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ILSI Health and Environmental Sciences Institute

AGRICULTURAL CHEMICAL SAFETY ASSESSMENT (ACSA)

ADME Task Force

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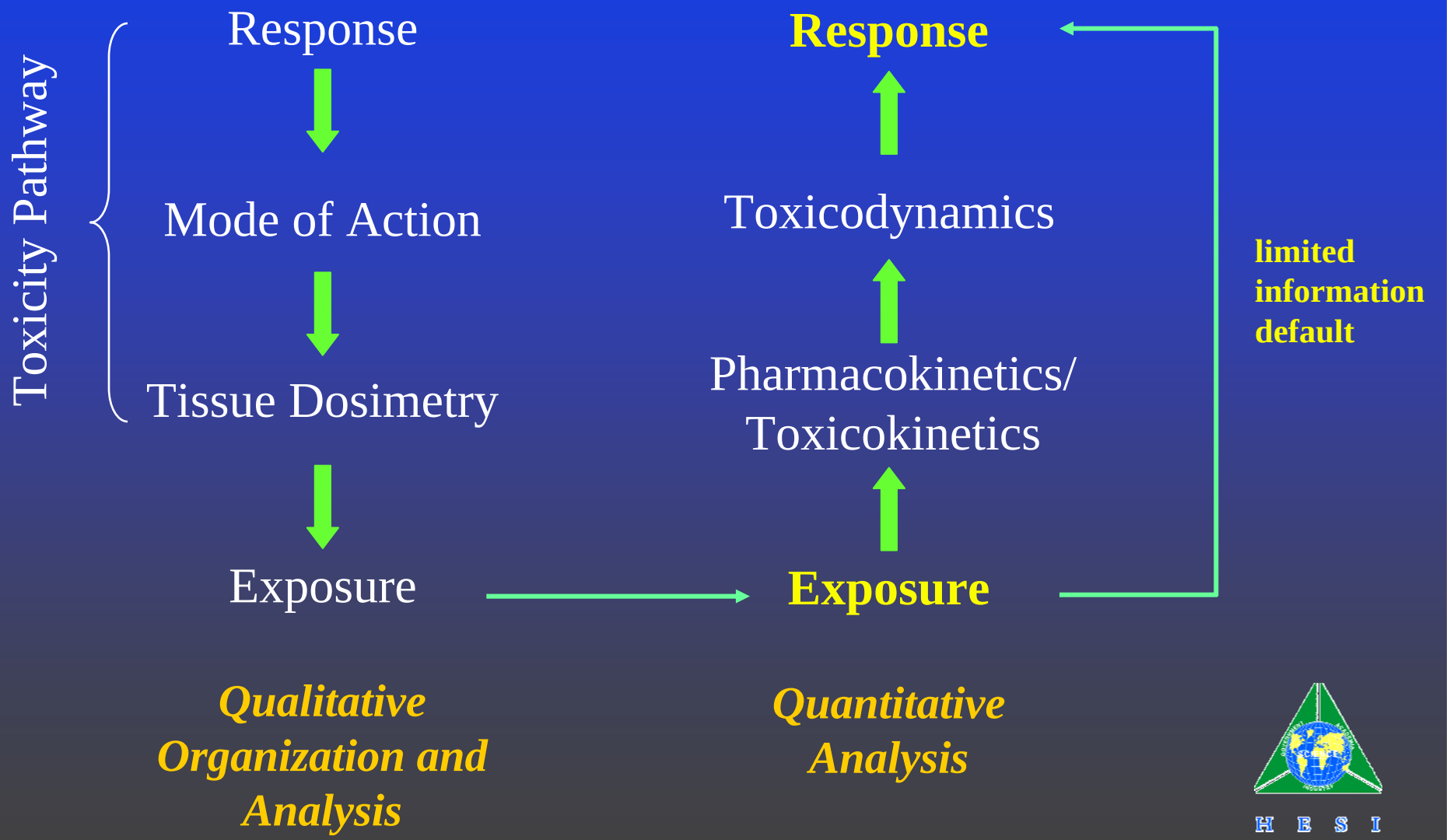
Hazard Characterization and Dose-Response Framework



