

# Early-Life Exposures to Medications

Shinya Ito, MD, FRCPC  
Hospital for Sick Children  
University of Toronto

# DISCLOSURE

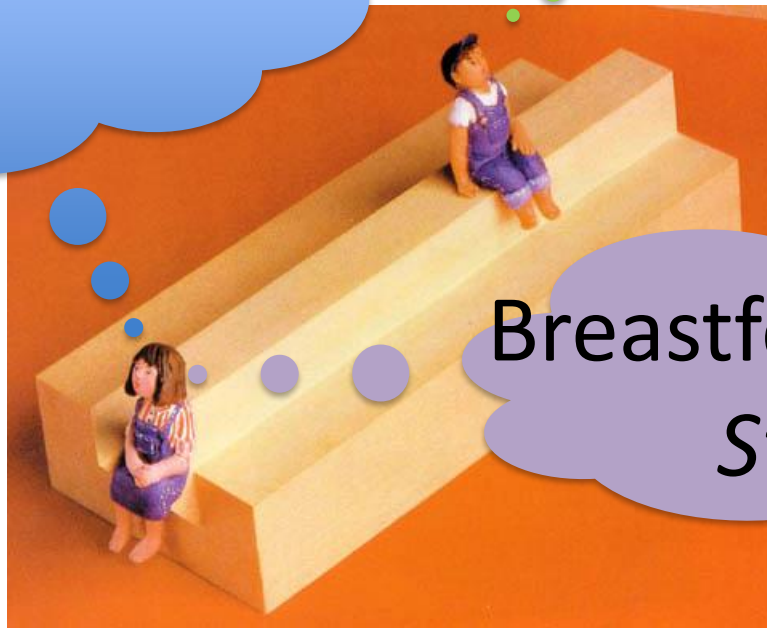
- Funded by **Canadian Institutes of Health Research**



- Received funding for other projects not directly relevant to this presentation from:
  - UCB
  - Novartis

