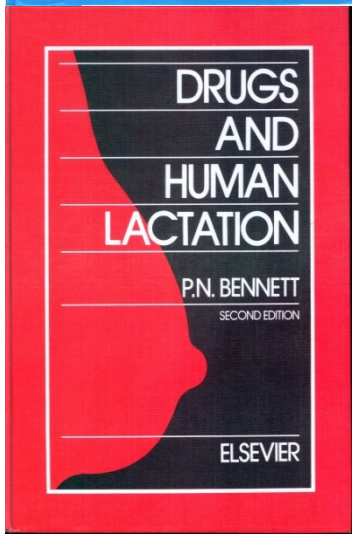
Average Milk Volume = 150 mL/kg/day
(fully breastfed)

Weight-Adjusted % Maternal Dosage or Relative Infant Dosage (RID)

$$RID = \frac{\text{Infant's daily dosage (mg/kg)}}{\text{Mother's daily dosage (mg/kg)}} \times 100$$

RID Classification System





- **Acceptable**
  - < 10% of maternal dosage
- **Caution**
  - 10% to 25% of maternal dosage
- **Unacceptable**
  - >25% of maternal dosage
  - inherent toxicity (eg, cytotoxics)
  - credible reported toxicity

Bennett PN ed. Drugs and human lactation. Elsevier 1988 & 1996.

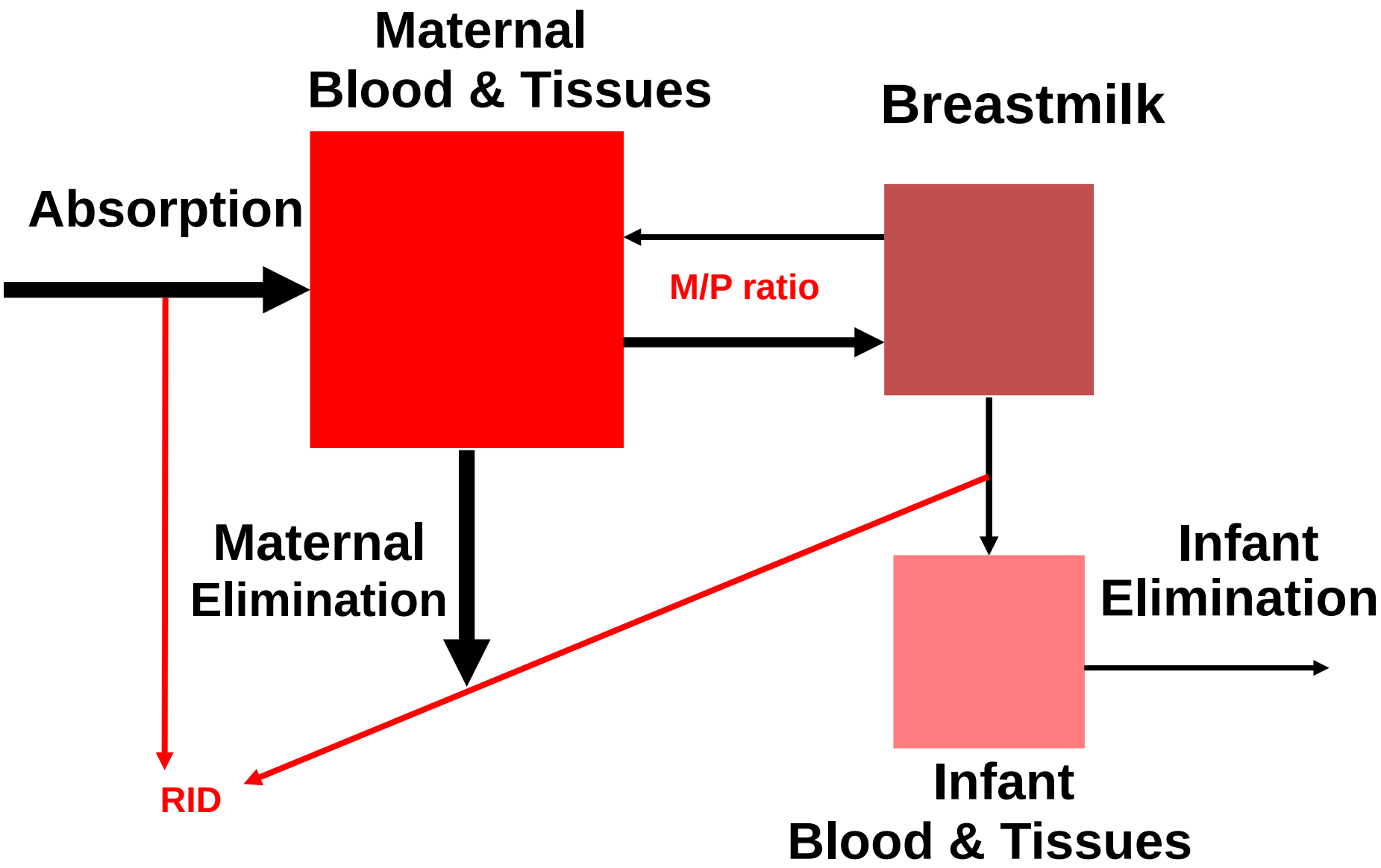
RID for 205 Drugs

Relative Dosage*	Percentage of Drugs		Adverse Reactions (%)
< 1%	47%		0%
1-4.9%	28%	87%	2%
5-9.9%	12%		8%
10-24.9%	10%		19%
> 25%	3%		100%

***Wt. adjusted**

Bennett PN, Notarianni LJ. Br J Clin Pharmacol 1996;42:P673-4. Abstract.