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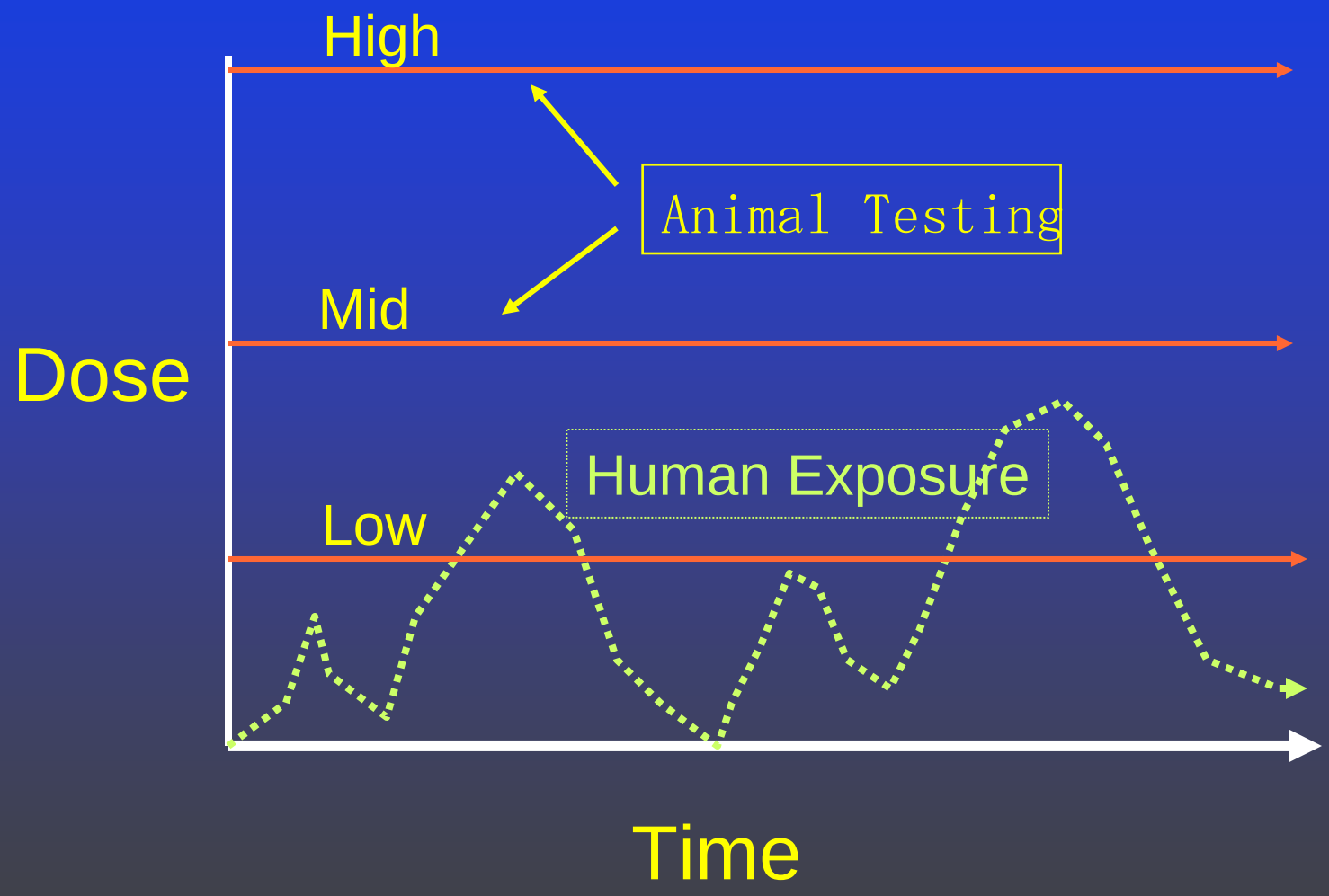
Dose-Response-Time



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Purpose of ADME Studies

- Dose-Response: Obtain information to help determine the relationship between the concentration of free compound in plasma and the toxicological response.
- Risk: Provide data that assists in the design and interpretation of toxicity studies and the determination of risk.

