

Biotransformation & ToxCast

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Overview

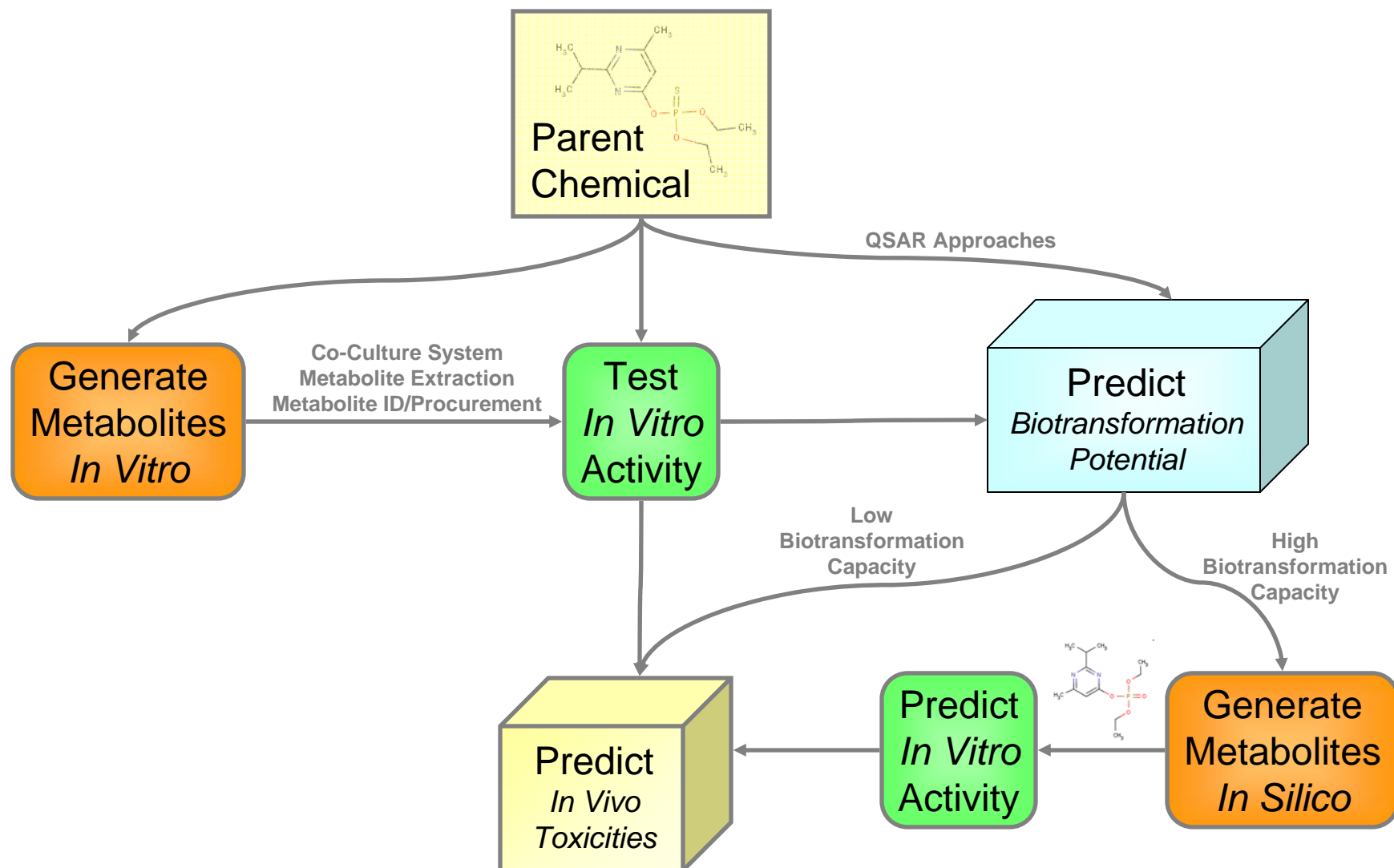
- ToxCast Biotransformation Overview
- Parent/Metabolite Analysis
- Examples of Biotransformation
- Conclusions & Next Steps

