SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Introduction to Route-to-Route Extrapolation

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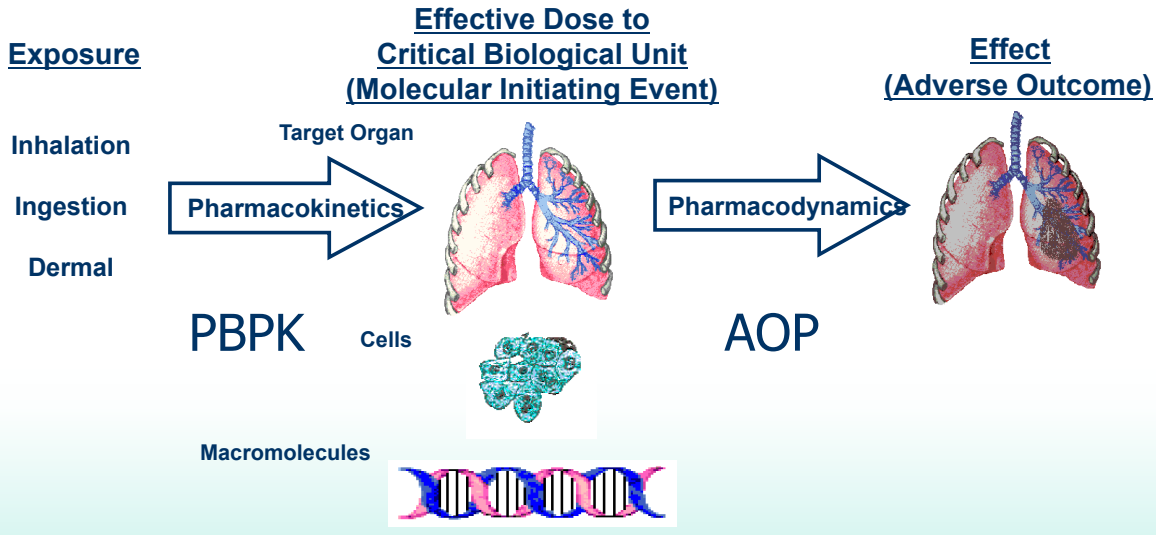
Biologically Based Dose-Response Modeling



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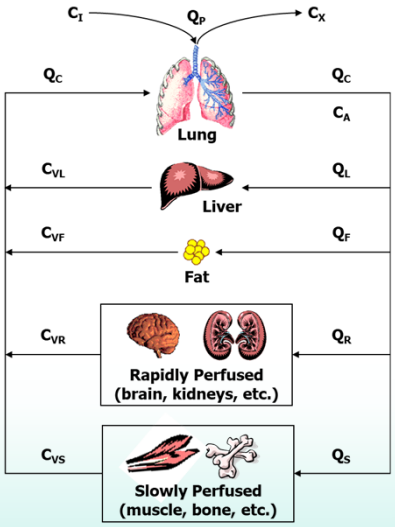
Physiologically Based Pharmacokinetic Model

- Model structure
  - anatomy
  - metabolism / transport processes
- Model parameters
  - physiological data (organ weights, blood flows)
  - biochemical data (partitioning, metabolism)
- Model equations
  - mass-balance equations
  - one equation for each tissue
  - Inter-connected by equation for blood
  - Example: metabolizing tissue (liver)

$$dA_L / dt = Q_L \times (C_A - C_L / P_L) - V_{max} \times C_L / P_L / (K_M + C_L / P_L)$$



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Physiologically Based Pharmacokinetic Modeling

The primary purpose of a PBPK model is to define the relationship between an external measure of (administered) exposure/dose and an internal measure of (biologically effective) exposure/dose in human exposures of concern and relevant toxicity studies, considering species and exposure route differences.