Teratogenic vs Early  
Life Exposures

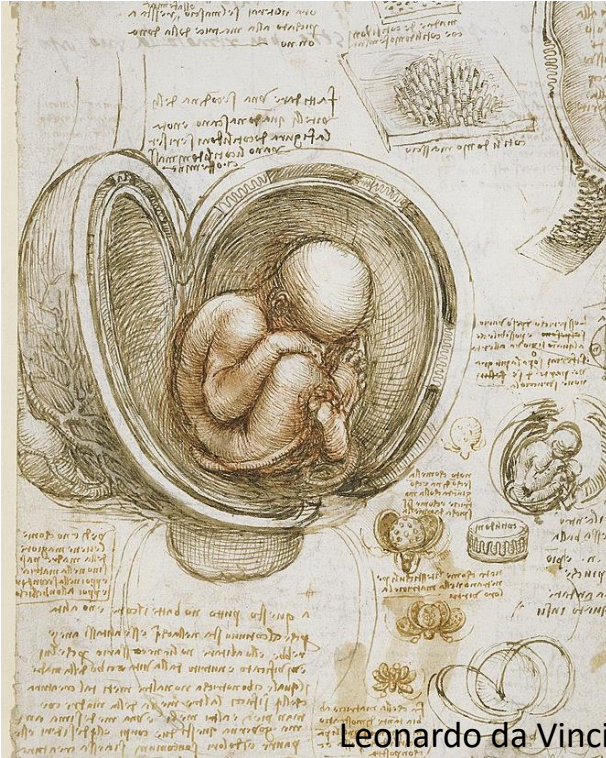
PK characteristics  
of ELE



Breastfeeding and Drugs  
*Study design*

# Early-Life Exposures to Medications

**In utero**



Leonardo da Vinci

**via breast milk**



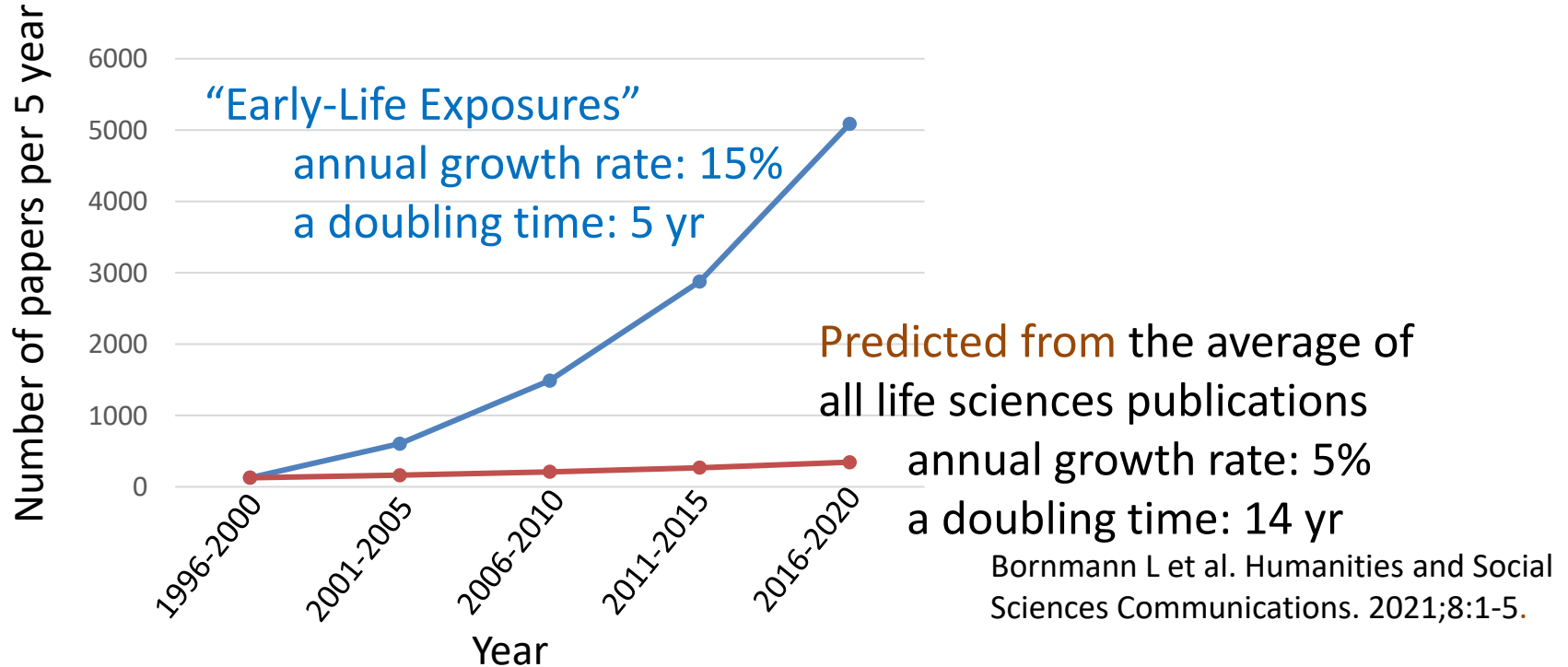
Pierre-Auguste Renoir

**Pediatric drug therapy**



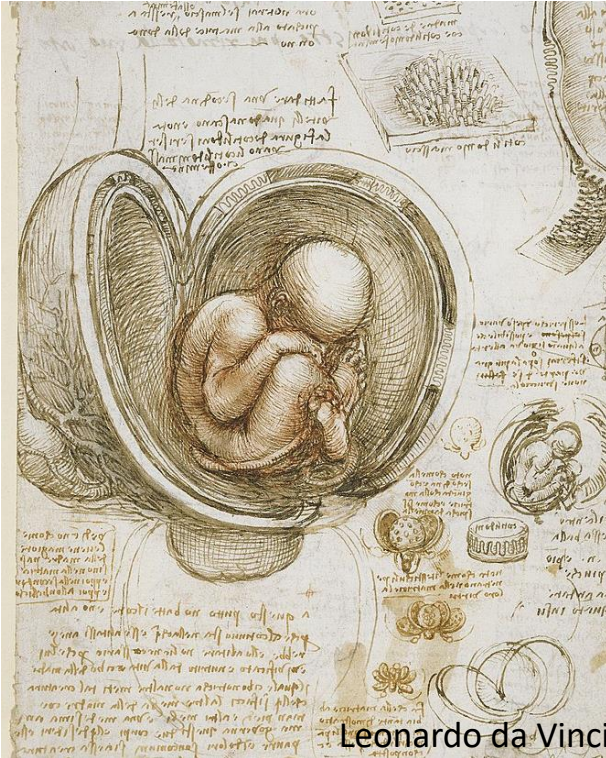
N. Rockwell

# Growth rate of the phrase “Early-Life Exposures” in Google Scholar



# Early-Life Exposures to Medications

**In utero**



Leonardo da Vinci

**via breast milk**



Pierre-Auguste Renoir

**Pediatric drug therapy**

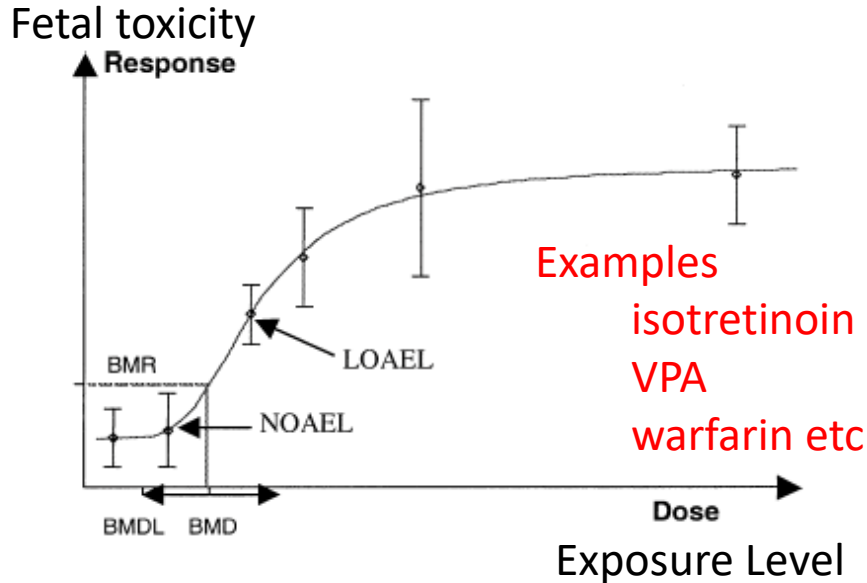


N. Rockwell

# Dose Response



# Dose-Response Principle



Such a dichotomization (toxic vs nontoxic)... does not correspond to the biological reality in which a chemical is only positive or negative in the context of dose level and other features of the exposure.....

Filipsson et al. Critical Reviews in Toxicology  
2003;33:505

Daston GP, et al. Birth Defects Research Part B:  
Developmental and Reproductive Toxicology.  
2014;101(6):423-8.



# Shepard's criteria: human teratogenicity



1923 - 2016

**“Proof” of Human Teratogenicity**  
**TERATOLOGY 50:97–98 (1994)**

**THOMAS H. SHEPARD, M.D.**  
*Department of Pediatrics*  
*University of Washington*  
*Seattle, WA 98195*

***A recent example of its application***

**Zika Virus and Birth Defects — Reviewing the Evidence  
for Causality**

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H.,  
Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

Rasmussen SA, et al. *New England Journal of Medicine*. 2016;374(20):1981-7.