ToxCast

Biotransformation

- ToxCast_320
 - 309 Unique Chemical Structures
 - 13 Parent-Metabolite Pairs
 - 1 Replicate (DBP)
 - 3 Parent Chemicals Share Common Metabolite (ETU)
- ToxCast Assays (500+ Endpoints)
 - Cell-Based
 - HCS & Cytotoxicity
 - w/ & w/o Metabolic Competency
 - ADME (CYP Inhibition & Induction/Suppression)
 - NR (Binding & Transcription Factor Activation)

Conceptual Model for Incorporating Biotransformation in Predictive Modeling



High Parent vs. Low Metabolite
 Low Parent vs. High Metabolite

ToxCast In Vitro Endpoints (n=627)

- ACEA
- Attagene
- BioSeek
- Cellumen
- CellzDirect
- Gentronix
- NCGC
- Novascreen
- Solidus

Parent/Metabolite Combinations

Metiram-zinc
 ETU2

Maneb
 ETU1

Mancozeb
 ETU3

DBP1
 MBP1

DBP2
 MBP2

Malathion
 Malaoxon

Diazinon
 Diazoxon

DMP
 MHP

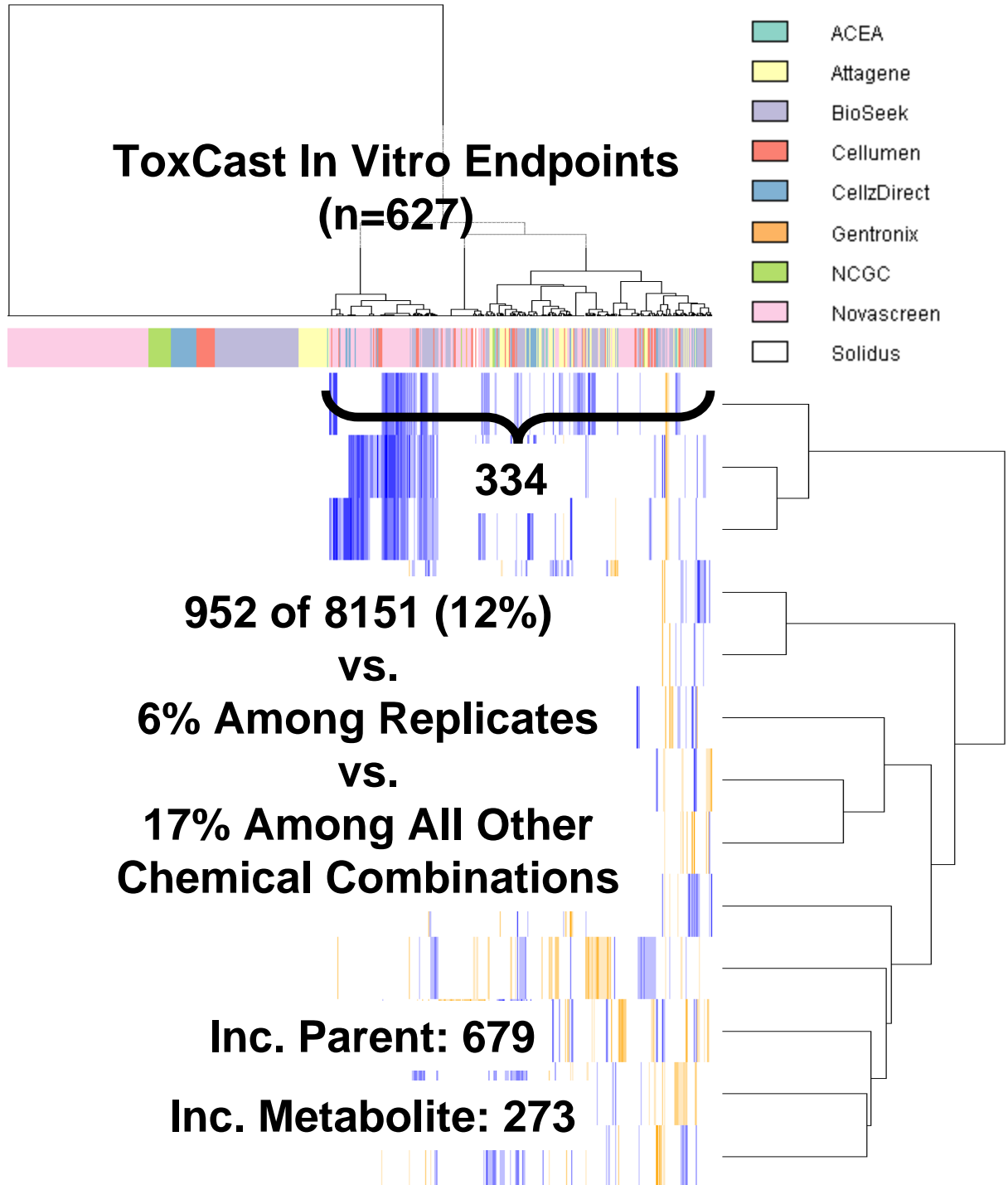
Atrazine
 Deisopropylatrazine

