

Cross-species and Life Stage PBPK Modeling of BaP and DBC

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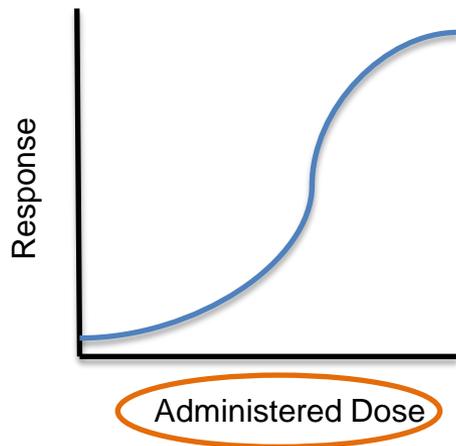
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Background

- ▶ Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous, often carcinogenic
 - Combustion by-products, found at ~half of Superfund sites
 - Exposure is increasing as energy consumption rises
- ▶ Benzo[a]pyrene (BaP) is the prototypic carcinogenic PAH
- ▶ Dibenzo[def,p]chrysene (**DBC**) is a less prevalent but highly potent transplacental carcinogenic PAH
 - Carcinogenicity associated with CYP1B1 bioactivation
- ▶ How do we extrapolate results from gavage studies in rodents to relevant human exposures?

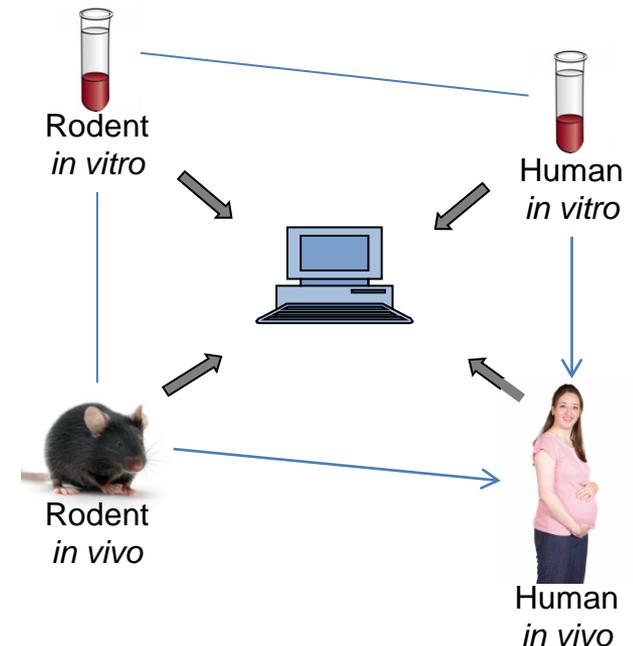


Defining “Dose” is Key

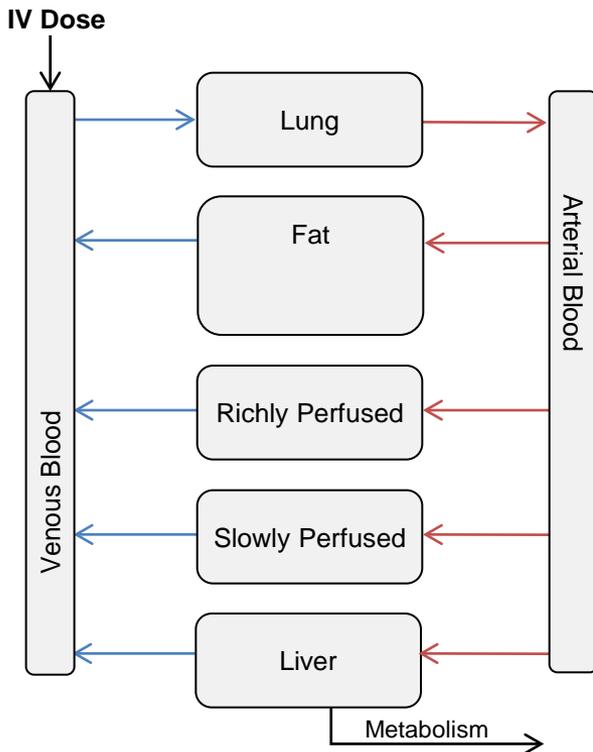


- ▶ Parent chemical vs. metabolite?
- ▶ What is the “internal dose” most closely associated with mode of action?
- ▶ What factors govern “internal dose”?