# Shepard's criteria of teratogenicity: *essential*

1. **Proven exposure to agent at critical time(s)**
2. **Consistent findings by  $\geq 2$  high-quality epidemiologic studies**
  - with control of confounding factors,
  - sufficient numbers,
  - exclusion of positive and negative bias factors,
  - prospective studies if possible, and
  - relative risk  $\geq 6$
3. **Careful delineation of clinical cases;** a specific defect or syndrome, if present, is very helpful
4. **Rare environmental exposure that is associated with rare defect**

# Teratogen\*

Agents, substances or factors which cause physical or functional defects (harmful effects) in the fetus.

**\*The Greek τέρας *teras*: monster.**



# First Exposure



University of Toronto ✓

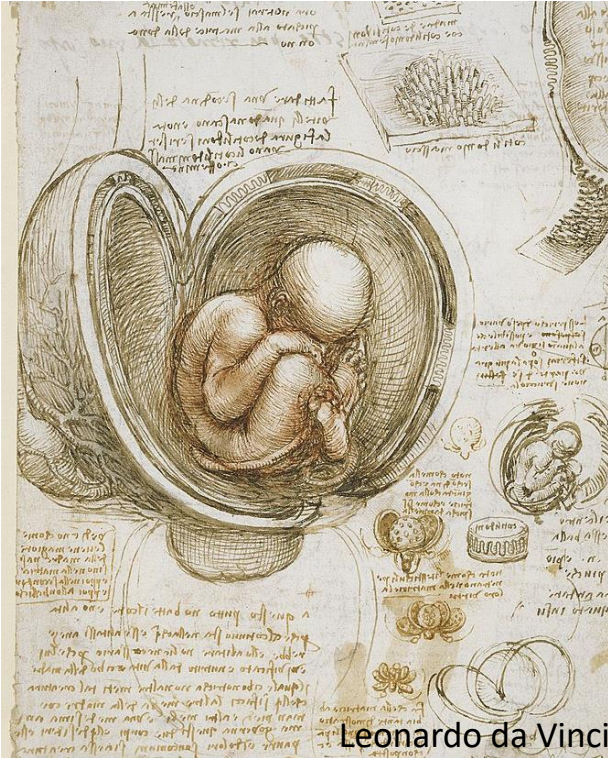
May 24, 2022 · 🌐

First Exposure, a new information hub & research network at Dalla Lana School of Public Health will fill crucial gaps in health care for mothers and infants. 💙 [uoft.me/7Zk](https://uoft.me/7Zk)