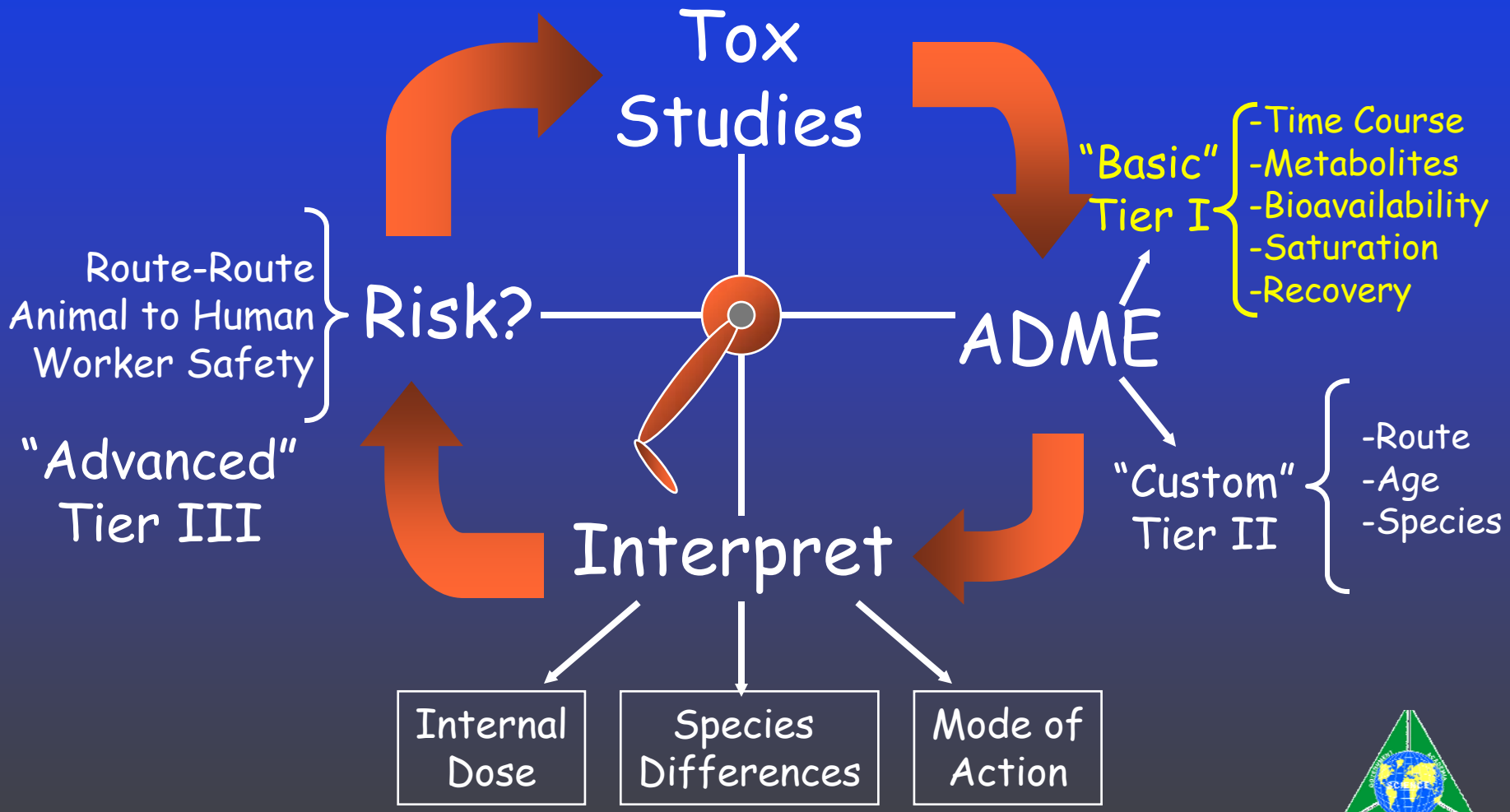
Objectives

- Develop guidance for the careful, tier-wise collection of PK data that would better define dose across…
  - species
  - life stages
  - route
  - frequency and duration of exposure

Objectives (continued)

- Provide recommendations that would help in…
  - Toxicology study design
  - Interpretation
  - Risk Assessment

Working through the process…



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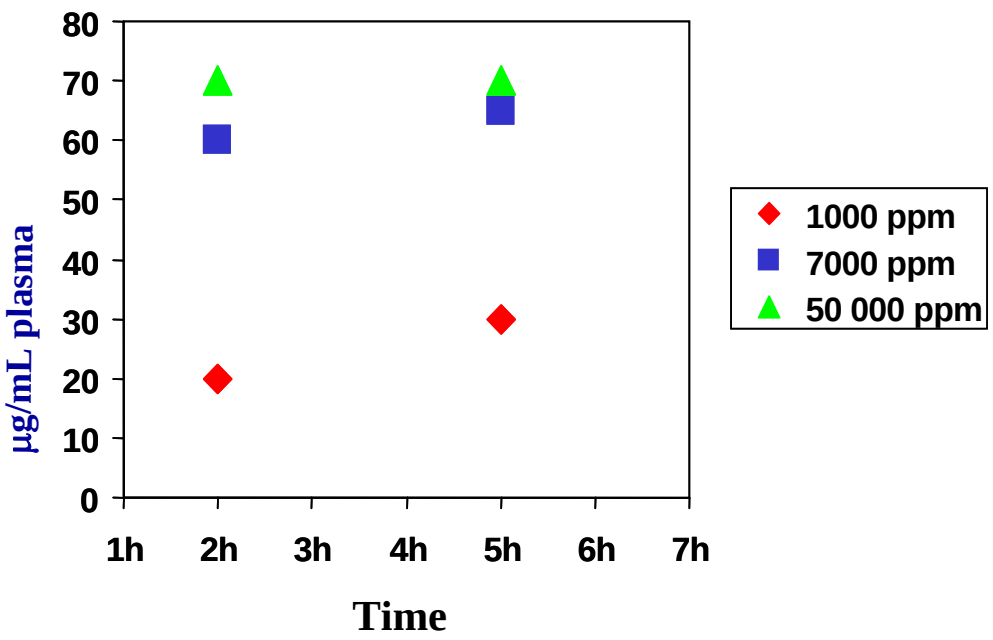
“Basic” Tier I