- ▶ Physiologically based pharmacokinetic (**PBPK**) modeling
 - Mathematical description of physiological and biochemical processes
 - Facilitate estimation of internal dose
- ▶ Validated PBPK models are *predictive* – extrapolate between:
 - High and low doses
 - Organisms of interest
 - Different routes of exposure



PBPK Model Development - Structure



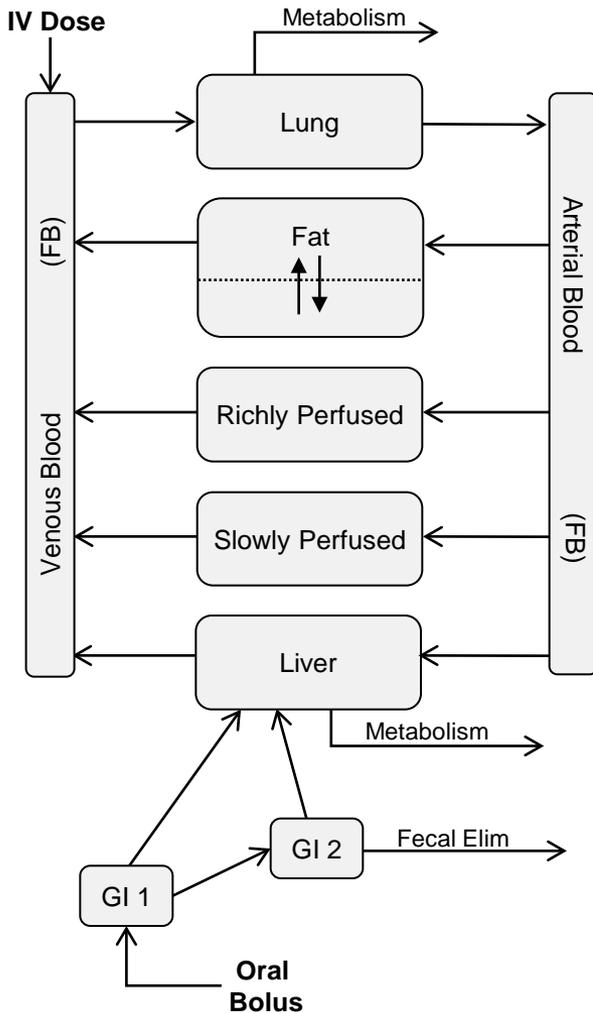
- ▶ Tissues are lumped according to blood flow
- ▶ Tissues of interest are described individually
- ▶ Concentration in each tissue compartment (CT) is determined continuously based on
 - Compartment volume (VT)
 - Blood flow (QT)
 - Concentration in arterial blood (CA)
 - Blood:Tissue Partitioning (PT)
 - Metabolism and/or elimination processes