# Early-Life Exposures to Medications

**In utero**



Leonardo da Vinci

**via breast milk**



Pierre-Auguste Renoir

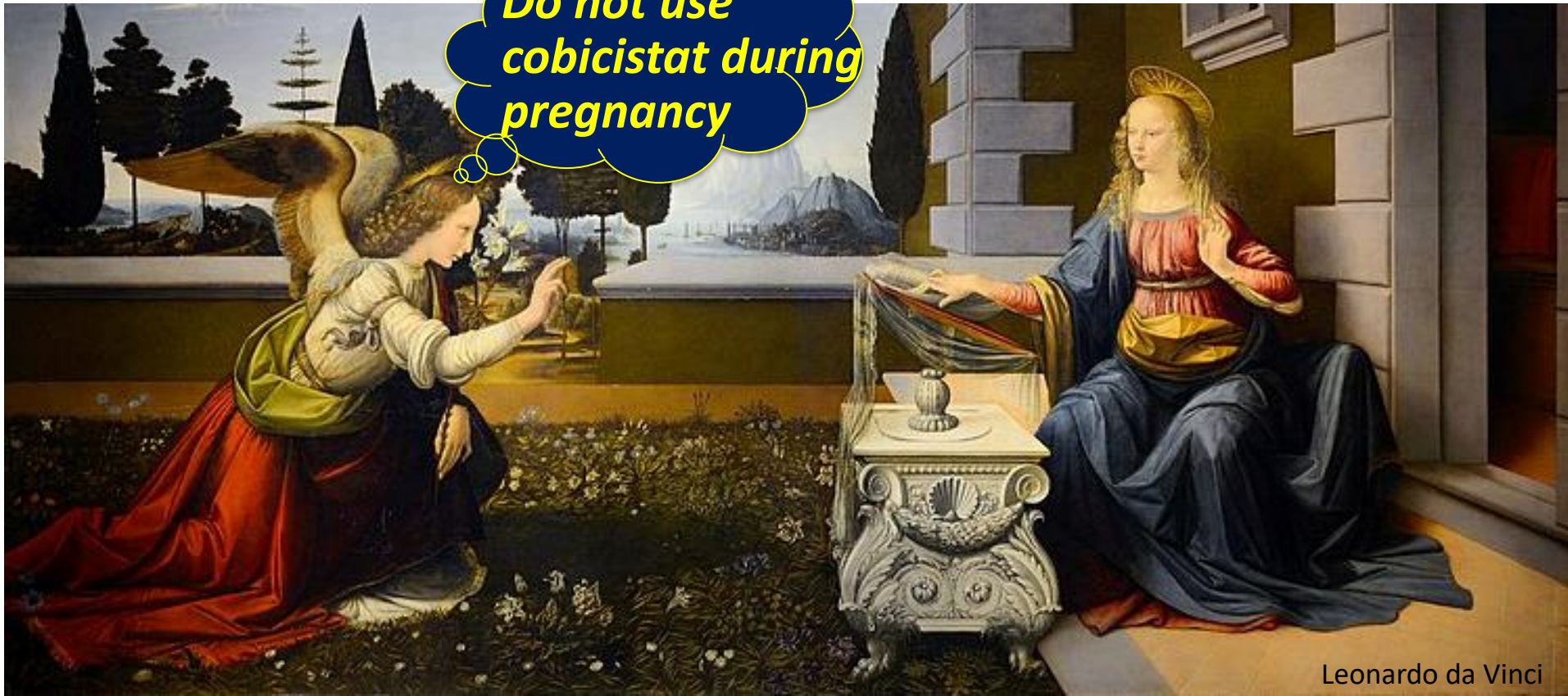
**Pediatric drug therapy**



N. Rockwell

# Announcement (FDA: June 2018)

*Do not use  
cobicistat during  
pregnancy*

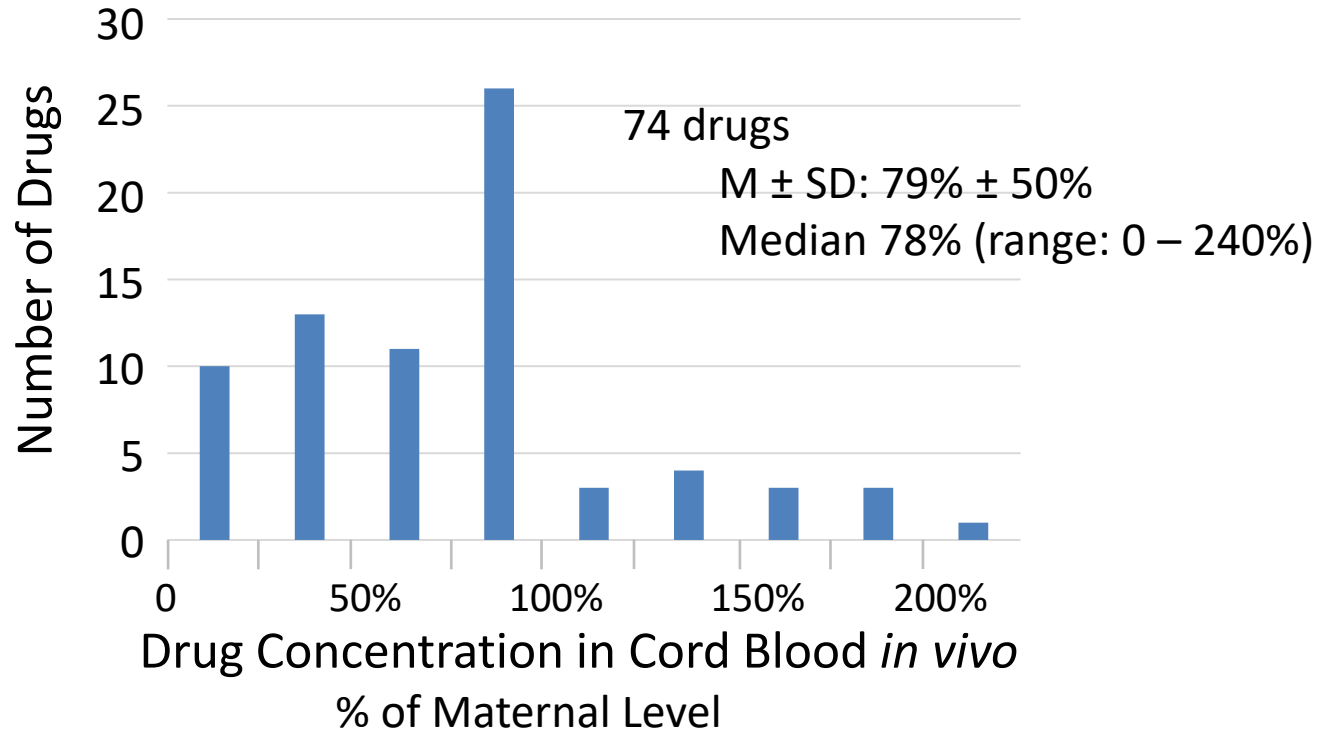


# $CL_{ORAL}$ in pregnancy (% of non-pregnancy)

<b>Drug</b>	<b><math>CL_{ORAL}</math> (CL/F)</b>	<b>Enzyme</b>
Metoprolol	>200%	CYP2D6
Midazolam	200%	CYP3A4
Indinavir*	200%	CYP3A4
Lamotrigine*	200%	UGT1A4
Labetalol	160%	UGT1A1/2B7
Nicotine*	160%	CYP2A6
Phenytoin	145%	CYP2C9
Proguanil*	116%	CYP2C19
Caffeine	35%	CYP1A2