Clinical Model



Modeling the M/P Ratio

Early Modeling Attempts

TABLE 1. *Comparison of the Performance of Various Models in the Prediction of M/P Values*

Drug	M/P_{obs}[2]	M/P[3] pH part[n]	M/P[4] M & L	M/P[5] Fleisch[1]	M/P[6] Phase	M/P[7] log transf§
Temazepam	0.14	1.00	0.45	0.03	0.03	0.05
Mefloquine	0.15	1.57	1.97	0.03	0.03	0.09
Zolpidem	0.16	1.04	0.77	0.1	0.1	0.35
Tiapamil	0.44	1.16	1.13	0.28	0.29	0.81
Chlormethiazole	0.73	1.00	0.55	0.41	0.39	0.84
Moclobemide	0.69	1.04	0.86	0.57	0.55	0.89
Chloroquine	1.4	1.53	1.26	0.7	0.71	1.42
Procainamide	3.2	1.58	1.45	1.3	1.4	2.5
Sotalol	3.74	1.53	1.86	1.58	1.63	2.63
Quazepam	4.13	1	0.32	0.07	0.07	3.43
		$r^2 = 0.09$ $p = 0.4$	$r^2 = 0.01$ $p = 0.75$	$r^2 = 0.36$ $p = 0.07$	$r^2 = 0.37$ $p = 0.06$	$r^2 = 0.97$ $p < 0.00001$
Year of publication:		**1981**	**1985**	**1987**	**1990**	**1990**
Method:		**pKa only**	**QSAR (MW, lipid sol.)**	**pKa, lipid solubility & protein binding**		

Begg EJ, Atkinson HC. Pharmacol Ther 1993;59:301-10.

Log-Transformed Phase Distribution Model

Acidic drugs

$$\ln M/P = -0.41 + 9.36 \ln(Mu/Pu) - 0.69 \ln F_{up} - 1.54 \ln K$$

Basic drugs

$$\ln M/P = 0.03 + 2.28 \ln(Mu/Pu) + 0.89 \ln F_{up} + 0.51 \ln K$$

Mu/Pu = M/P ratio of unbound drug
***F*up = fraction of drug unbound in plasma**
***K* = constant related to lipid partitioning**

Begg EJ, Atkinson HC. Pharmacol Ther. 1993;59:301-10.

Quantitative Structure-Activity Relationship (QSAR) Modeling of the M/P Ratio

Agatonovic-Kustrin Model

- Nonlinear neural network
- 26 molecular descriptors
- 60 drugs
- R^2 = 0.962 vs 0.805 for log transformed phase distribution model

Anal. Chim. Acta 2000;418:181-95.

Katritzky Model

- CODESSA Pro software package
  - Proprietary
  - developed by the authors at U. Florida
- 7 molecular descriptors
- 115 drugs
- $R^2 = 0.791$

Bioorg. Med. Chem. 2005;13:1623-32

Abraham Model

- Nonlinear artificial neural network
- 5 “Abraham descriptors”
  - PharmaAlgorithms Absolv software
  - Proprietary
  - ACD Labs, Toronto
- 179 drugs & environmental pollutants

Eur. J. Med. Chem. 2009;44:2452-8

Abraham Model Results

Reference	Total no.	Variable	No. of descriptors		RMSE for training and test sets		
			Start[a]	Final[b]	Training	Internal test	External test
This work	179	$\text{Log}(1 + M/P)$	5	5	0.056	0.109	0.090
This work	179	$\text{Log}(M/P)$	5	5	0.203	0.193	0.334
[17]	60	$\text{Log}(M/P)$	61	26	0.590		0.425
[19]	100[c]	$\text{Log}(M/P)$	850	7	0.324		0.332[d]

[a] Original number of descriptors calculated.
[b] Number of descriptors used in the model.
[c] Fifteen of the original 115 drugs were excluded.
[d] Error of the plot of observed and predicted values.