Chlorpyrifos-methyl
 Chlorpyrifos oxon

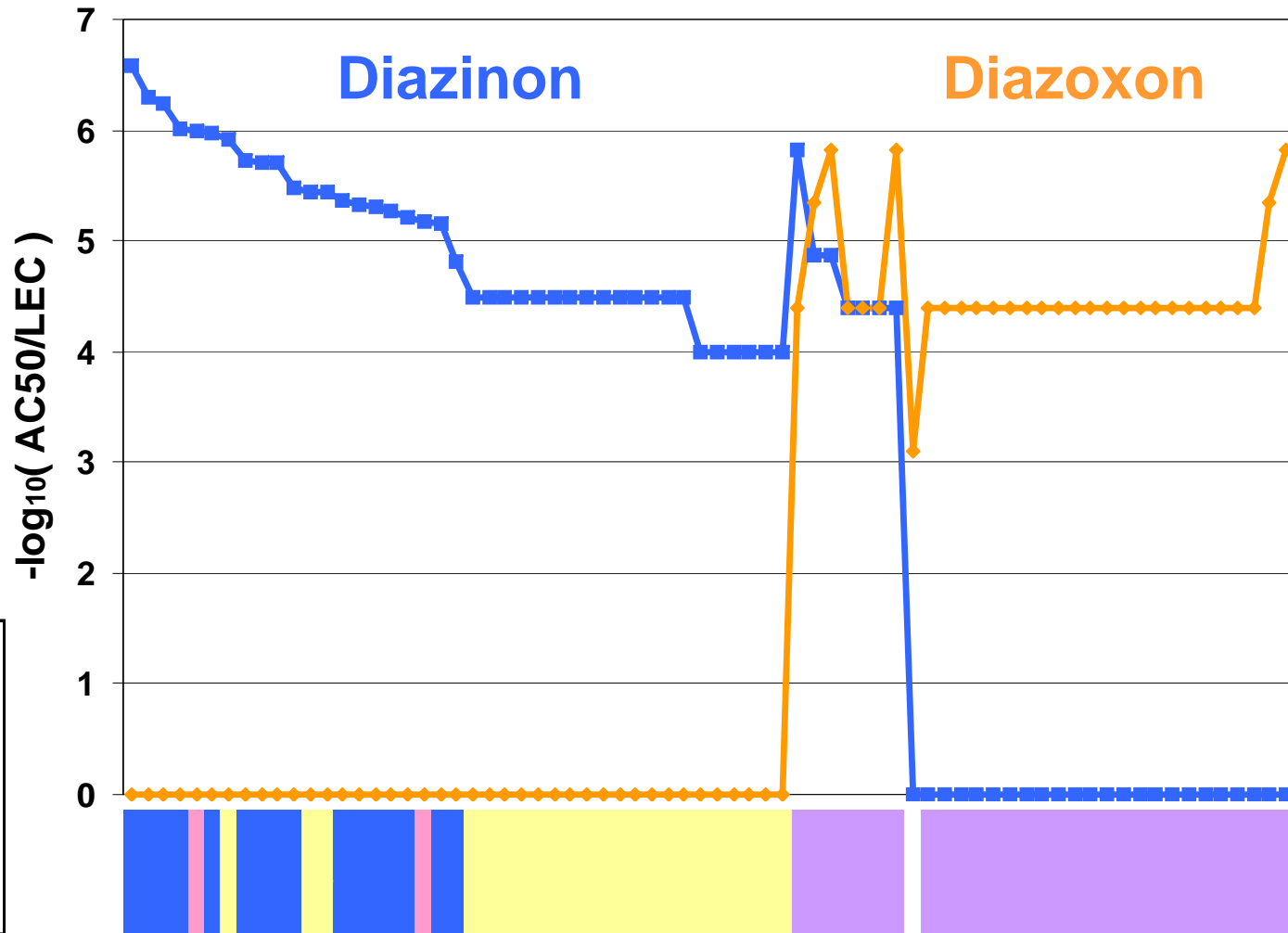
Methoxychlor
 HPTE

Metam-sodium
 Methyl isothiocyanate

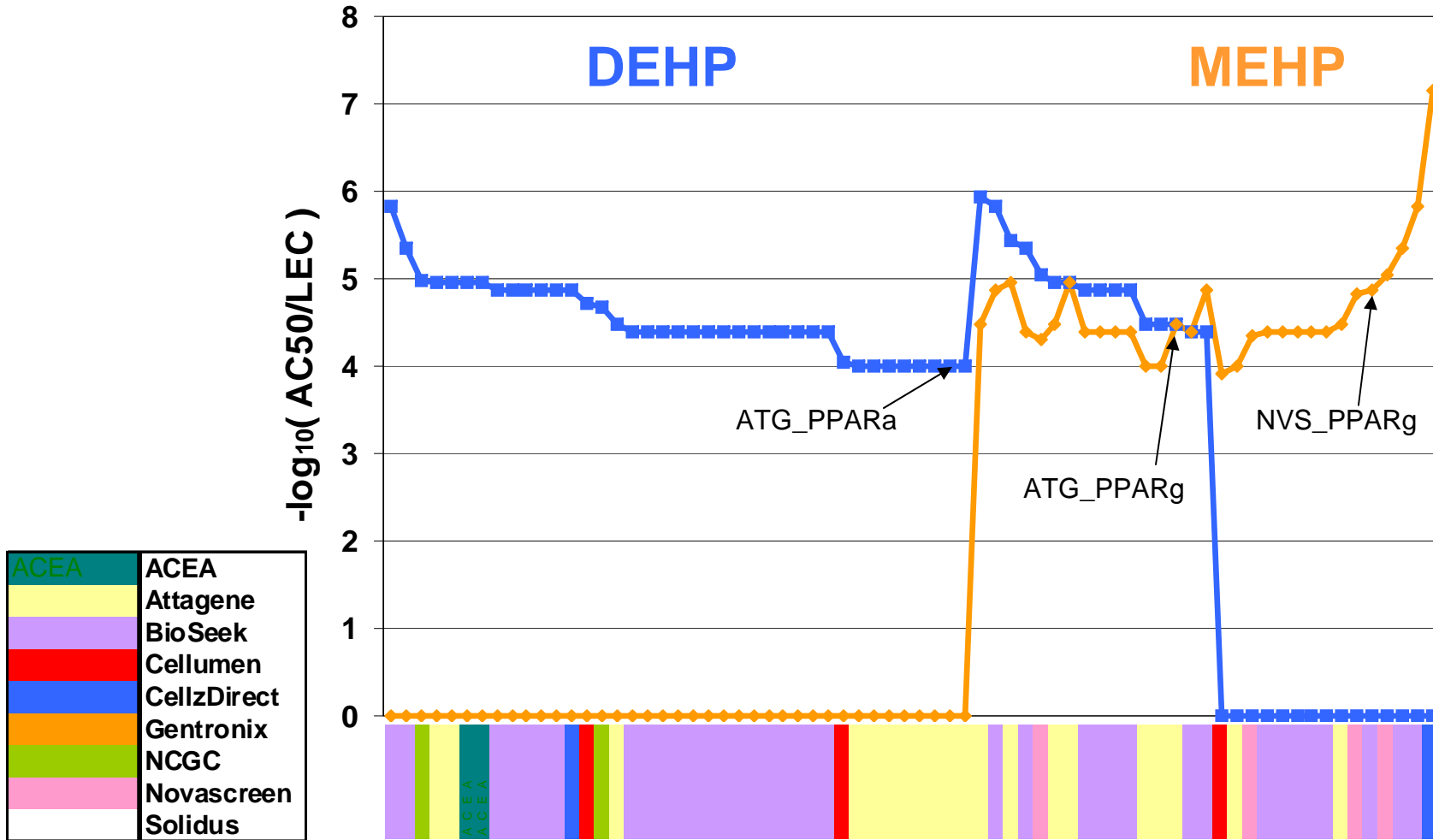
DEHP
 MEHP



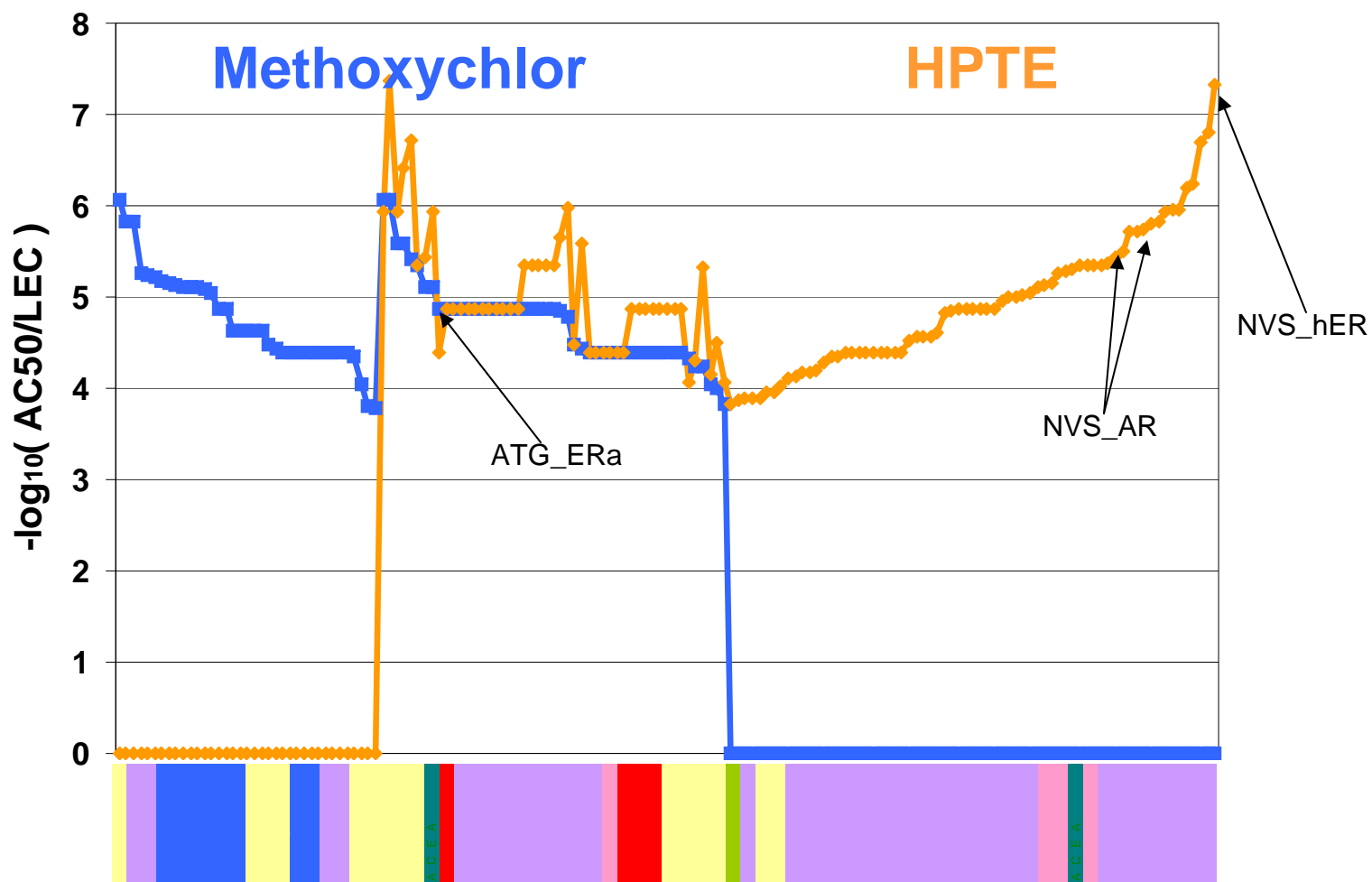
Comparing Parent & Metabolite Bioactivity Profiles