\*: clinical consequences *suspected*

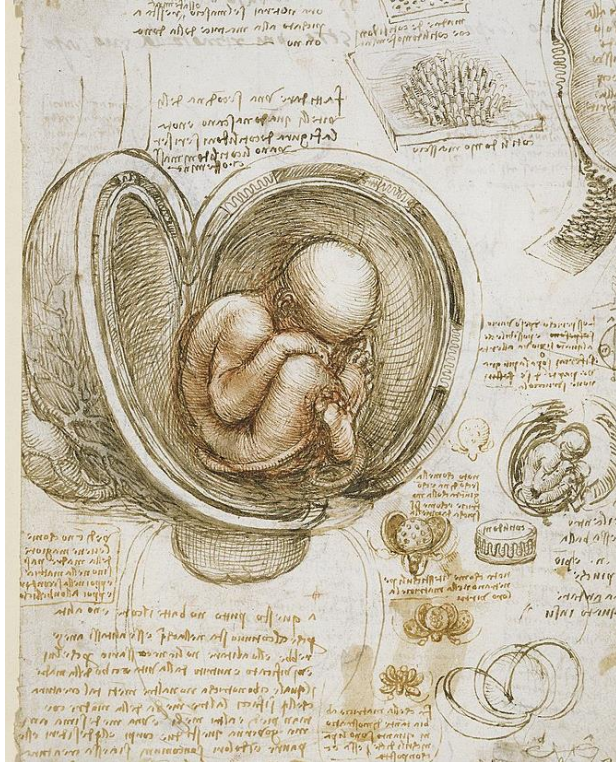
# Drug transfer across placenta





# Serum [C]

## Mother $\geq$ Fetus

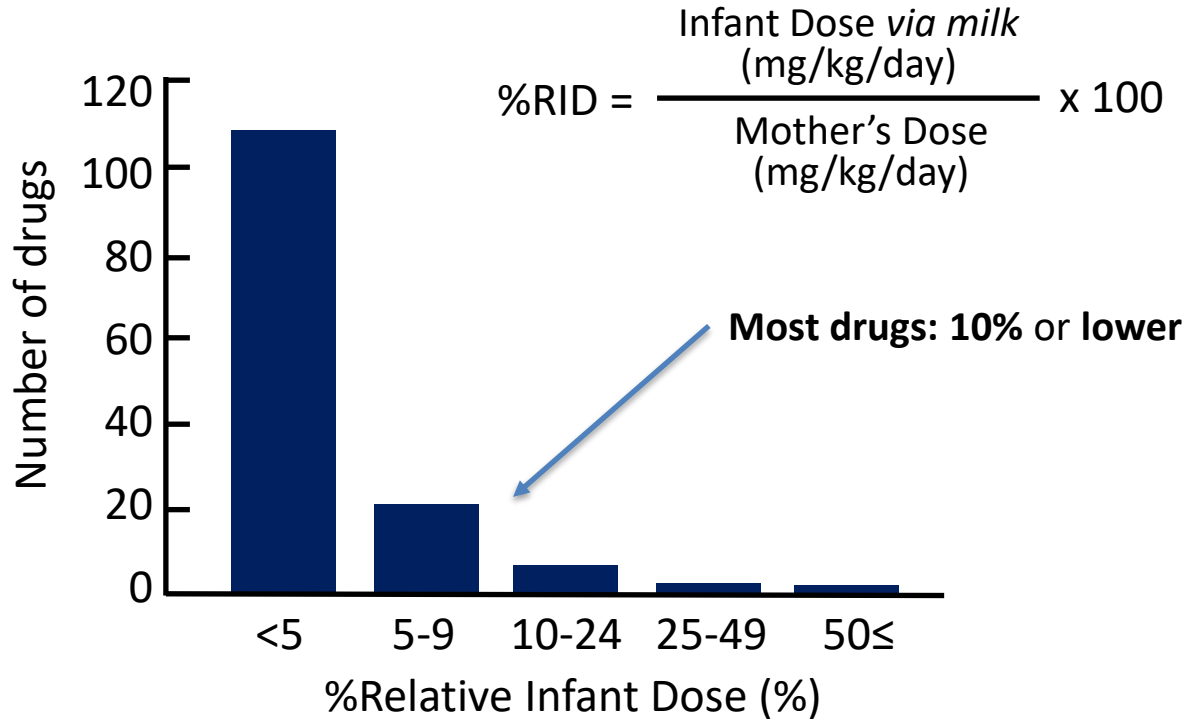


# Serum [C]

## Mother $\gg \gg$ Fetus

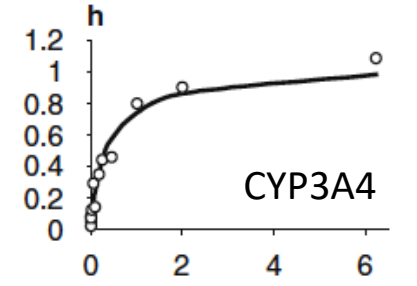
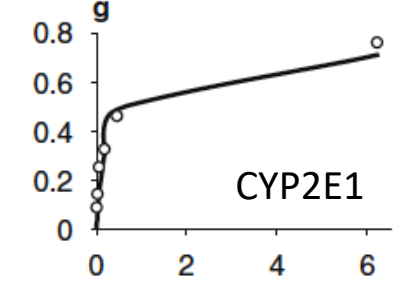
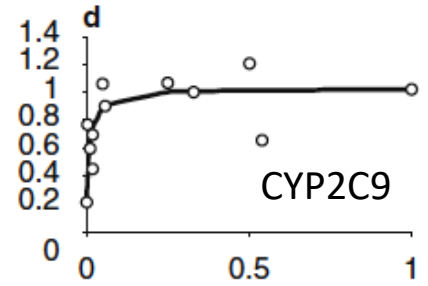
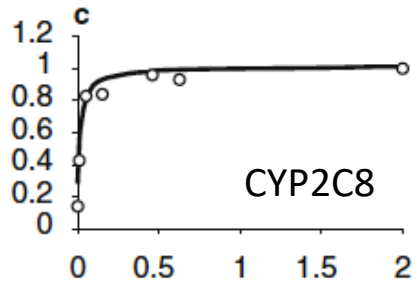
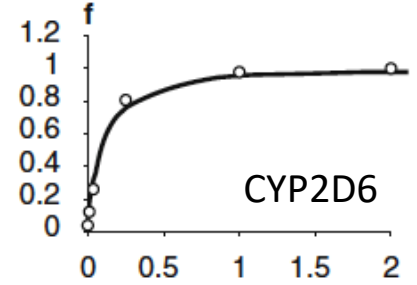
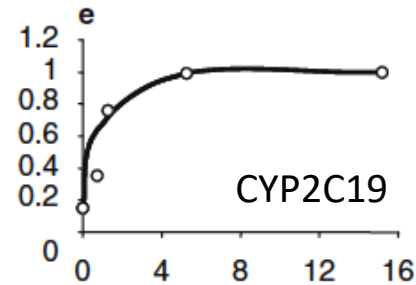
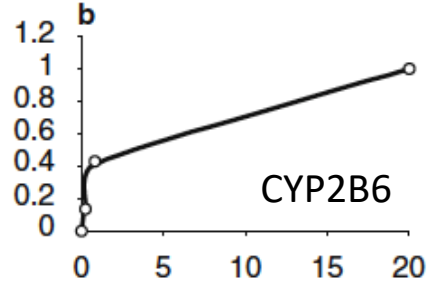
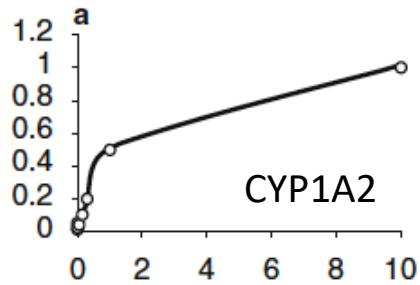