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Areas of Application of PBPK Modeling

- Chemical risk assessment
- Drug development research and evaluation
- Interpretation of human biomonitoring data
- *In vitro* to *in vivo* extrapolation
- Evaluation of early-life susceptibility

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Summary: PBPK Modeling in Risk Assessment

- Most important impact: Estimating cross-species and route-to-route equivalence
- Challenge: Selection of dose metric based on mode of action
  - Toxicity Due to Parent Chemical Exposure
    - Pharmaceuticals, dioxins, nicotine
  - Toxicity Due to Circulating Metabolite
    - Phthalates, glycol ethers, trichloroethylene
  - Toxicity Due to Reactive Metabolite
    - Methylene chloride, vinyl chloride, chloroform

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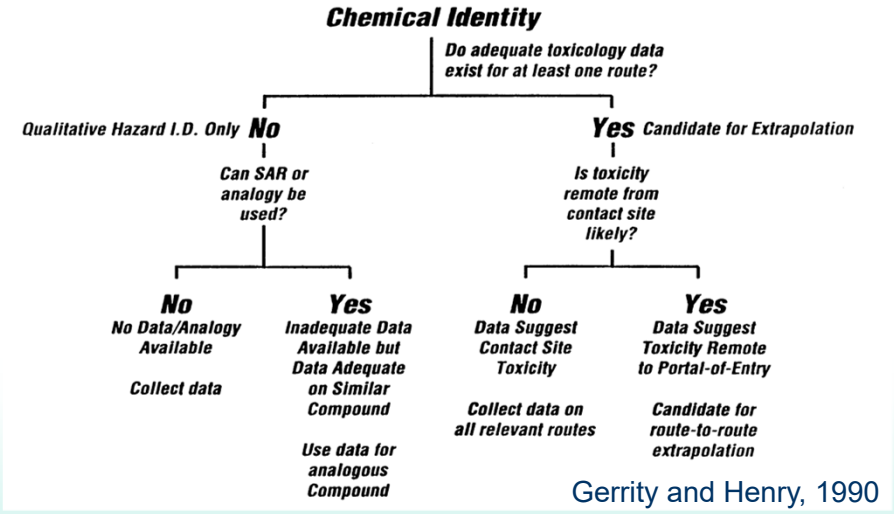
Decision Tree for Route-to-Route Extrapolation



Gerrity and Henry, 1990

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Decision Tree for Route-to-Route Extrapolation

Option 4: Data Suggest Toxicity Remote to Portal-of-Entry

- Use of Default Absorption Values
- Direct Measure of Absorption Efficiency
- Measure of Bioavailability by Internal Marker
- **Development of a Comprehensive Delivered Dose Description**

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Considerations in Route-to-Route Extrapolation

- Route-specific uptake
  - Inhalation and dermal: Uptake directly into systemic blood
    - Bypasses presystemic clearance
  - Oral: Uptake through gut tissue into portal blood
    - Complicated absorption processes, dependent on many factors
- Route-specific metabolism
  - Inhalation and dermal: limited metabolism
    - Important primarily for portal of entry effects
  - Oral: pre-systemic metabolic clearance in gut and liver
    - Much greater than pre-systemic clearance in lung or skin

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Safety Assessment for All-Trans Retinoic Acid Using Route-to-Route Extrapolation

- NDA: New proposed use as a topical skin treatment for wrinkles
- FDA concern: Potentially teratogenic
  - 13-cis isomer (Accutane): known human teratogen
- Problem: human topical radiolabel studies unable to distinguish active metabolites
- FDA suggestion: Use PBPK model to provide assurance of safety for intended use
- Approach: Compare fetal doses resulting from maternal dermal use with those associated with teratogenicity in oral animal studies

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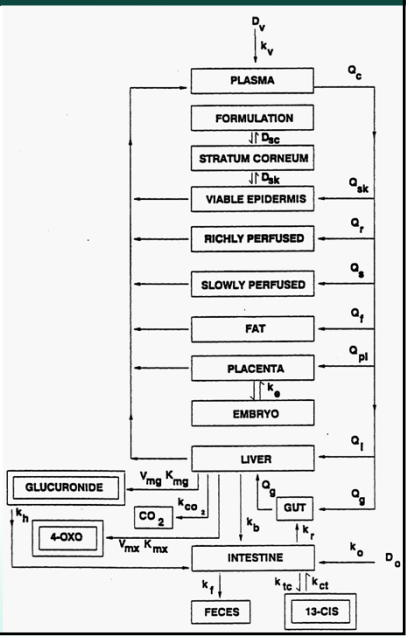
PBPK Model for All-Trans Retinoic Acid

