Liver
Brain
Metab
Placenta
Lung
Richly Perf.
Poorly Perf.
Mammary
Liver
Gut

Maternal Model
Neonatal Model
Embryo/Fetal Model

Liver
Gut
Lung
Metab
Poorly Perf.
Poorly Perf.
Poorly Perf.
Mammary
Liver
Metab
Gut

Embryo/Fetal Model
Outline

• Risk/Safety Assessment Context
• Postnatal Exposure
• ADME
• Applications of Dosimetry in Toxicity Studies Design, Interpretation, Risk Assessment
Risk/Safety Assessment in a Mode of Action Context

Exposure

Pharmacokinetics
Tissue Dosimetry

Pharmacodynamics
Toxicity Pathway

Response

Standard pharmaceutical analysis

limited information environmental default
Evaluating Risks for Early Ages

• Extrapolation from adult to children
  – Changes in exposure
  – Changes in pharmacokinetics/toxicokinetics
  – Changes in pharmacodynamics/toxicodynamics

• Extrapolation across-species for relevant life stage
  – Toxicity studies
    • developmental (in utero),
    • 2-generation reproductive/developmental,
    • developmental neurotoxicity
    • early life cancer studies
  – Exposure, PK, PD (critical window of susceptibility)
Mapping Cross-species

Placental transfer

Lactational transfer

Food/water Consumption

PK&PD

PK&PD

PK

PD

Effect Observed

PKPD

Effect Observed

Food/water Consumption

Placental transfer

Lactational transfer

PKPD

PKPD

PKPD

Birth

Weaning
Postnatal Exposure

- Diet
- Drinking water
- Lactational transfer
- Gavage (experimental)
- Dermal
- Inhalation
Changes in Body Weight and Food Consumption of Rat Dam

![Graph showing changes in body weight and feed consumption over prebreed, gestation, and lactation stages for early and late phases.](image)
Changes in Consumption/BW of Rat Dam

Consumption/BW (g/kg/day)

Prebreed, Gestation, Lactation

early
late
How do we do toxicity studies?

- Constant ppm (diet, water)
- Adjusted ppm (lactation)
  - 86 g/kg during gestation
  - 160 g/kg week 1 lactation: 1.9x
  - 199 g/kg week 2 lactation: 2.3x
  - 240 g/kg week 3 lactation: 2.8x
- Constant gavage
- Adjusted gavage (gestation)
  - gd 14 mg/kg/day till birth
Children’s Exposures

• Children generally consume more food and water in proportion to BW compared to adults
• Children’s diets and activities differ from adults
• Children are treated with pharmaceuticals
Postnatal Pharmacokinetics

• Who?
  – Infants (premature, neonates)
  – Children
  – Puberty
  – Young adults, adults

• What?
  – Absorption
  – Distribution
  – Metabolism
  – Excretion
Absorption

• Inhalation
• Dermal
• Gastrointestinal
  – Passive diffusion
  – Transporters
Lead

• Greater uptake in children than adults
  – Lung absorption: 42% vs 15-30%
  – GI absorption: 42-53% vs 7 – 15%

• Nutritional status has major impact
  – Lead absorption inverse to calcium, iron, & other metals
  – Lipid facilitates absorption

Distribution

• Physiological changes: infants 80% water, adults 60%
• Serum binding proteins
• Tissue distribution
  – Passive diffusion (partition coefficients)
  – Transporters
  – Intracellular depots
# Serum Protein Binding Modeling

<table>
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<tr>
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<th>Albumin (μM)</th>
<th>SHBG (nM)</th>
<th>AFP (nM)</th>
<th>Estradiol (nM)</th>
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<tr>
<td>Male</td>
<td>560</td>
<td>28</td>
<td>-</td>
<td>0.084</td>
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<td>0.2-1.1</td>
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<td>-</td>
<td>55</td>
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<tr>
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<td>-</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>410</td>
<td>-</td>
<td>0.1-1.0</td>
<td>0.05-0.2</td>
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<tr>
<td>Pregnancy</td>
<td>410</td>
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<td>700</td>
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<td>44,700</td>
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<tr>
<td>Neonate-pnd 2</td>
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<td>28,900</td>
<td>0.02</td>
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<td>pnd 21</td>
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</tbody>
</table>

Serum Protein Binding

• Fetal accumulation of diazepam (DZP) and desmethyldiazepam (DsZP) appears due to greater protein binding.
• Decreased serum protein binding in mother and neonate of DZP and DsZP was related to increased free fatty acid levels.
• Diazepam clearance fastest in infants and slowest in premature infants/elderly
• High newborn and maternal binding for phenytoin and salicylate.