# Drug exposure via milk is low



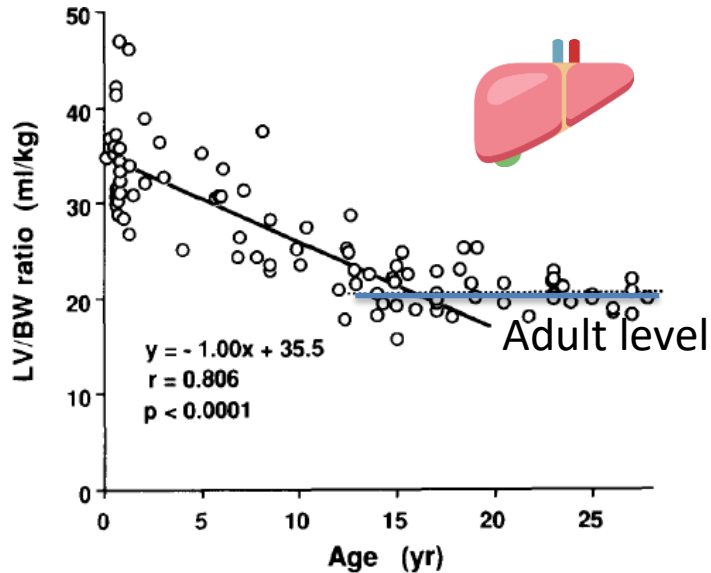
# Development of drug metabolizing enzymes

*Fractional expression  
In liver (relative to adult)*

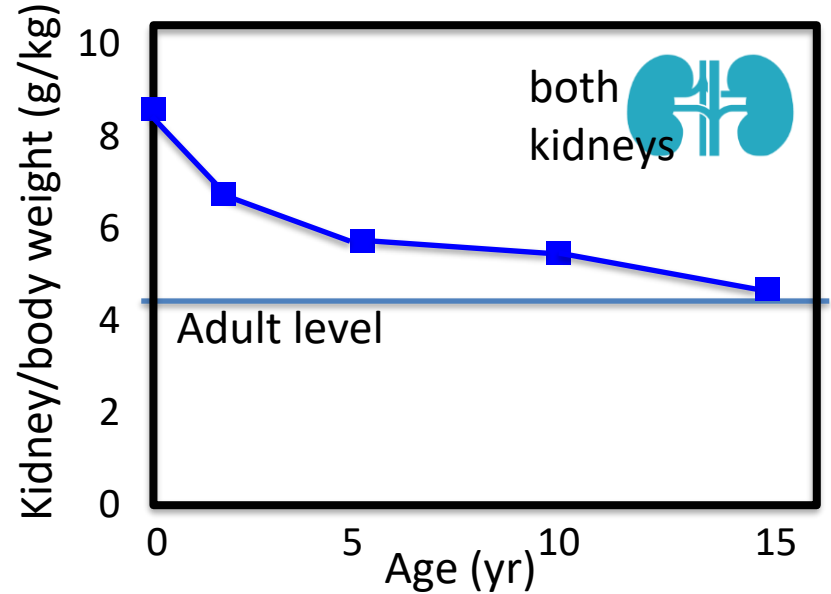


Age (yr)

# Organ size per body weight

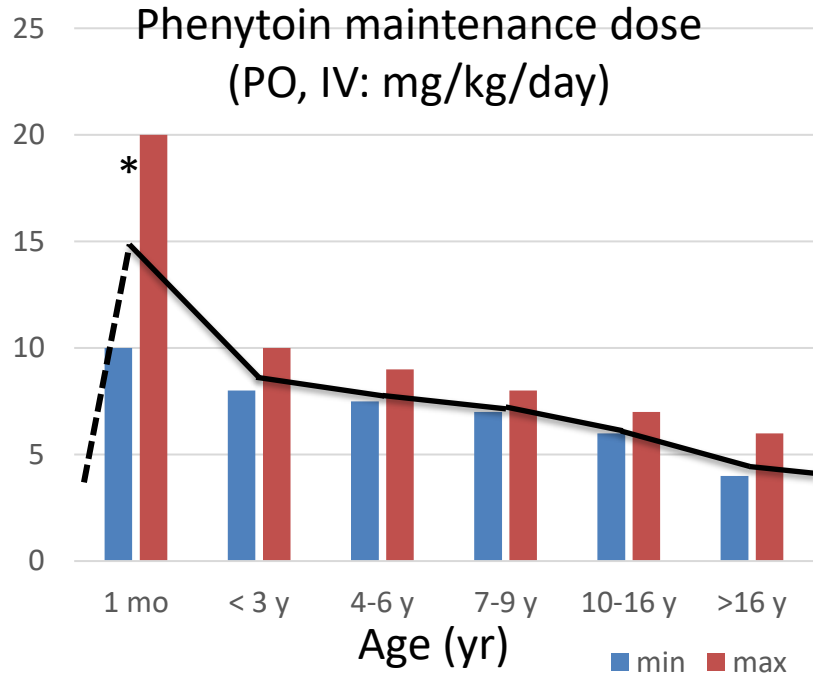


Urata et al. Hepatology. 1995;21(5):1317-21.