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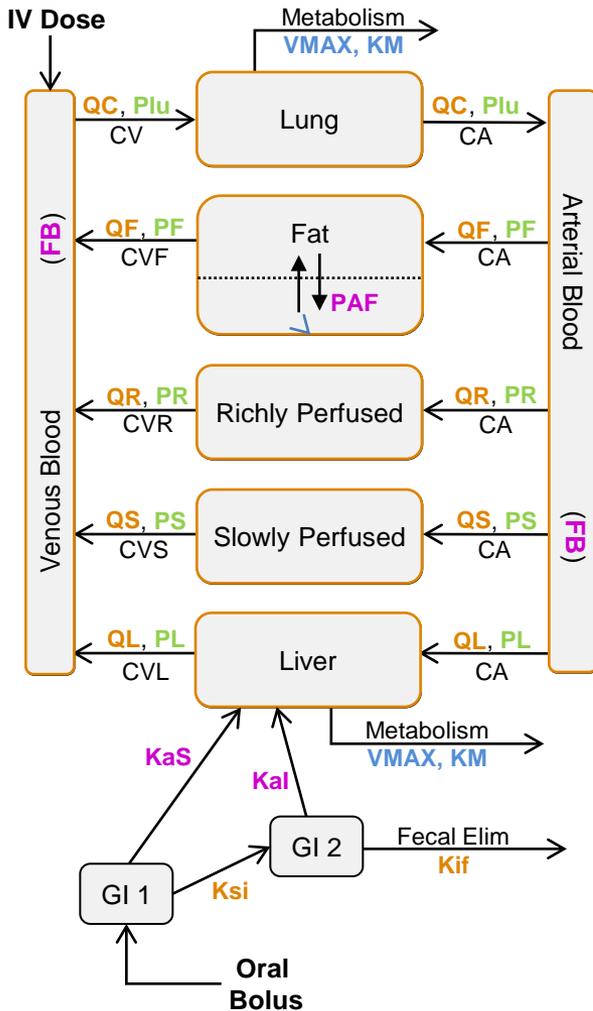
PBPK Model Development - Structure



- ▶ Well-mixed tissue compartments
 - Diffusion limited fat
- ▶ Fractional binding in blood
- ▶ Saturable metabolism in liver and lung
- ▶ Two compartment theoretical GI tract for absorption of oral dose



PBPK Model Development - Parameterization



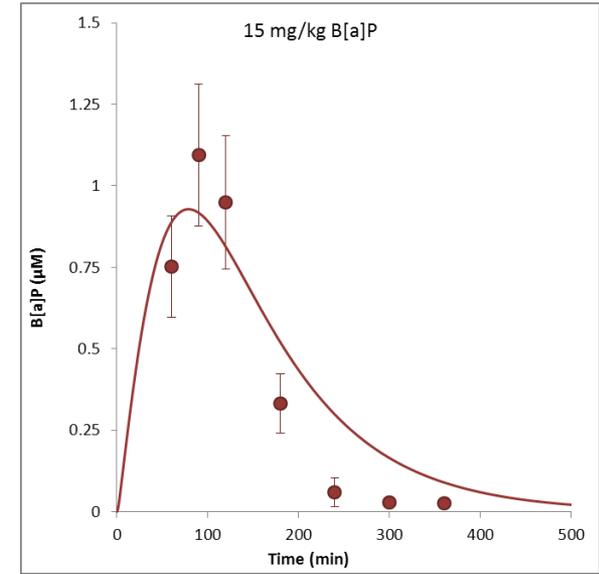
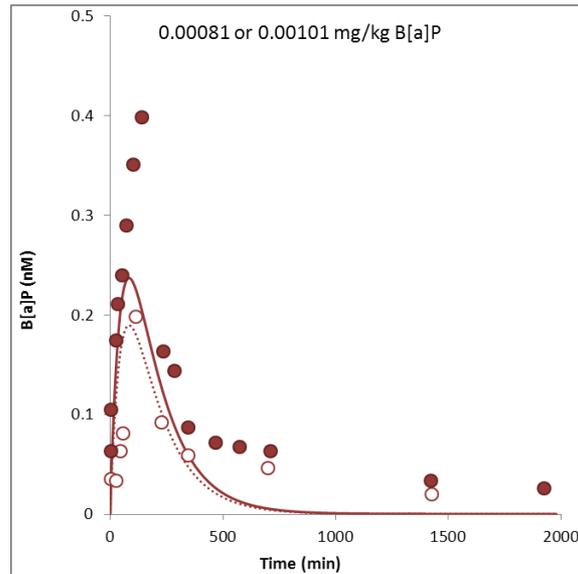
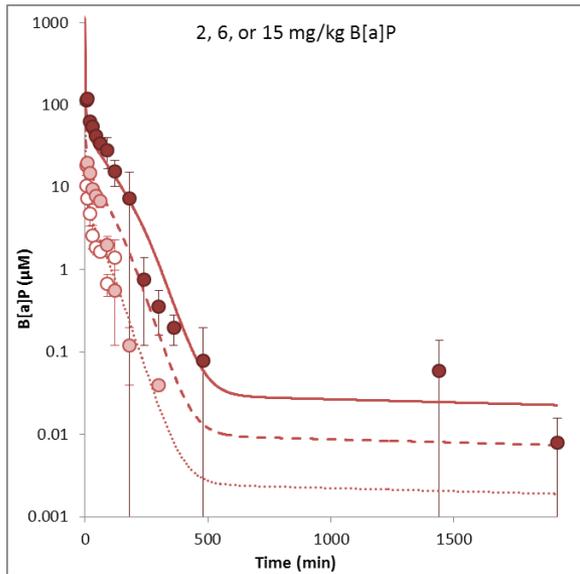
- ▶ Standard **measured** physiological values (literature)
 - Tissue volume
 - Blood flow
 - GI motility
- ▶ **Measured** biochemical parameters (literature)
 - Metabolic rate constants
- ▶ **Estimated** from physical-chemical properties and tissue composition using published algorithms
 - Tissue:Blood partition coefficients
- ▶ **Optimized** by curve fitting to select PK data
 - GI Absorption
 - Fat permeability
 - Blood binding