McCarver DG. Pediatrics. 2004 Apr;113(4 Suppl):969-72
Rat Partition Coefficients: Trichloroethylene

Mahle D, Gearhardt J, Lipscomb JC, Barton HA (manuscript in preparation)
Metabolism

- Developmental expression can be species specific
- Fetal & adult enzymes
- Birth “kicks off” expression of some enzymes
- Developmental expression may be tissue specific
- Infants versus children
- Development of gene regulatory processes poorly characterized (e.g., AhR, CAR, PXR)
- Pharmacokinetics integrates metabolism changes with changes in liver volume and blood flow.
Cytochrome P450

• 1A: 1A1 fetal hepatic & extrahepatic adult; 1A2 adult (1 year 50% adult levels) – theophylline clearance slow in humans, rats, rabbits; pubertal down-regulation, decreased caffeine clearance

• 2C: Not fetal, Increases after birth (1 year 30% adult levels)

• 2E: 3rd trimester, increases after birth (adult levels at 3 mths), similar across species

• 3A: fairly constant levels but 3A7- fetal, 3A4 and 3A5 – adult (20-40% total liver & small intestine CYP)

Flavin-Containing Monooxygenases

- Organic nitrogen, sulfur, phosphorus compounds (overlapping with CYPs)
- Diminished levels in infants
- FMO1: Fetal liver, highest 8 – 15 weeks, declined, 3 days after birth not detectable
- FMO3: Adult liver, onset of postnatal expression variable, generally detectable 1 – 2 years, intermediate levels till 11 years, increased 11 – 18 years
- Extrahepatic developmental expression unknown
Aldehyde Dehydrogenases

Phase II Enzymes

- Glutathione transferases (13 human forms): GSTP1 – fetal, GSTA & GSTM – fetal and adult
- Glucuronyl transferases (16 human forms):
  - UGT1A1 (bilirubin) triggered by birth and reaches adult levels by 3 – 6 mths of age
  - UGT2B increases after birth, apparently associated with neonate chloramphenicol toxicity
- Epoxide hydrolase (2 forms): fetal & adult
- Sulfotranserase (11 forms): differential patterns
Childhood Metabolism & PK

- Acetaminophen toxicity: children appear less sensitive due to greater ability to conjugate (sulfate, glucuronide) than adults
- Studies of drug clearance indicate greatest variability in infants (<6 mths)
- Clearance in children tends to be more rapid than adults (combination of liver size, blood flow, enzyme development)
Excretion

• Generally dependent upon transporters
• Biliary
• Urinary
  – Kidney function develops postnatally in humans and rats, but to a much greater extent in rats
  – Full kidney function in humans at 2 – 3 years: combination of tubular secretion and glomerular filtration
  – Transporter development: PFOA elimination in rats (largely OAT2) develops sexually dimorphic expression around puberty
Risk/Safety Assessment
Applications

• Can we evaluate dosimetry in reproductive/developmental toxicity studies to improve upon current use of maternal dose?
• Can we use PBPK models to help answer relatively importance of exposure versus PK/PD?
• FDA incentives and requirements for pediatric PK.
PBPK Models for Early Life

• Review

• DDE – You et al., 1999

• Perchlorate
  – Rat – lactational (Clewell RA et al., 2003), in utero (Clewell RA et al., 2003)
  – Human – adult (Merrill et al., 2005)
Physiological Parameters in PBPK Models

Cardiac Index vs Age

PBPK model often scale flows and clearances (including metabolism) by BW^{0.75} and tissue volumes by BW. This is an ASSUMPTION!!
Fig. 4. Sensitive periods of various organs of BD rats in transplacental and neonatal carcinogenesis and teratogenesis by direct and indirect alkylating substances. Malformations of the auricles induced by cyclophosphamide, 20 mg/kg. Abscissa: days after observed coitus and birth respectively; ordinate: yield.
Vinyl Chloride and Life Stage – Sprague Dawley rat liver angiosarcomas

Barton HA, Cogliano VJ, Flowers L, Valcovic L, Setzer RW, Woodruff TJ.
Assessing susceptibility from early-life exposure to carcinogens. Environ Health Perspect. 2005 Sep;113(9):1125-33

Summary

• For adverse effects following developmental exposures, increasingly need to evaluate dosimetry in toxicity study species and humans for the relevant window of susceptibility

• Absent knowledge of the critical period, evaluate each pharmacokinetically definable period in toxicity study species and humans (characterizes uncertainty)
REFERENCES


McCarver DG. Applicability of the principles of developmental pharmacology to the study of environmental toxicants. Pediatrics. 2004 Apr;113(4 Suppl):969-72