- Oral Bioavailability (iv, oral)
- Metabolism and Elimination
- Dose-Dependent PK
- Repeated-Exposure PK
- Blood levels in toxicity studies

Assisting in Dose Selection

- Dose selection for chronic studies would be improved with a bioavailability assessment.
- This is an example of saturation of oral absorption at doses >7000 ppm in diet:

Plasma Time-Course: Dietary Exposure



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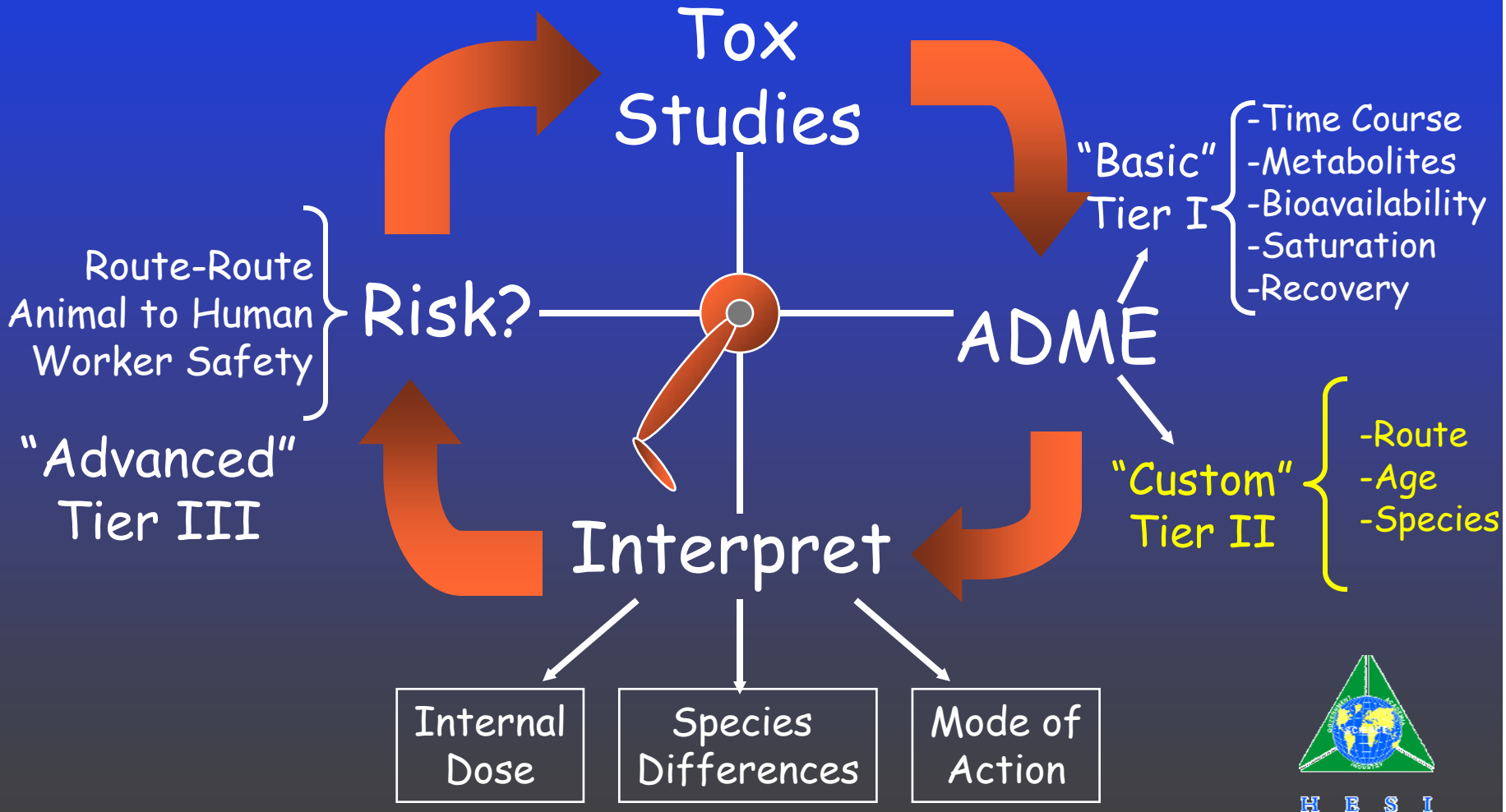
Working through the process…



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…For Interpretation

- Dose-Response
- Mode of Action
- Internal Dose

"Custom" Tier II Studies

- Non-rodent PK
- Tissue/fluid distribution (including fetus/milk)
- In vitro metabolism: rodents/humans
- Serum protein binding
- Biliary excretion/enterohepatic recirculation