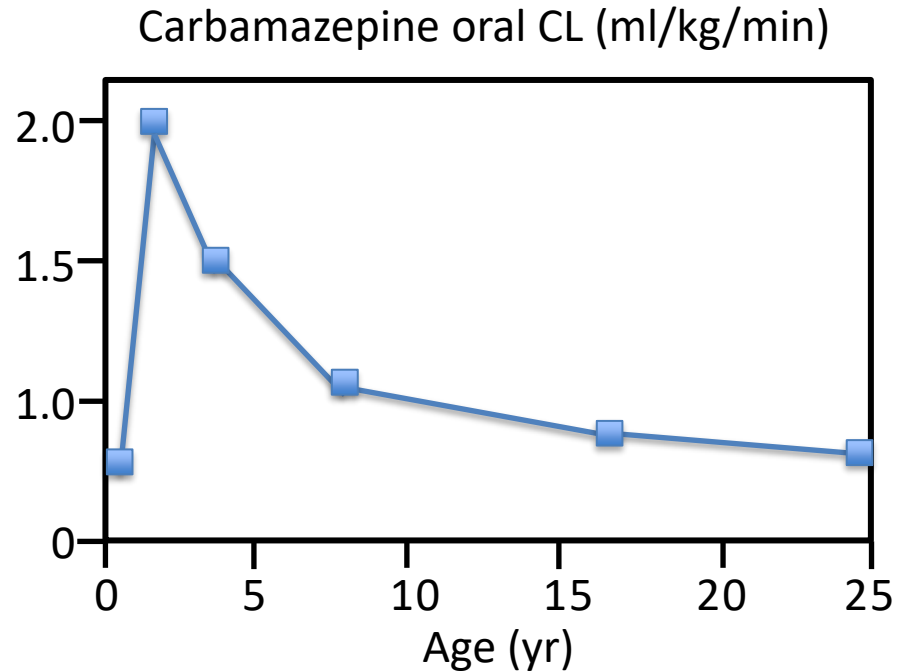
Modified from Valentin J. Annals of the ICRP. 2002 Sep 1;32(3-4):1-277

# Higher dose requirement and higher CL per body weight in the young



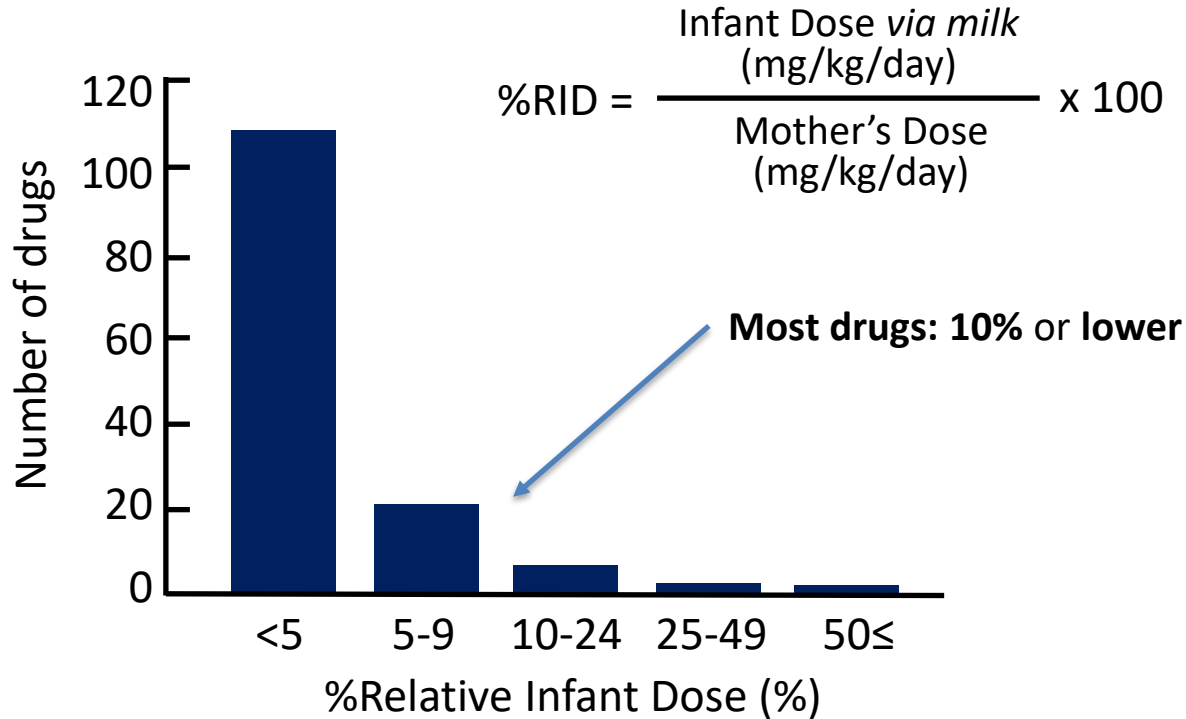
From SickKids formulary

\* Modified from Al Zabi et al. TDM 2006



Modified from: Johnson et al. Clin Pharmacokinet 2006; Tulloch et al. JPPT 2012

# Drug exposure via milk is low



# Allometry: a scaling principle

Sizes of body parts\* and whole body are **NOT DIRECTLY** proportional.



Isometry

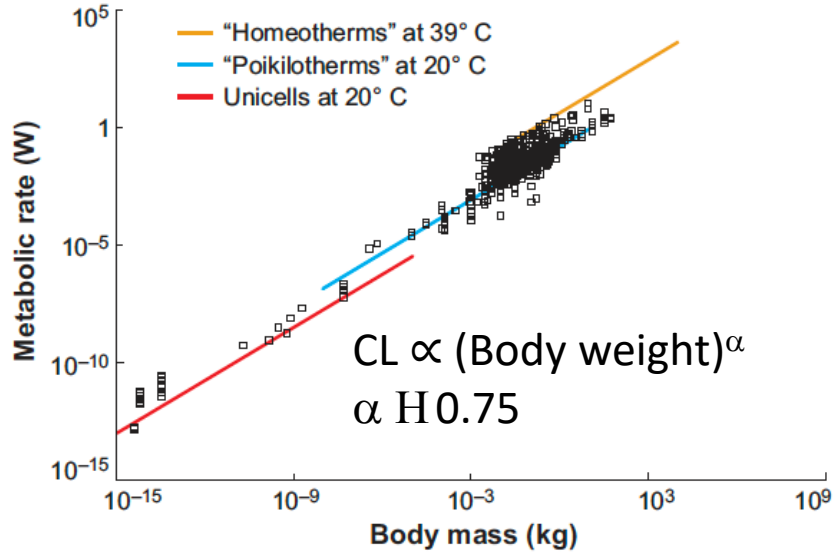
Shingleton, A. (2010) Allometry: The Study of Biological Scaling. *Nature Education Knowledge* 3(10):2