- Multiple routes
  - Intravenous, oral, and topical exposure
- Multiple metabolism pathways
  - glucuronidation/hydrolysis, ring/side-chain oxidation, isomerization to 13-cis isomer
- Multiple dose measures
  - parent, total retinoids (radioactivity), total active retinoids (not glucuronides)



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Parameter Identification for PBPK Model

- Physiological parameters–literature
- Tissue distribution–oral mouse studies and *ex vivo* human placenta study
- Metabolism–rat and monkey IV kinetics and oral metabolite identification studies
- Biliary excretion–rat studies with exteriorized bile ducts
- Urinary and fecal excretion–rat and human studies
- Human oral and topical absorption parameters–human *in vivo* and *in vitro* studies

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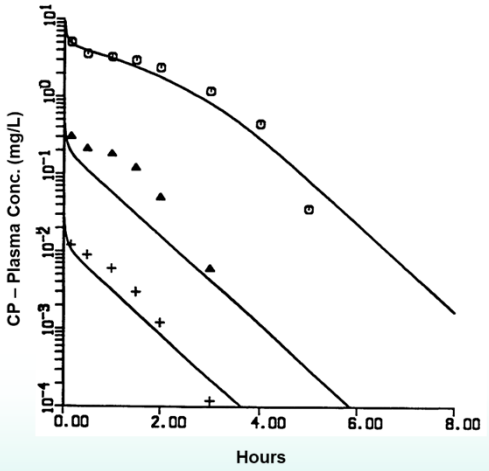
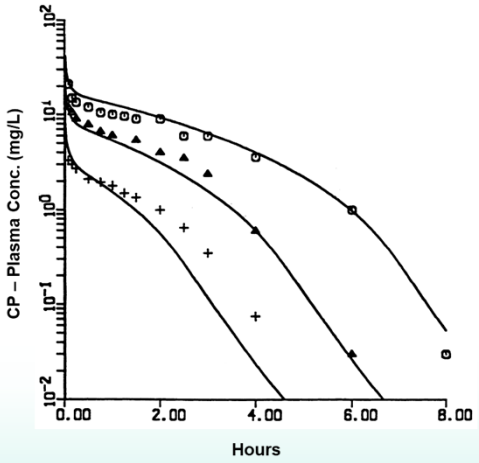
Rat, IV, ATRA
5.0, 0.25, and 0.015 mg/kg



Monkey, IV, ATRA 5.0, 2.5, and 1.0 mg/kg



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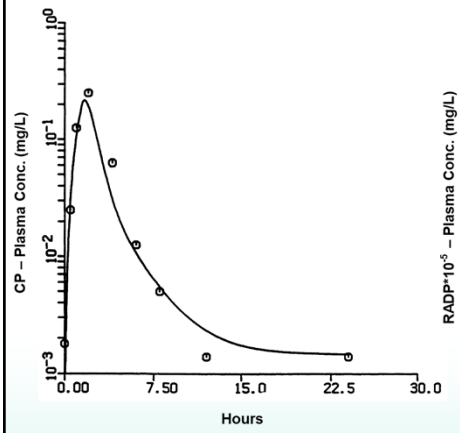
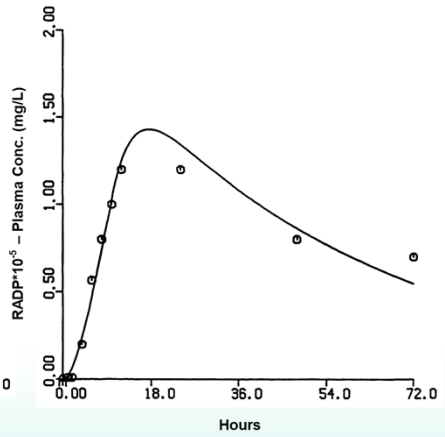
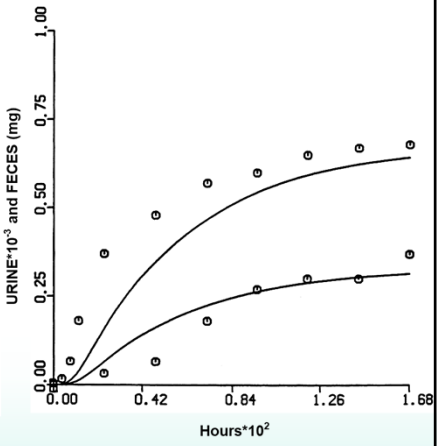
Human, Oral, ATRA
1.1 mg/kg