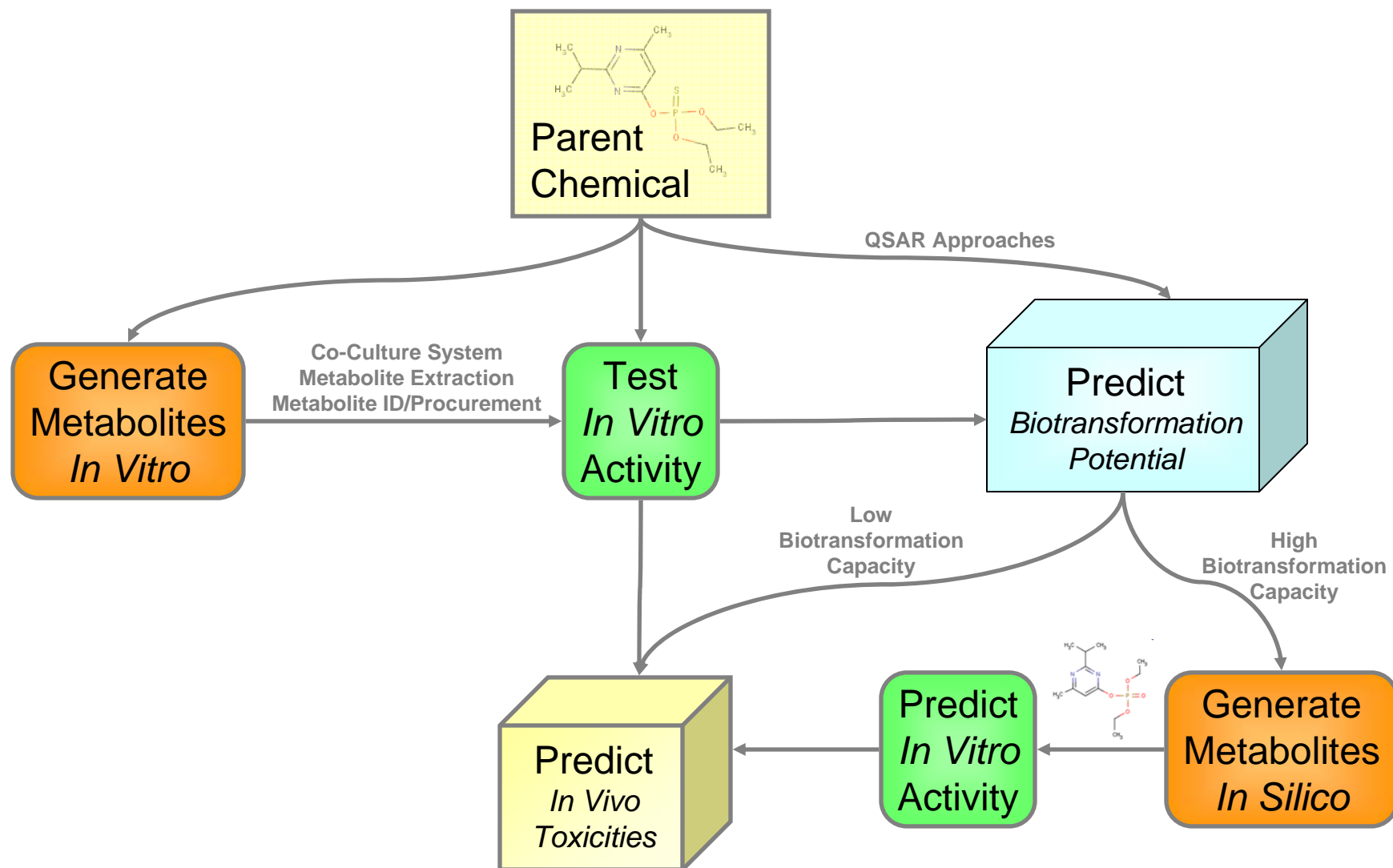
Comparing Parent & Metabolite Bioactivity Profiles