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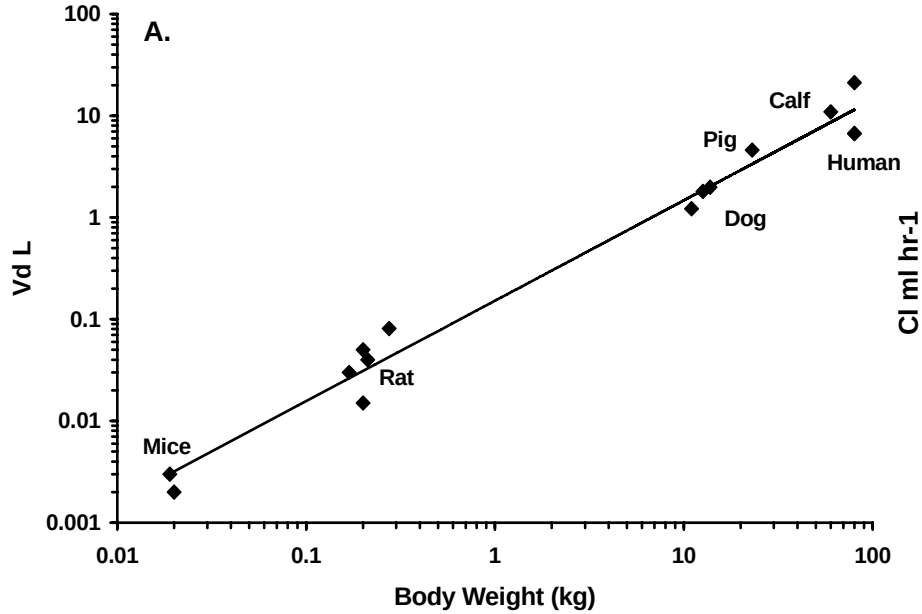
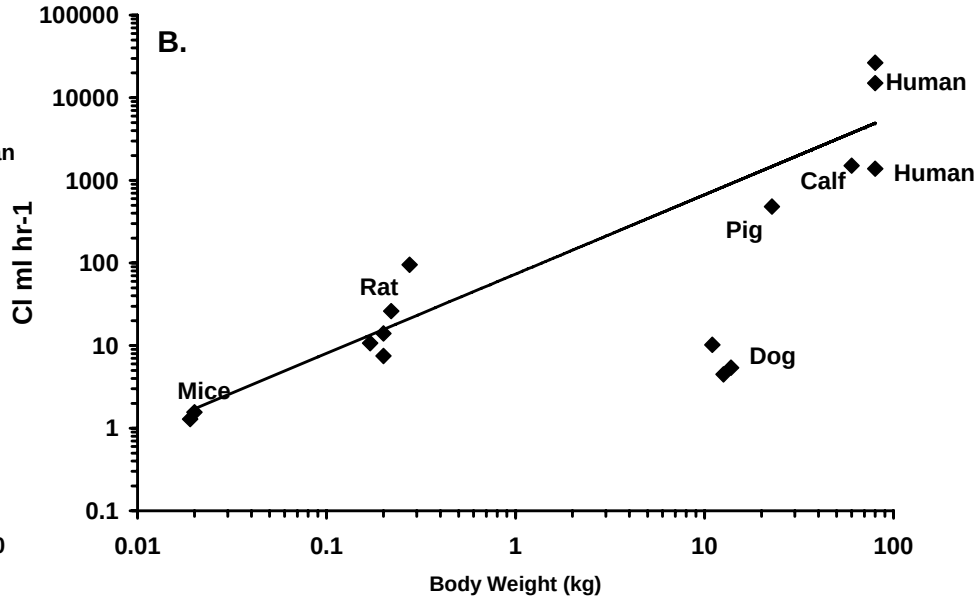
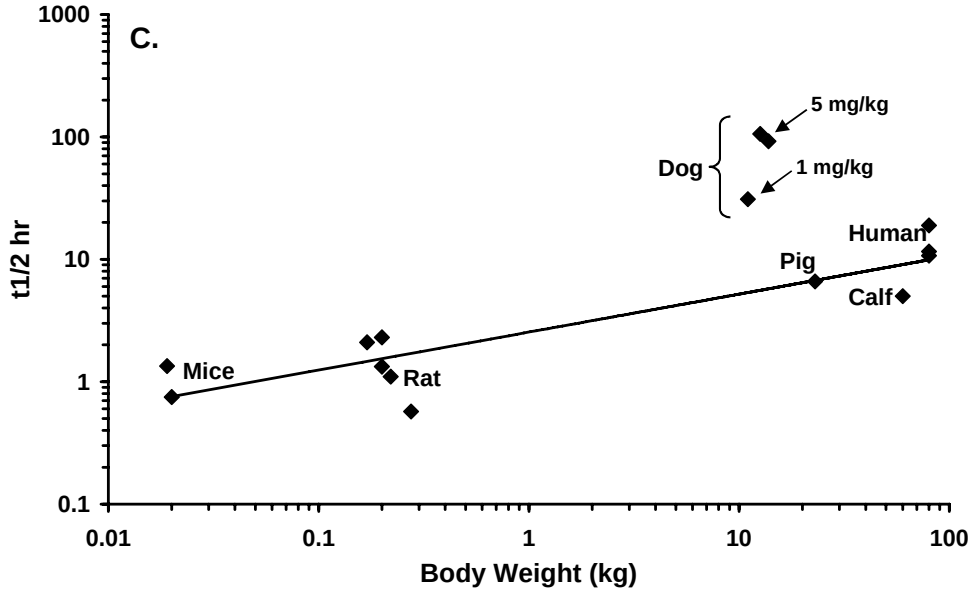
Example: Species Relevance