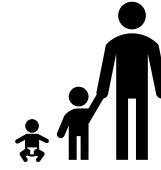
Allometry



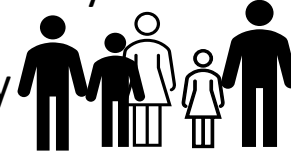
# Allometry context



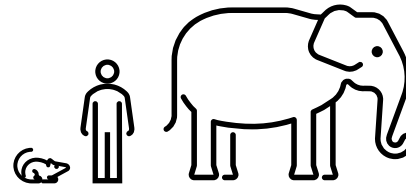
1. Ontogenic allometry



2. Static allometry



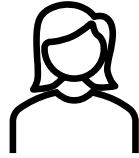
3. Evolutionary allometry





# Allometry-based equivalent dose

Daily dose 600 mg  
(10 mg/kg/day)



60 kg woman



0.02 kg (20 g) mouse

Allometric scaling (to achieve the same blood level)

$$600 \text{ mg}/(60 \text{ kg})^{0.75} = (\text{mouse daily dose})/(20\text{g})^{0.75}$$

mouse dose is: 1.5 mg/day, which is 1.5 mg/20g = **74 mg/kg/day**



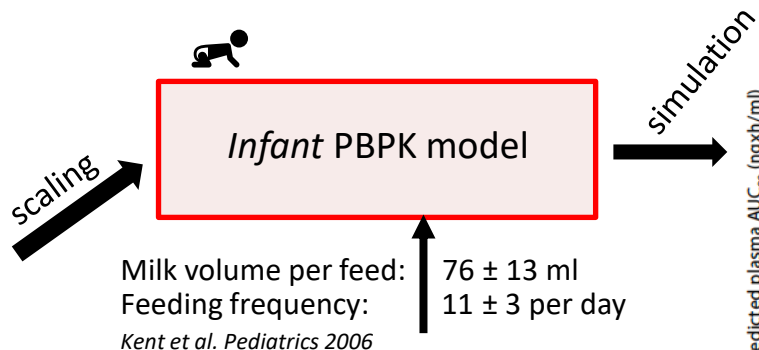
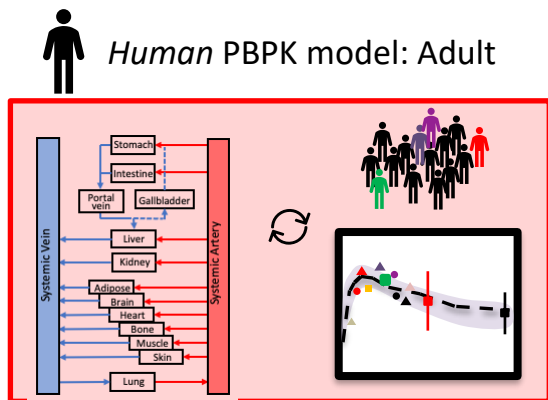
St Luke Drawing the Virgin  
by van der Weyden

*Museum of Fine Arts, Boston*

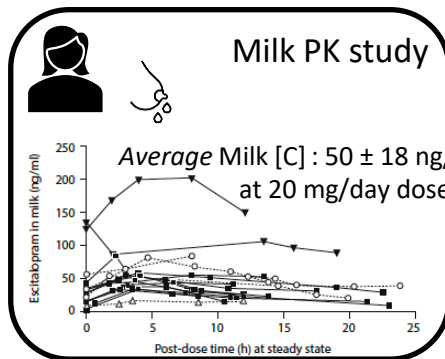
# Outline of modelling workflow

## Example: Escitalopram

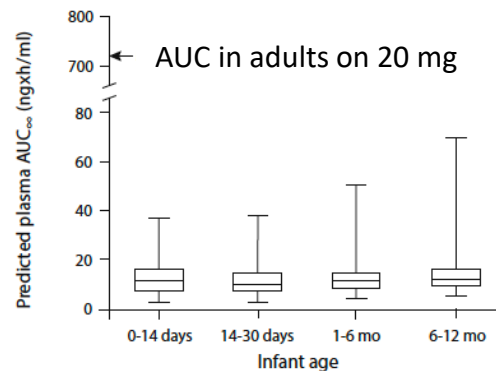
Delaney et al. Clin Pharmacokinet  
2018; 57:1603-11



Milk [C] (mean,  $\sigma$ )



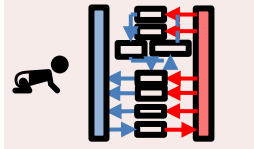
Infant plasma [C] simulated



# Knowledge evolution and study design

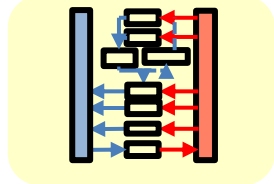
*Prediction of plasma [C] in infants exposed to drugs in milk*

Infant PBPK model



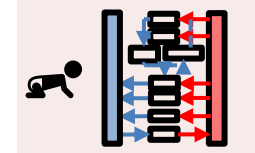
+

Milk PBPK model



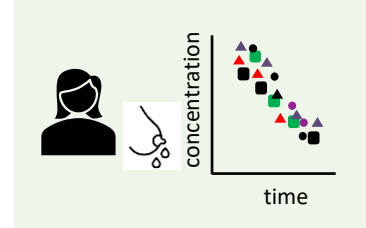
Getty Images

Infant PBPK model



+

Milk PK or milk popPK study



or

Infant PK or popPK study



# Generative AI

What is the probability of fetal toxicity if valproic acid is taken during pregnancy?

Answer (*perplexity AI*): ..... To obtain the most accurate and up-to-date information..... It is crucial to consult with health professionals, such as obstetricians, gynecologists or **teratology information services.**

....