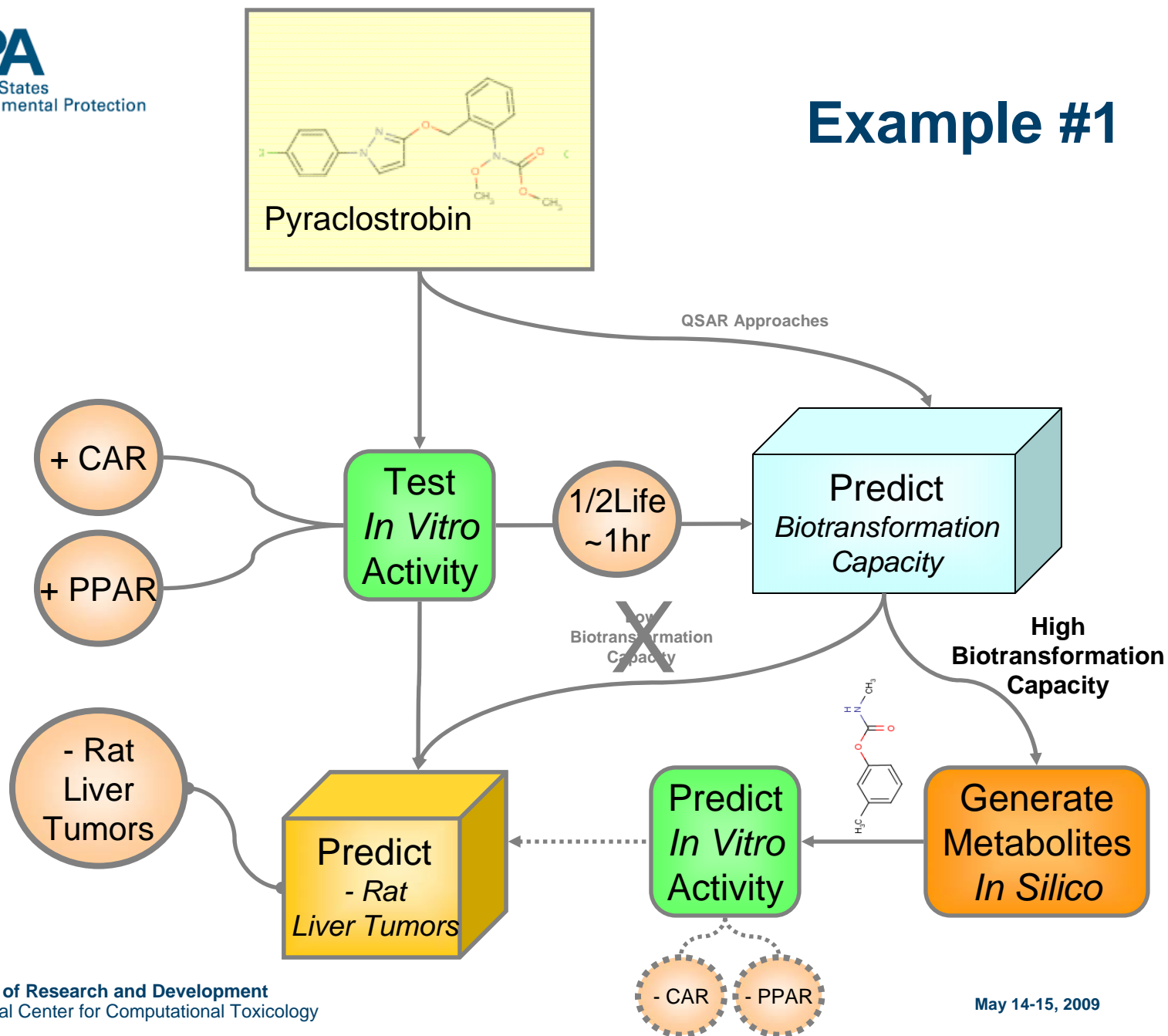
Comparing Parent & Metabolite Bioactivity Profiles