[17] = Agatonovic-Kustrin
[19] = Katritzky

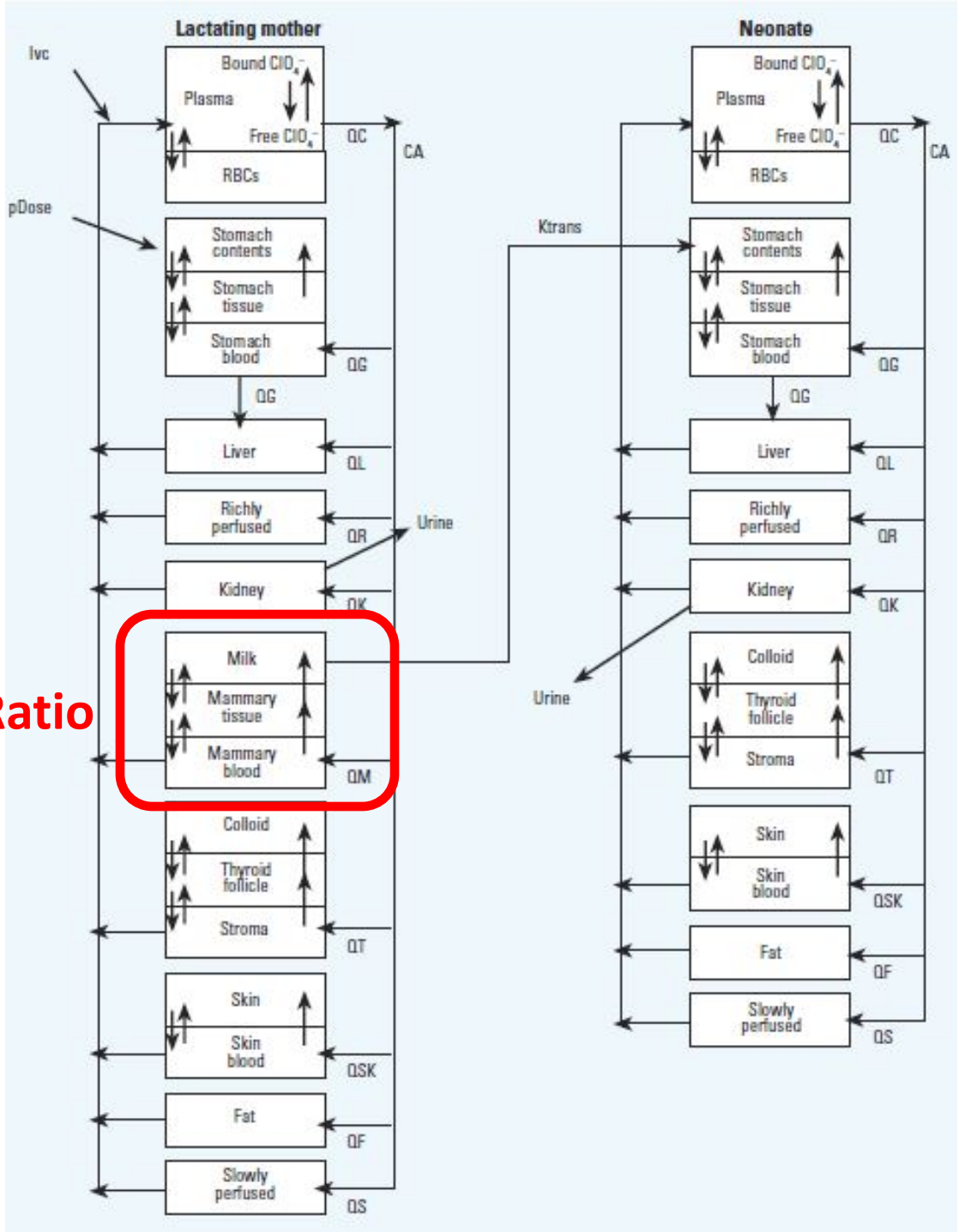
Eur. J. Med. Chem. 2009;44:2452-8

Predicting M/P

- QSAR modeling shows promise
- Independent validation is needed
  - Using high-quality clinical pharmacokinetic studies