Human, Topical, ATRA
50 µg





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Key Determinants in Safety Assessment for All-Trans-Retinoic Acid

- Species differences in predominant metabolism
  - rodents: oxidation to active form
  - primates: glucuronidation to inactive form
- Exposure route differences in bioavailability
  - rapid oral uptake can exceed capacity of glucuronidation pathway
  - slow topical uptake subject to high affinity clearance
- Kinetic differences between isomers in humans
  - all-trans: rapid glucuronidation /clearance
  - 13-cis: slow oxidation/clearance

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Comparison of Alternative Dose Metrics for Retinoic Acid Teratogenicity

Species	Route	Dose (mg/kg)	All-Trans-Retinoic Acid		Total Active Retinoids		Total Retinoids
			C_{Max} (ng/mL)	AUC (ng*hr/mL)	C_{Max} (ng/mL)	AUC (ng*hr/mL)	C_{Max} (ng-eq/mL)
Minimal Teratogenic Doses							
Mouse	Oral	4	1078	1516	2875	10188	3504
Rat	Oral	2.5	965	1763	1912	12204	2337
Monkey	Oral	5	2105	4768	2348	5715	5354
Clinical Doses							
Human	Oral	1.1	229	558	235	601	1305
Human	Topical	Therapy [a]	0.001	0.014	0.001	0.014	0.015
Human	Topical	Abuse [b]	0.035	0.44	0.035	0.44	0.51

[a] 0.05% formulation; face only; wash after 10 hours.
[b] 0.05% formulation; face, arms, chest; wash after 10 hours.

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Predicted All-Trans-Retinoic Acid CMax and AUC Predicted Under Hypothetical Extreme Situations

	Route	Dose (mg/kg)	Number of Days	All-Trans-Retinoic Acid		Total Active Retinoids	
				C_{Max} (ng/mL)	AUC (ng*hr/mL)	C_{Max} (ng/mL)	AUC (ng*hr/mL)
Minimal Teratogenic Doses (ATRA)							
Rat	Oral	2.5	1	943	2029	1918	13554
Rat	Oral	2.5	10	943	226320	1918	460320
Clinical Doses (Human)							
Endogenous				1.7	258	1.9	274
10% Absorption (40 kg person)	Topical	Abuse	1	0.18	2.1	0.18	2.1
10% Absorption (Fetal)	Topical	Abuse	35	0.18	151.2	0.18	151.2
10% Absorption (80 kg person)	Topical	Abuse	1	0.17	2.0	0.17	2.0
10% Absorption (Fetal)	Topical	Abuse	35	0.17	142.8	0.17	142.8

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Conclusions of PBPK Modeling for Retinoic Acid

- Conclusions of PBPK modeling: “Topical exposure results in four to five orders of magnitude lower internal exposure than minimal teratogenic doses for any meaningful measure of fetal exposure”
- FDA evaluation of PBPK model: “Internal exposure calculations are relatively insensitive to changes in the PBPK model which preserve correspondence with the experimental data”
- Result: Resolved FDA concern, discussions moved forward to labeling requirements. PBPK model cited in FDA approval of NDA.

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References

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