- The dog is uniquely more sensitive to organic acids like 2,4-D.
- Renal clearance studies suggest that the dog has a low capacity to excrete organic acids.
- Allometric comparison of the pharmacokinetic parameters: volume distribution (Vd), renal clearance (Cl) and plasma half-life ($t_{1/2}$) were conducted across species (including human).
- Conclusion: the dog is an outlier.

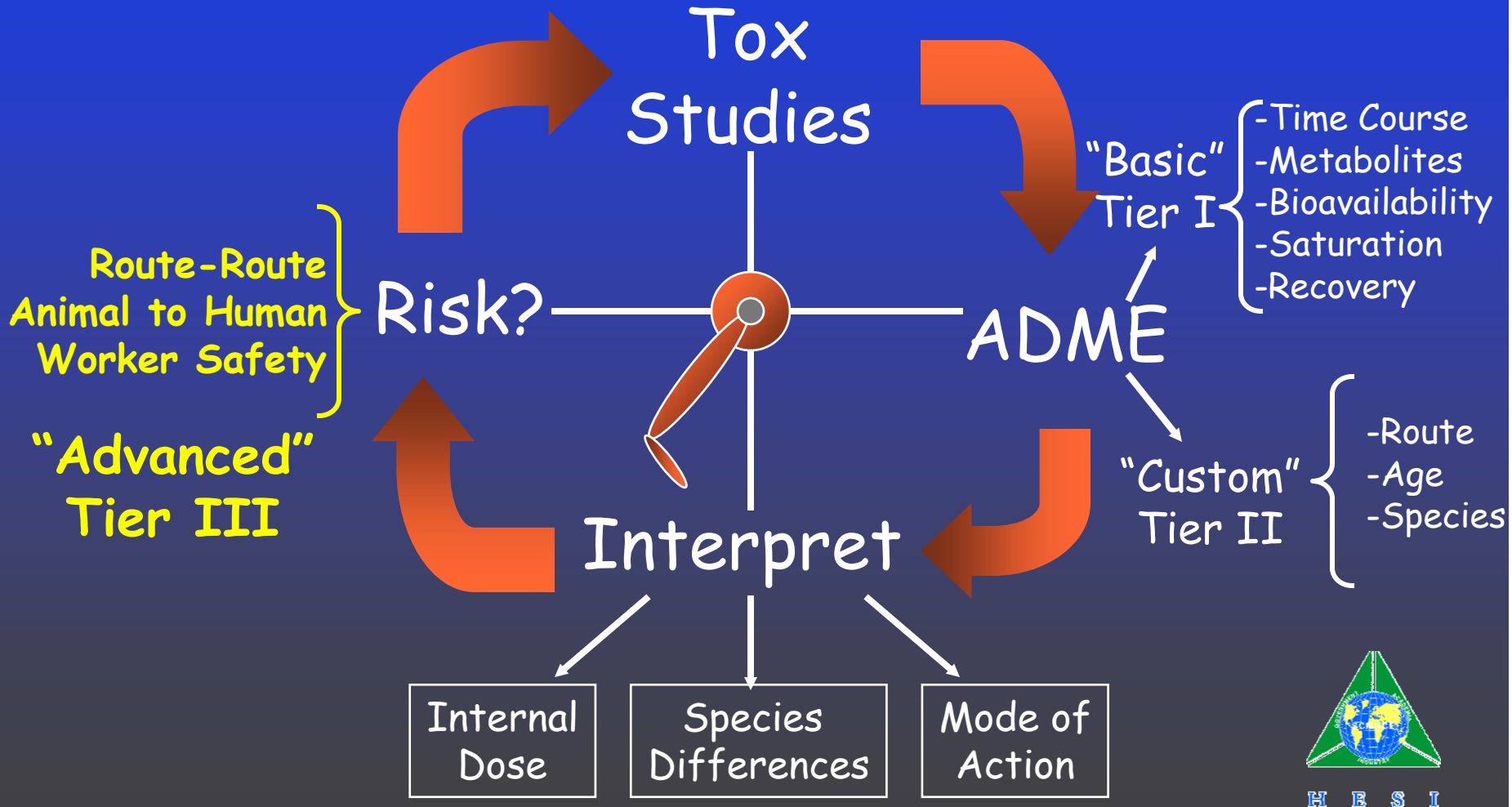
Comparative Species PK







Working through the process…



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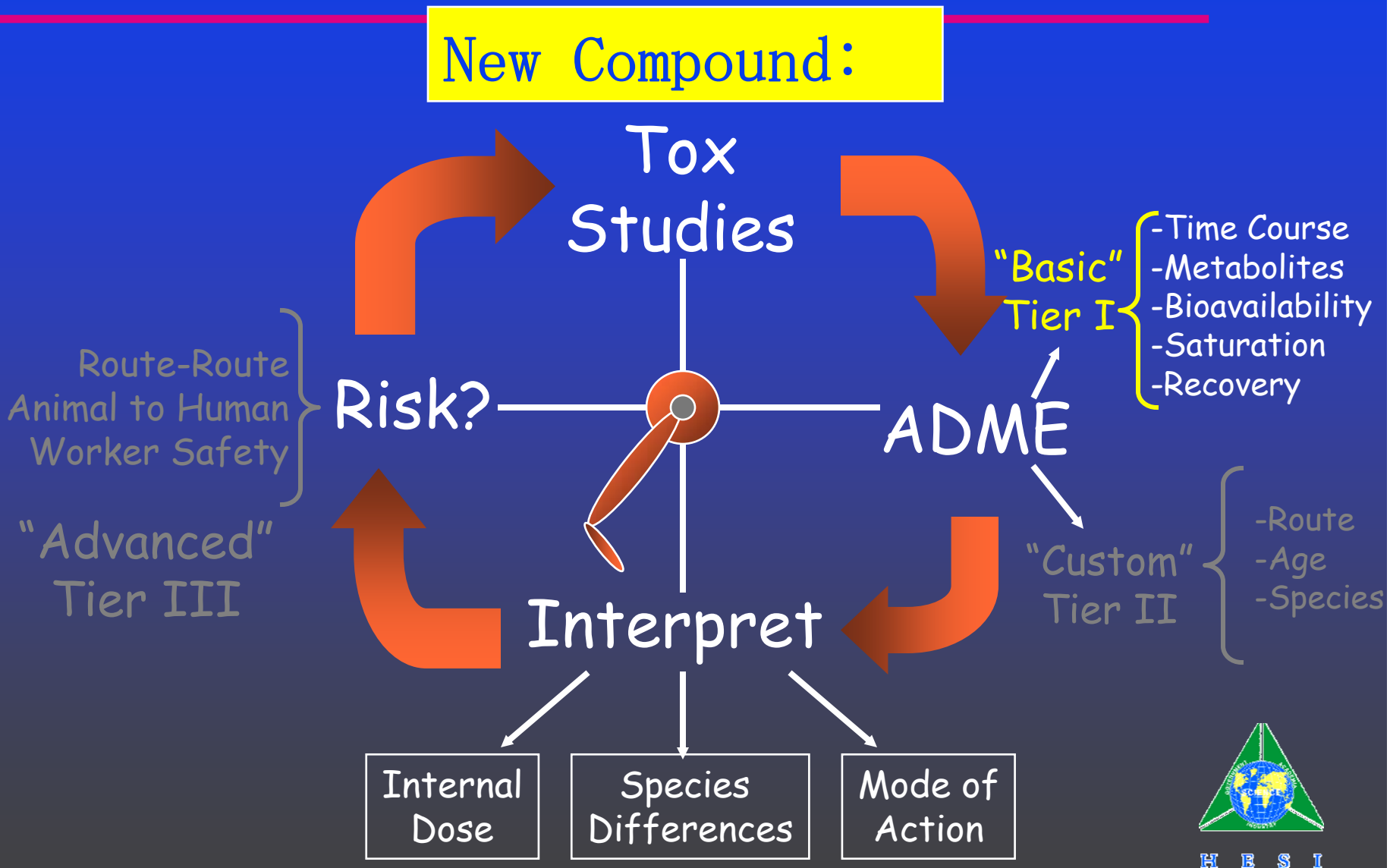
"Advanced" Tier III