Physiologically Based Pharmacokinetic (PBPK) Modeling

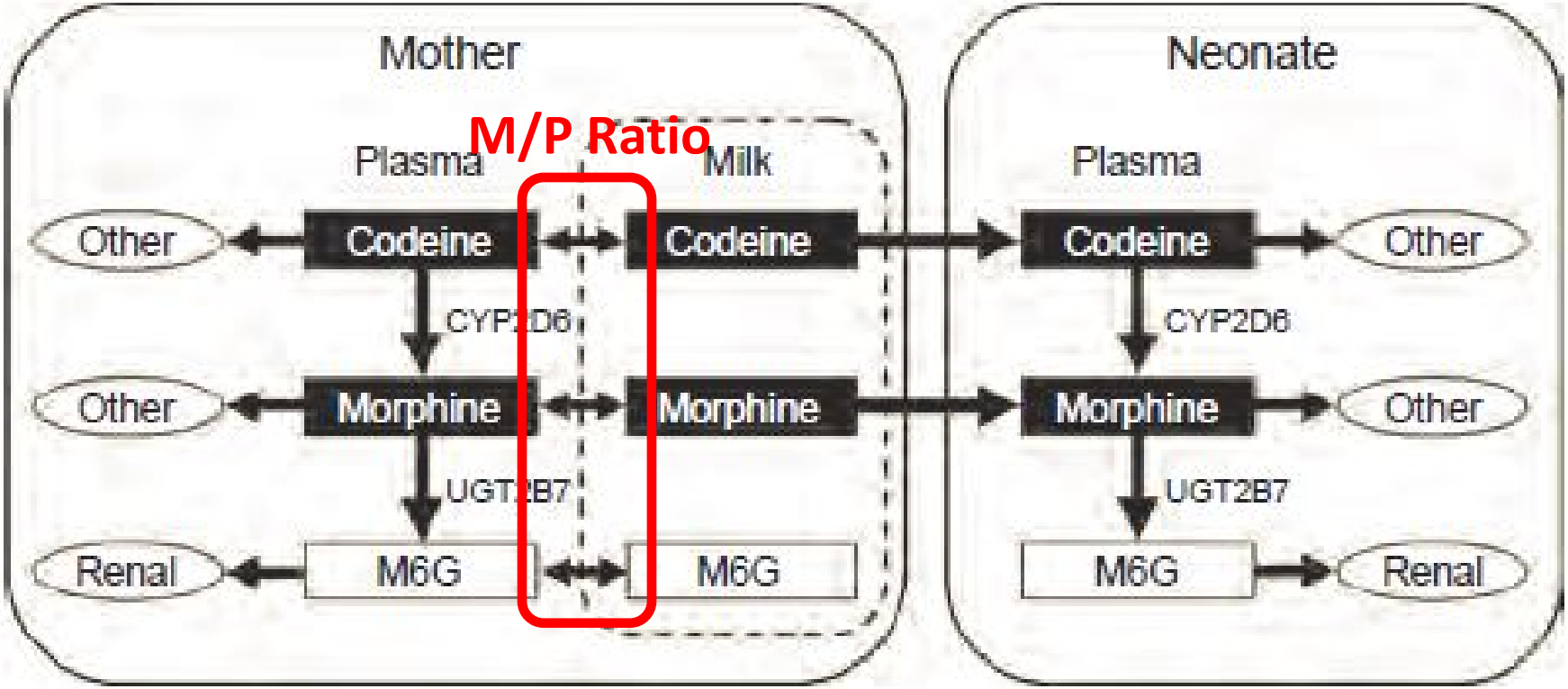
Perchlorate PBPK Model



M/P Ratio

Clewell RA, Gearhart JM. Environ Health Perspect 2002;110:A333-7.