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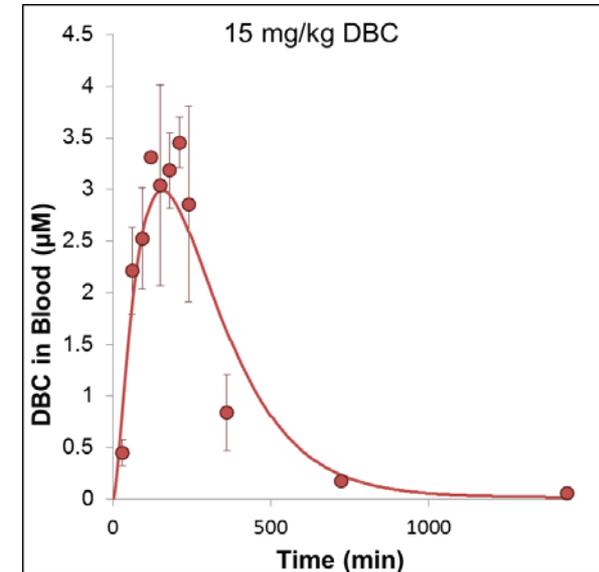
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Preliminary PAH Models – Crowell et al., 2011



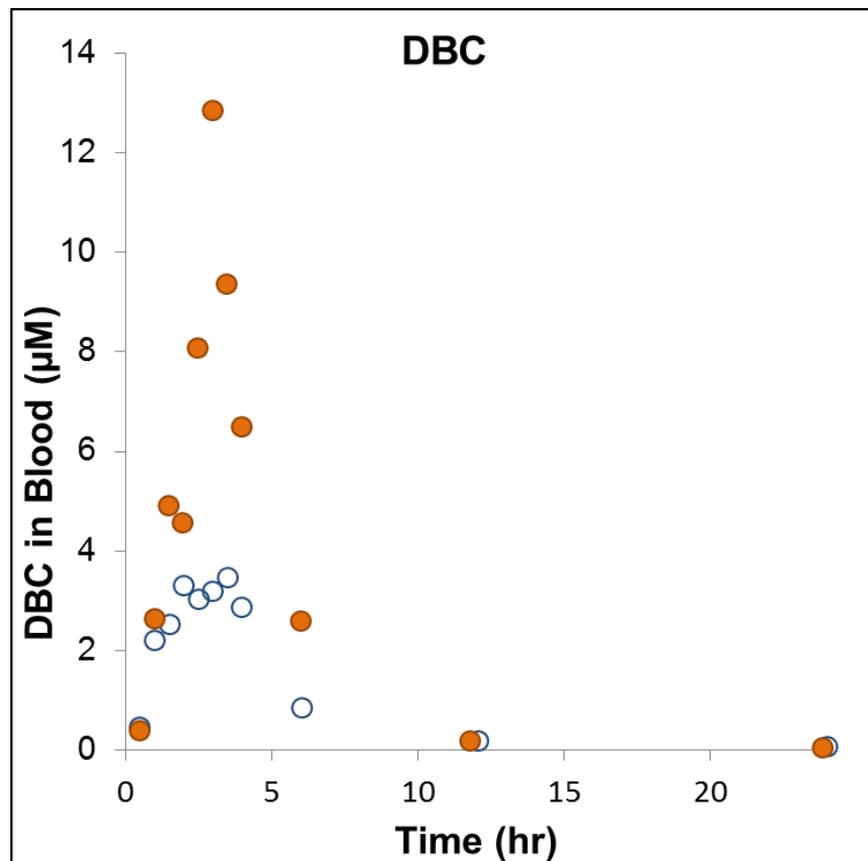
▶ Accurately predicted blood and tissue concentrations