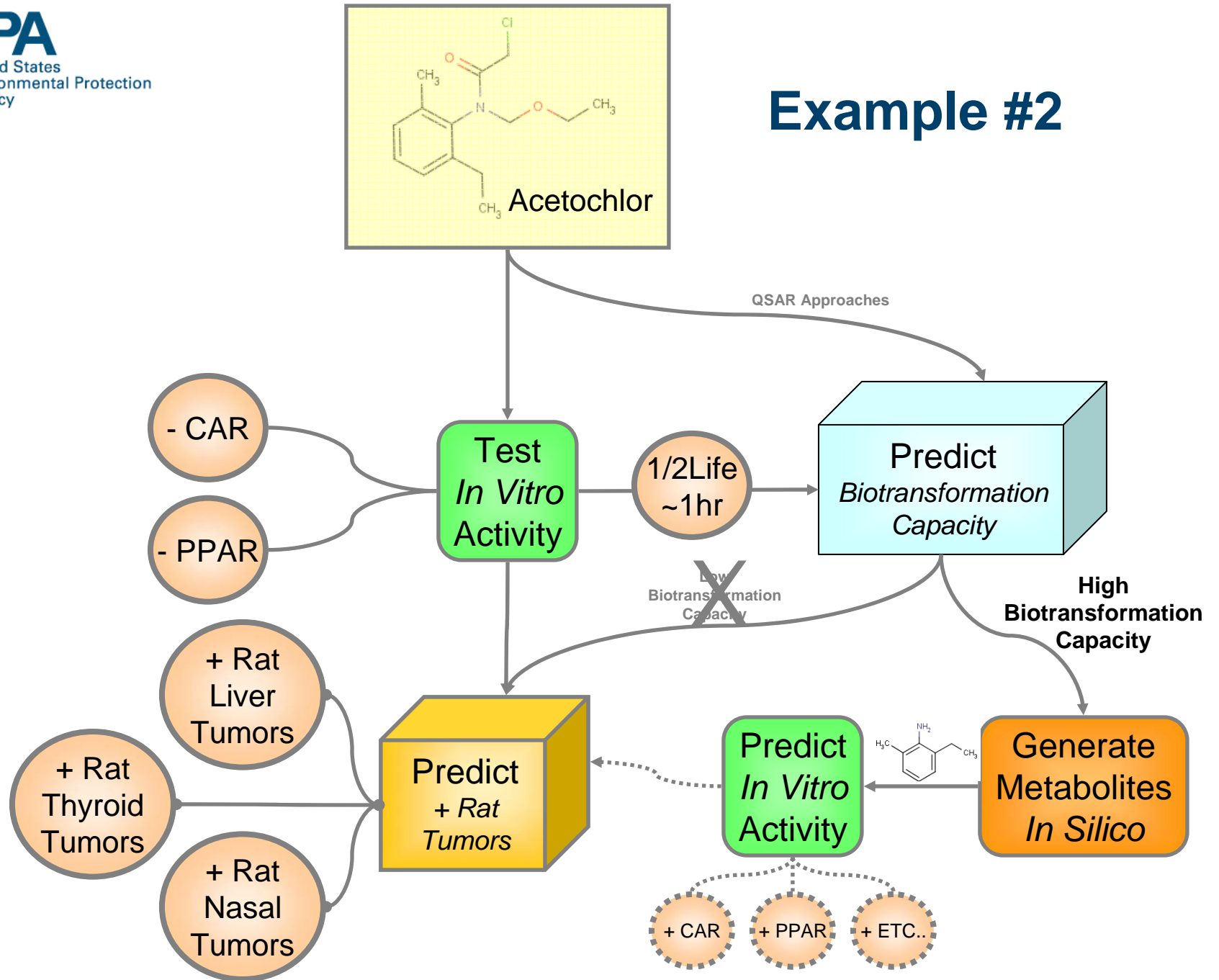
Conceptual Model for Incorporating Biotransformation in Predictive Modeling



Example #1



Example #2



Conclusions

- Specific parent and metabolite activities
- Certain assays are more sensitive to biotransformation
- Biotransformation is two-tailed
- Conceptual model incorporating biotransformation into predictive modeling

Next Steps

- ToxCast Phase II & Tox21: Identify and procure larger set of parent-metabolite pairs
- Anchor in vitro data to in vitro clearance data
- Anchor in vitro data to in vivo metabolism study data
- Develop predictive models of biotransformation & subsequent activity/toxicity