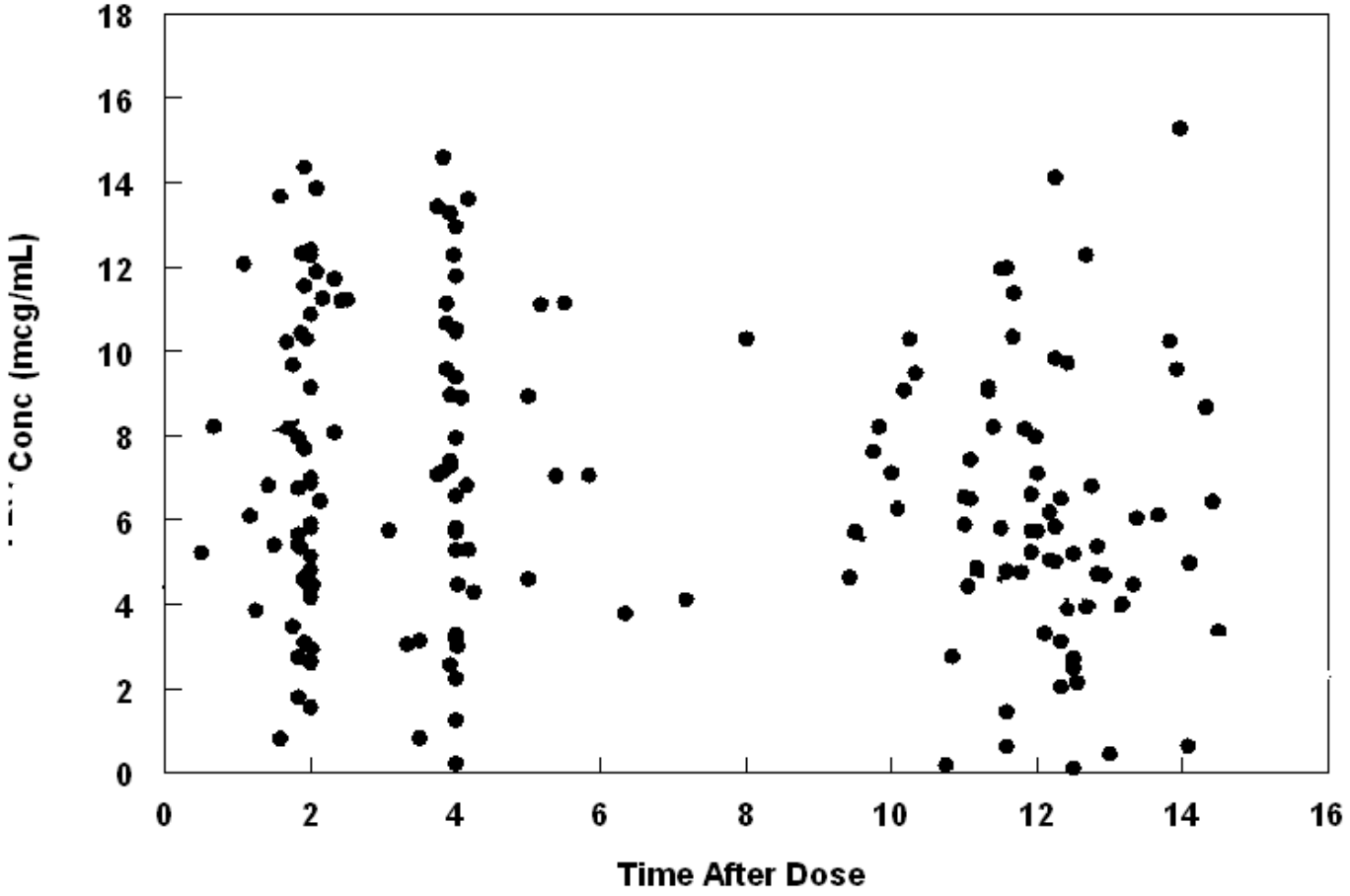
Codeine Toxicity Simulation



Willmann S et al. Clin Pharmacol Ther 2009;86:634-43.