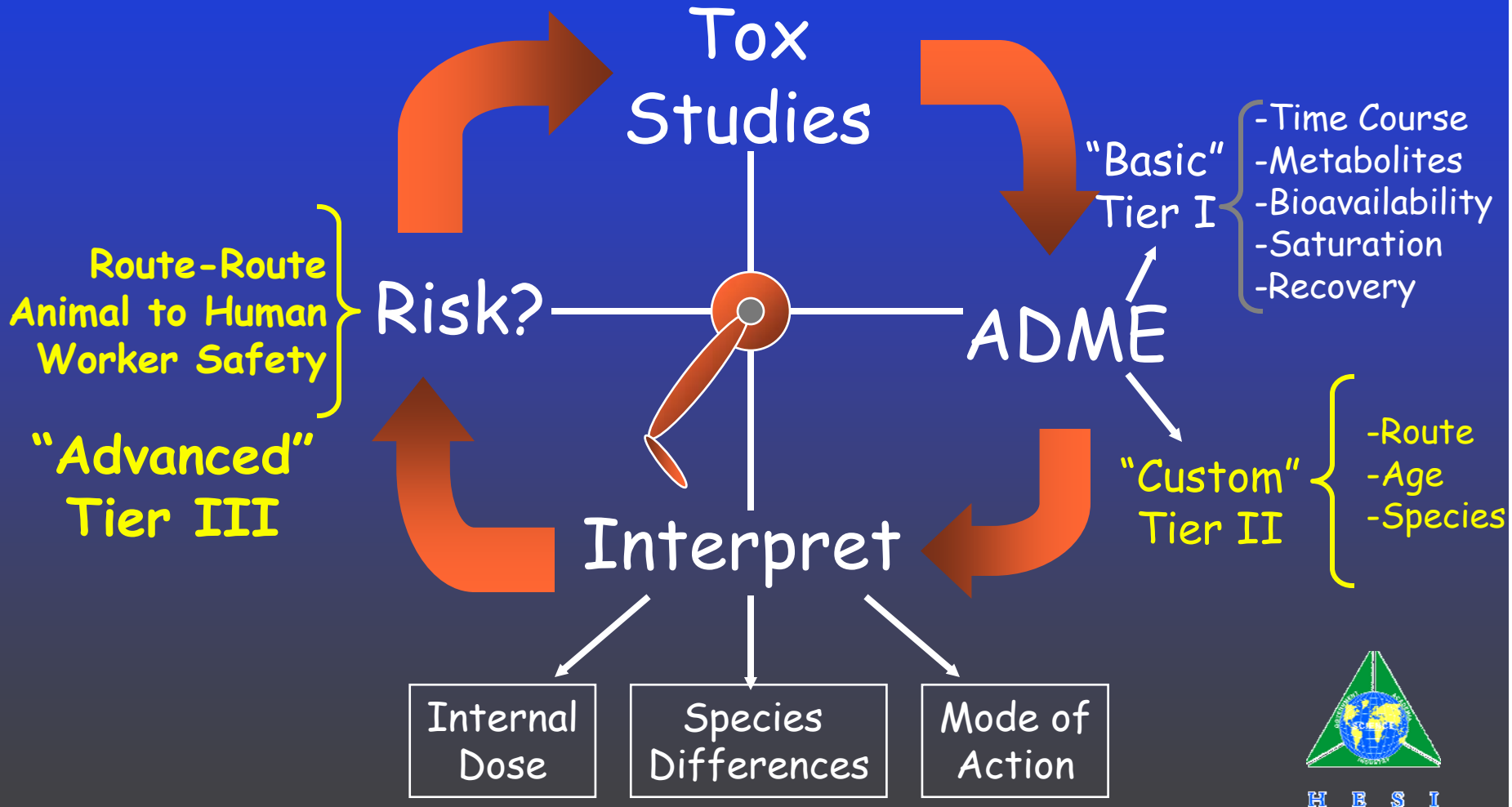
- Route-to-Route Extrapolation
  - Dermal
    - » In vitro rat/human
    - » In vivo rat
  - Inhalation
- Biomonitoring
- Human clinical PK

Working through the process…



Working through the process…

Mature Compound:



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Example Tier III Study: Human dermal absorption

- Dermal is a major exposure route.
- In vitro studies can provide an initial estimate of dermal absorption.
- In vivo studies with human volunteers can establish extent of dermal absorption.
- Direct application for assessing human health risk.

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Conclusions/Recommendations

- **To be useful, ADME studies need to:**
  - Help in the design of toxicity studies.
  - Help interpret results from toxicity studies.
  - Help assess risk.

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Conclusions/Recommendations (continued)

- **Generalized tiered approach**
  - ***Basic*** (Tier I), which would include data that are crucial for toxicity study design including dose selection, half-life determinations for recovery period determination, and the identification of major metabolites.
  - ***Custom*** (Tier II), which would include data needed for study interpretation, absorbed dose estimates, and duration/route extrapolations.
  - ***Advanced*** (Tier III), which would include data to support the understanding of a compound's mode of action and allow the derivation of pharmacodynamic concordance.

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ADME Task Force Members

Co-Chairs: Hugh Barton (USEPA) and Timothy Pastoor (Syngenta Crop Protection)

- Karl Baetcke (US EPA)
- Jan Chambers (MS State University)
- Janet Diliberto (US EPA)
- Jeff Driver (infoscientific.com)
- Chuck Hastings (BASF)
- Sesh Iyengar (Bayer CropScience)
- Robert Krieger (University of CA, Riverside)
- Bernhard Stahl (Bayer CropScience)
- Chuck Timchalk (Pacific NW National Laboratory)

LIAISONS:

- Alan Boobis (Imperial College London) – Systemic Toxicity Task Force
- Larry Sheets (Bayer Corporation) – Life Stages Task Force

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