- Many orders of magnitude of exposure
- Multiple routes of exposure
- Rats and mice
- BaP and DBC



PBPK Modeling of Pregnancy - DBC

- ▶ Pregnancy affects DBC pharmacokinetics
 - >3x higher C_{MAX} in blood and tissues
 - Not explained by pregnancy related physiological changes
- ▶ Activity based protein profiling (ABPP) of enzyme *activity*
 - Functional proteomics technique
 - Probes covering >75 microsomal enzymes important to PAH metabolism
- ▶ 2 to 10 fold reduction in enzyme activity in liver tissue of pregnant mice

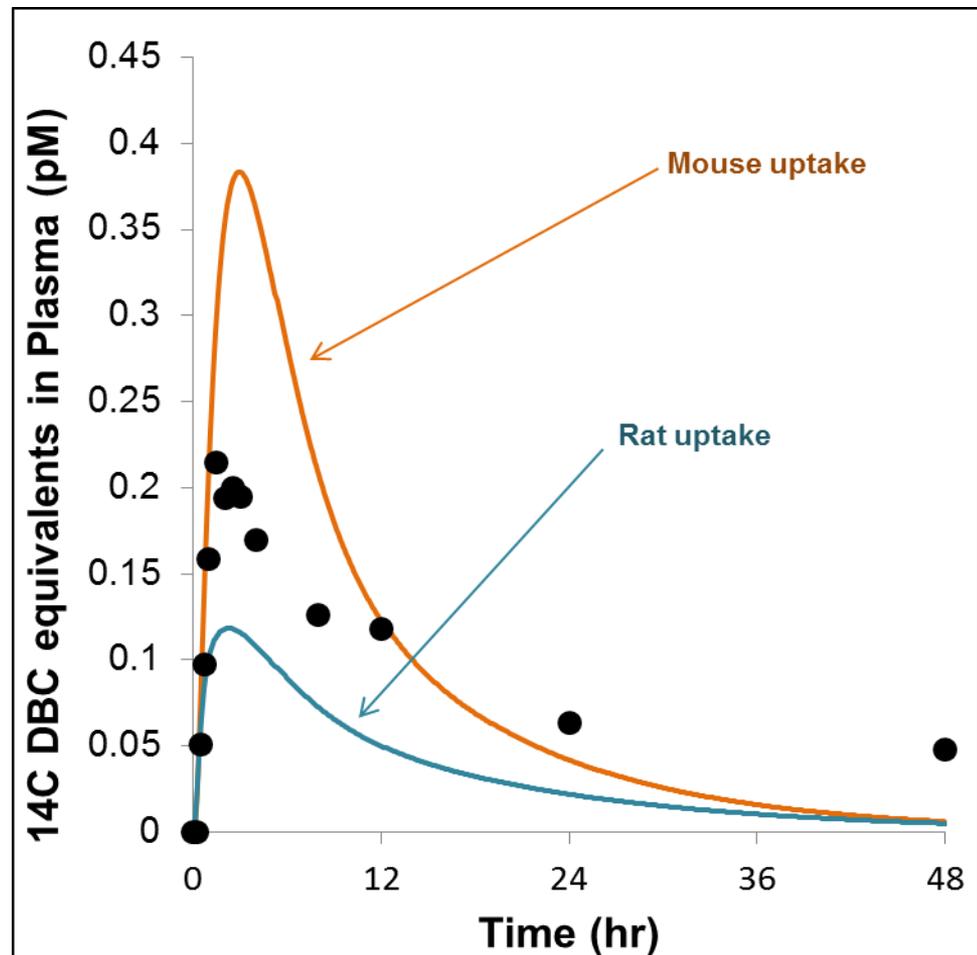


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Preliminary Modeling of Human Exposure