Population Pharmacokinetics

Data Collection Example



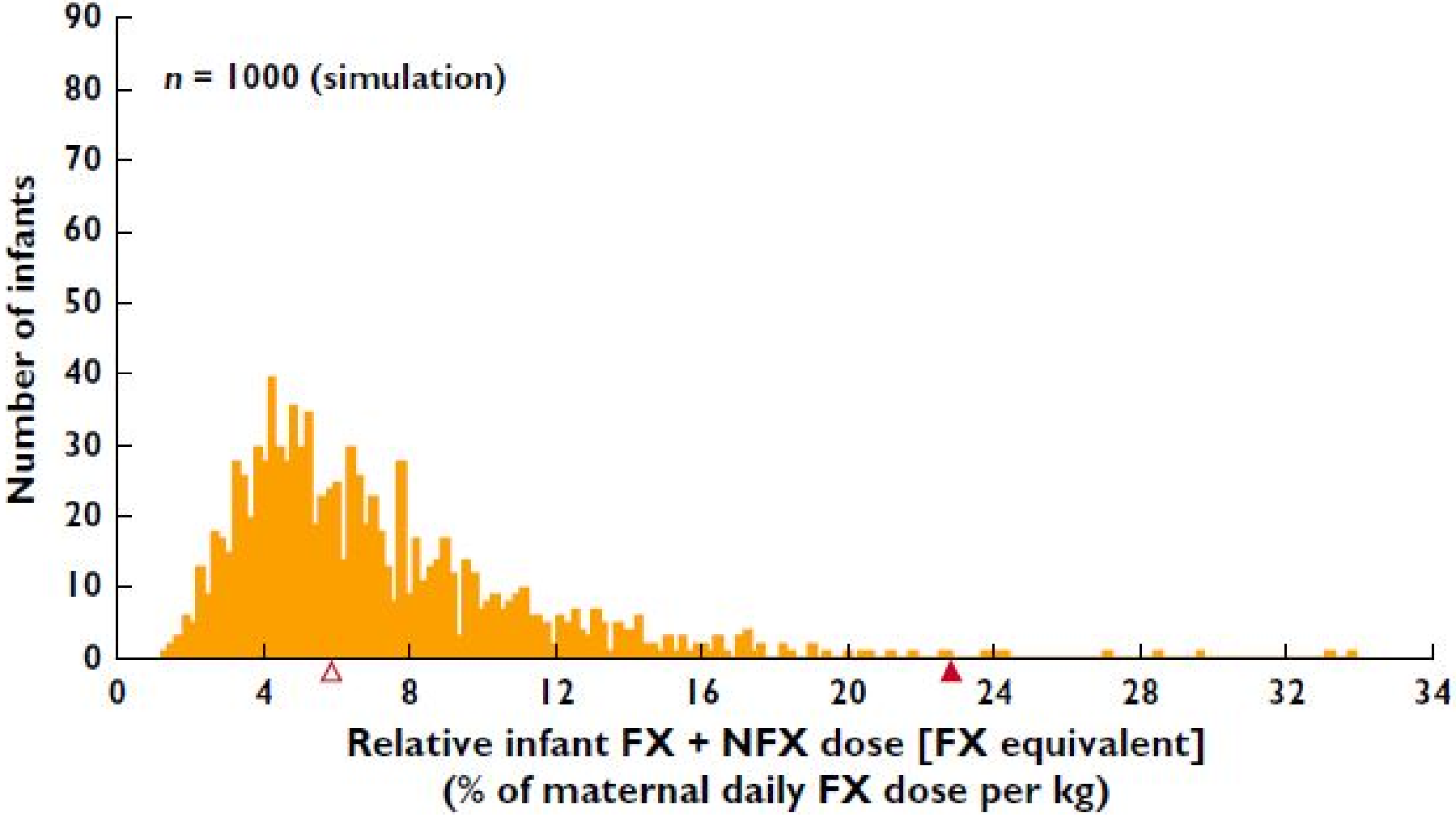

I THINK YOU SHOULD BE MORE SPECIFIC HERE IN STEP TWO
THEN A MIRACLE OCCURS

Fluoxetine Parameters from NONMEM

	Population mean estimate	RSE(%)*	Bootstrap evaluation Median	95%CI
Fixed effects (exp(θ))				
K_a (h^{-1})	0.016	13.3	0.016	0.0027, 0.041
V (l)	20.5	3.5	20.3	7.24, 72.0
CL ($l\ h^{-1}$)	13.4	6.9	13.1	10.6, 16.7
KFN	1.01	20.2	0.99	0.79, 1.2
Random effects				
Interindividual variability (ω)				
K_a (CV%)	111.4	174.2	137.2	52.2, 268.2
V (CV%)	22.8	133.9	84.9	32.4, 248.3
CL (CV%)	48.1	64.9	46.7	36.4, 58.3
KFN	48.1	46.8	47.5	30.8, 60.7
Residual variability (σ)				
FX(CV%)	28.1	58.2	26.9	20.5, 33.8
NFX(CV%)	29.8	56.1	29.1	19.4, 36.3

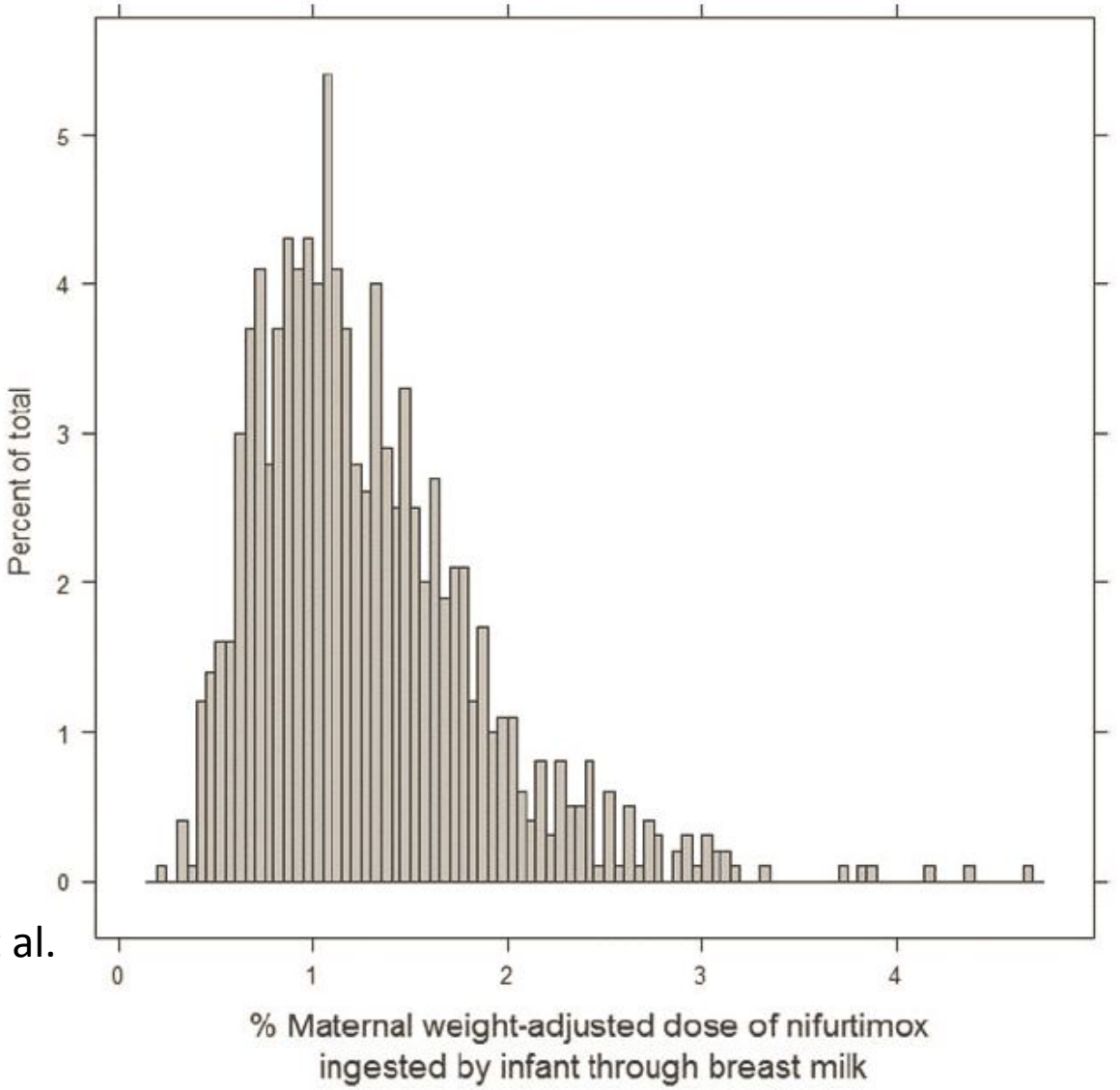
Tanoshima R et al. Br J Clin Pharmacol. 2014;78:918-28.

Fluoxetine + Norfluoxetine RID Projection



Tanoshima R et al. Br J Clin Pharmacol. 2014;78:918-28.

Nifurtimox RID Projection
M/P = 6



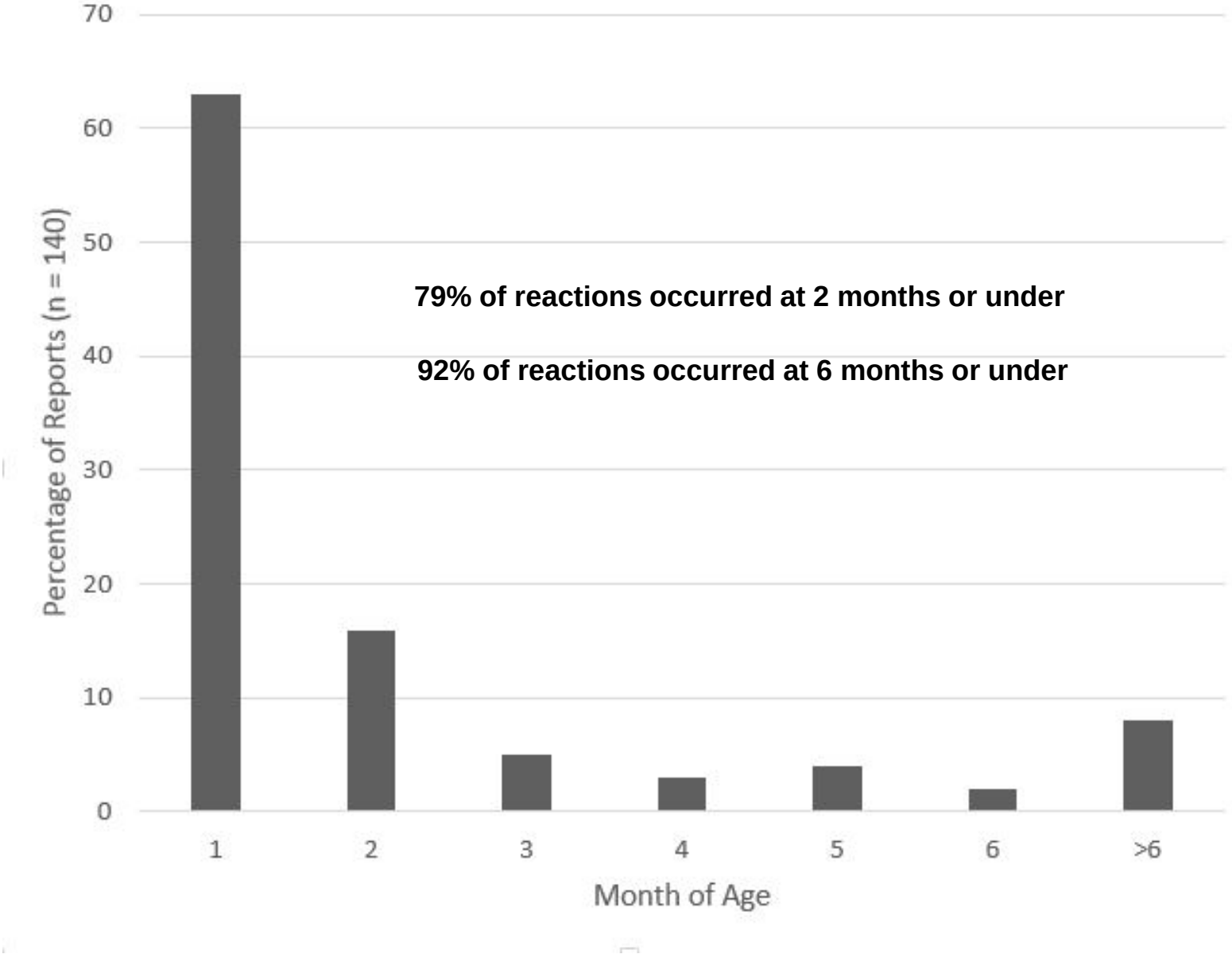
Garcia-Bournissen F et al.
Arch Dis Child
2010;95:224-8.