- ▶ Ultra-low doses of ^{14}C labeled DBC were administered to human volunteers
 - 30 ng bolus doses *below background PAH exposure*
 - Plasma and urine
 - Currently total ^{14}C , but using AMS to identify parent/metabolites
- ▶ Extrapolated human model for DBC
 - *In vitro* metabolic parameters measured in human microsomes
 - GI uptake parameters scaled from rodents
- ▶ Remarkably close to observed data

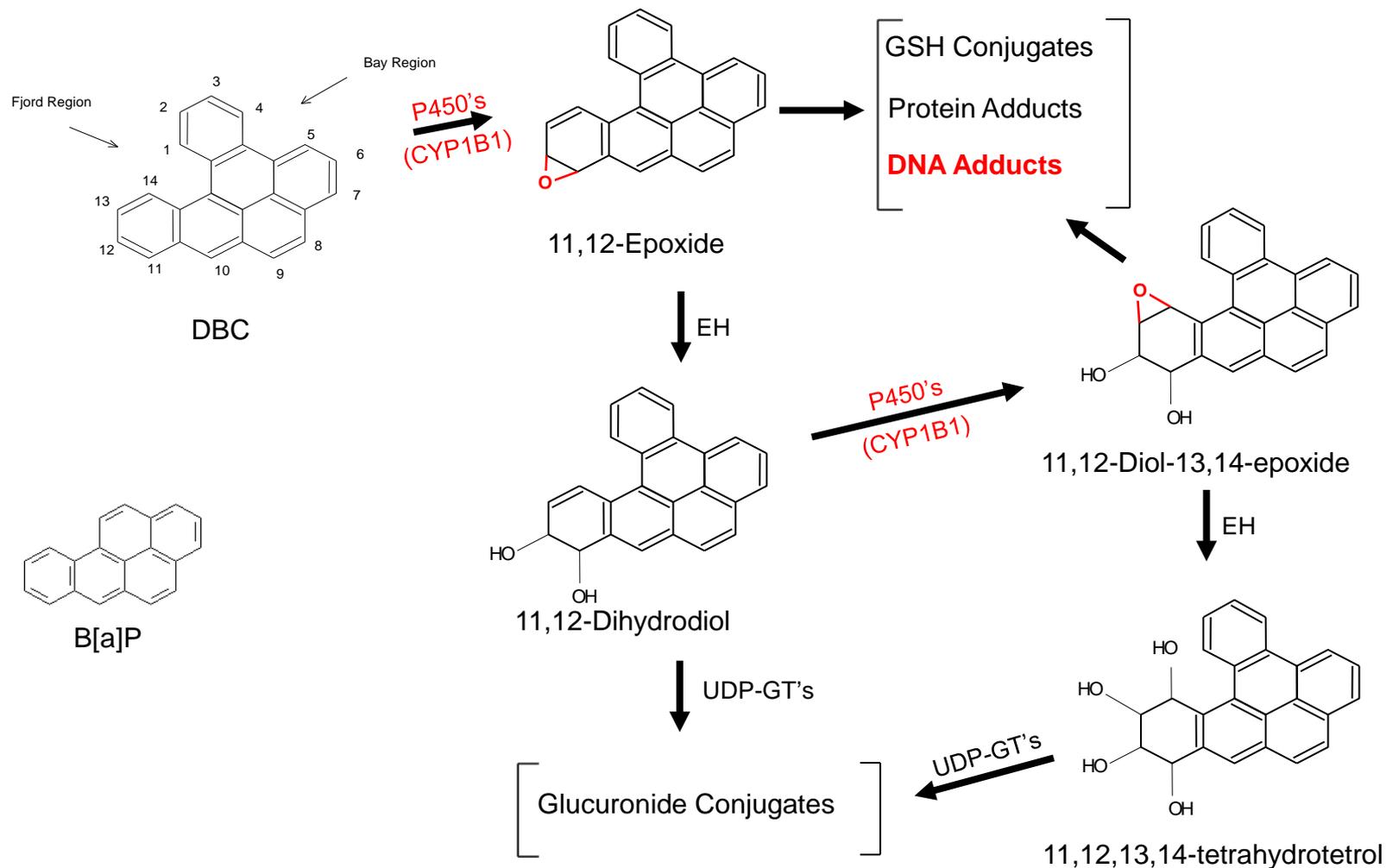


Ongoing and Future Research

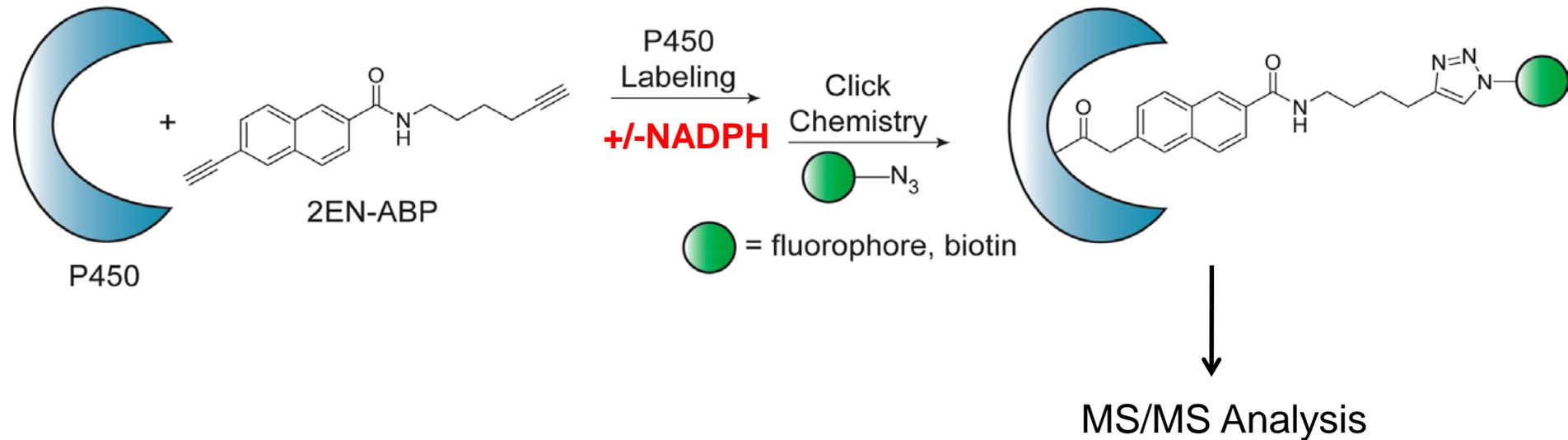
- ▶ Pharmacokinetic studies
 - **DBC** PK in fetal tissues (analysis underway)
 - Ultra-low dose PK in human blood and urine
 - DBC (analysis underway)
 - B[a]P (part of SRP renewal)
- ▶ Metabolism
 - Ontogeny studies of P450 development, distribution
 - ABPP enzyme activity for key life stages (analysis underway)
 - Mouse: Adult, pregnant, fetal, neonatal, weanling
 - Human: early fetal tissues
- ▶ Continuing development, refinement, and application of PBPK models

...Questions?

Metabolism Key to Mode of Action (Simplified Scheme)



Activity-Based Protein Profiling



Activity-Based Protein Profiling

- ▶ Currently includes probes for >75 microsomal enzymes
- ▶ Includes multiple isoforms of enzymes important for PAH metabolism
 - P450s
 - Epoxide Hydrolases
 - Glutathione-S-Transferases
 - UDP-Glucuronosyl Transferases
- ▶ Probes developed for mouse and human enzymes
- ▶ Currently evaluating impact of DBC and pregnancy in mouse liver, lung, fetus
- ▶ Will augment mouse and human ontogeny studies in year 4
- ▶ Propose to expand enzyme coverage and applications in renewal