The RID

- PBPK and population PK methods show promise in predicting the RID & its variability
- The RID does not tell the whole story
  - Does not account for
    - Relative toxicity of drugs
    - “Outlier” drugs with long half-lives (e.g., fluoxetine)
    - Infant age

IMPORTANT CLINICAL VARIABLE: INFANT AGE

Adverse Reactions by Age



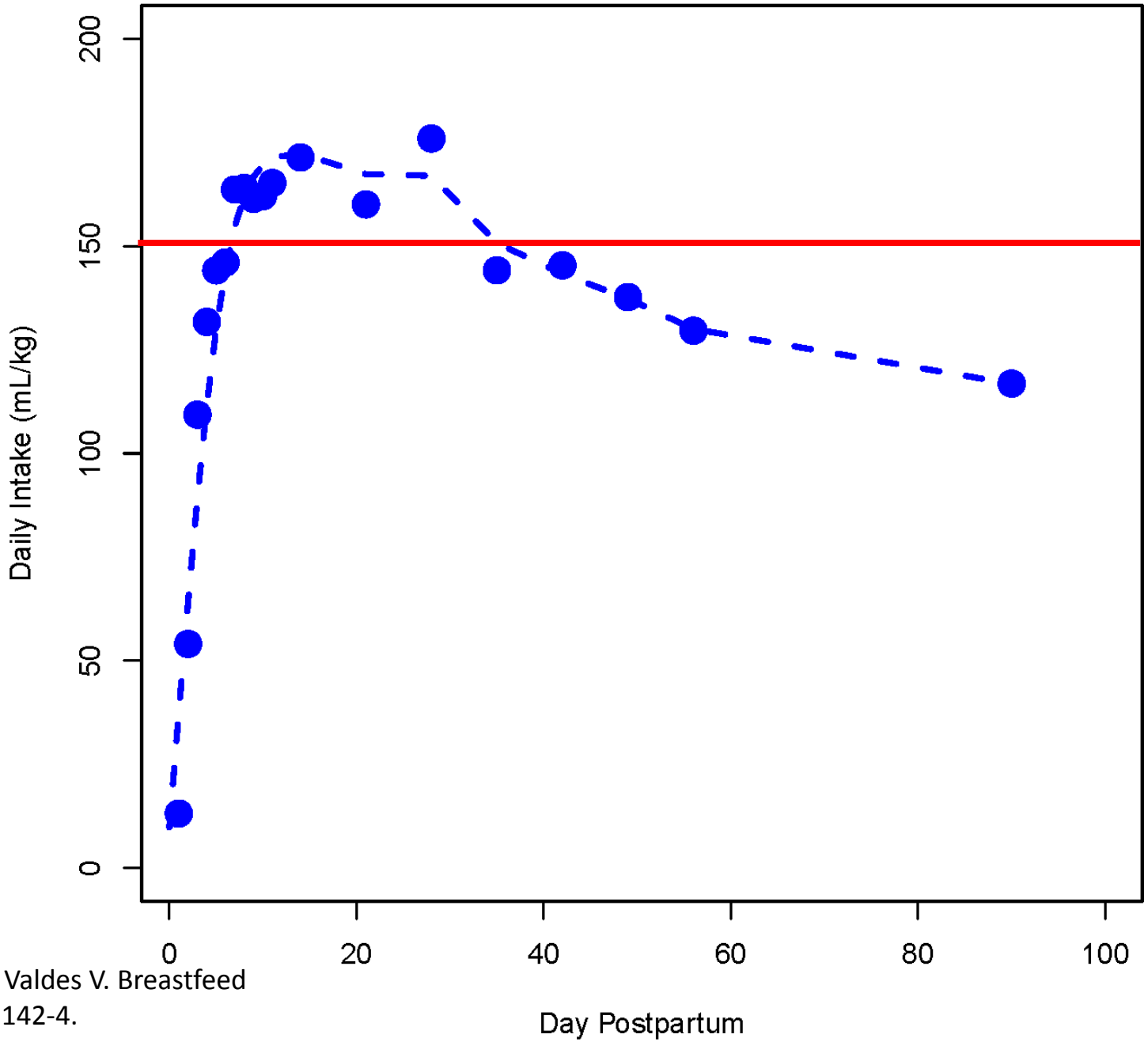
Anderson PO et al. Clin Pediatr 2016;55:236-44..

ADR Study Comparison

Age Range	Published Cases[1,2]	French Pharmacovigilance[3]
≤1 month	63%	67%
1-2 months	16%	11%
≤2 months	79%	78%
	n = 140	n = 174
CNS depressants	58%	35+%

1. Anderson PO et al. Clin Pediatr 2003;42:325-40.
2. Anderson PO et al. Clin Pediatr 2016;55:236-44.
3. Soussan C et al. Eur J Clin Pharmacol 2014;70:1361-6.

Daily Milk Volume Over Time



Anderson PO, Valdes V. Breastfeed Med 2015;10:142-4.

Summary

- Few drugs pass into breastmilk in large amounts
- In silico modeling shows promise as a screening tool to identify drugs of concern
  - M/P prediction
  - Followed by population or PBPK projections
- Modeling should not replace human studies
  - Milk and plasma sampling to validate models
  - ADR monitoring—pharmacology matters
    - Long-term developmental data
  - Infant age matters (a lot!)
- Most drugs are not a problem during breastfeeding