Addressing Potential Age-related Sensitivity to Pyrethroids and Pyrethrins

Council for the Advancement of Pyrethroid Human Risk Assessment (CAPHRA)

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The Primary Question

Are Children More Sensitive than Adults to Possible Neurological Effects following Pyrethroid Exposure?

Age-related Sensitivity: Basis for EPA's Concern

- Literature Suggests Age-related Sensitivity
  - 20-fold greater sensitivity of young rats to deltamethrin & cypermethrin (Type II)
    - High dose, but not lower doses
  - No age related difference with cismethrin or permethrin (Type I)
- Developmental Neurotoxicity (DNT) Studies (6)

Addressing Age-Related Sensitivity to PYR

- Developmental Neurotoxicity Study
  - Costly, uses 100s of animals
  - EPA Review of Submitted DNTs (2009-10)
    - ″It has been determined that, for pyrethroid pesticides, DNTs do not provide sensitive endpoints for risk assessment or provide sufficient information related to the susceptibility of infants and children; furthermore, the effects they do show can be found in other guideline studies.″
  - No more DNTs required for pyrethroids

Addressing Age-Related Sensitivity to PYR

- EPA Request for proposals (2010)
  - "For study design/protocols to evaluate potential differential sensitivity between juvenile and adult rats."
- Industry response
  - Broader approach not only to address differential sensitivity between adult and juvenile rats, but also to address human relevance of rat findings
  - Program developed and underway since late 2010

Challenges

- Extrapolation
  - Animal to human
  - Adult to juvenile
  - High dose to low dose
- Need to Use New Test Systems
  - Non-guideline studies - research level, no protocols
  - Ensuring data quality and integrity

CAPHRA Program Working Hypotheses

- Age-related sensitivity to pyrethroids observed in rats is limited to high doses - due to pharmacokinetic differences between adult and juveniles
- Differences in the ontogeny of pyrethroid metabolizing enzymes between rat and humans mean that *developing* rat may not be the best model for the *developing* human
- PBPK models using experimentally determined parameter values can be used to predict tissue levels in early life stage humans and to characterize risk

Challenges – Tools

- Targeted Testing
  - High throughput testing
  - Tissue-based test systems
  - Whole animals
- Dose-response & Extrapolation Modeling
  - Rat vs. human, Adult vs. juvenile
  - Physiologically-based Pharmacokinetic (PBPK) modeling

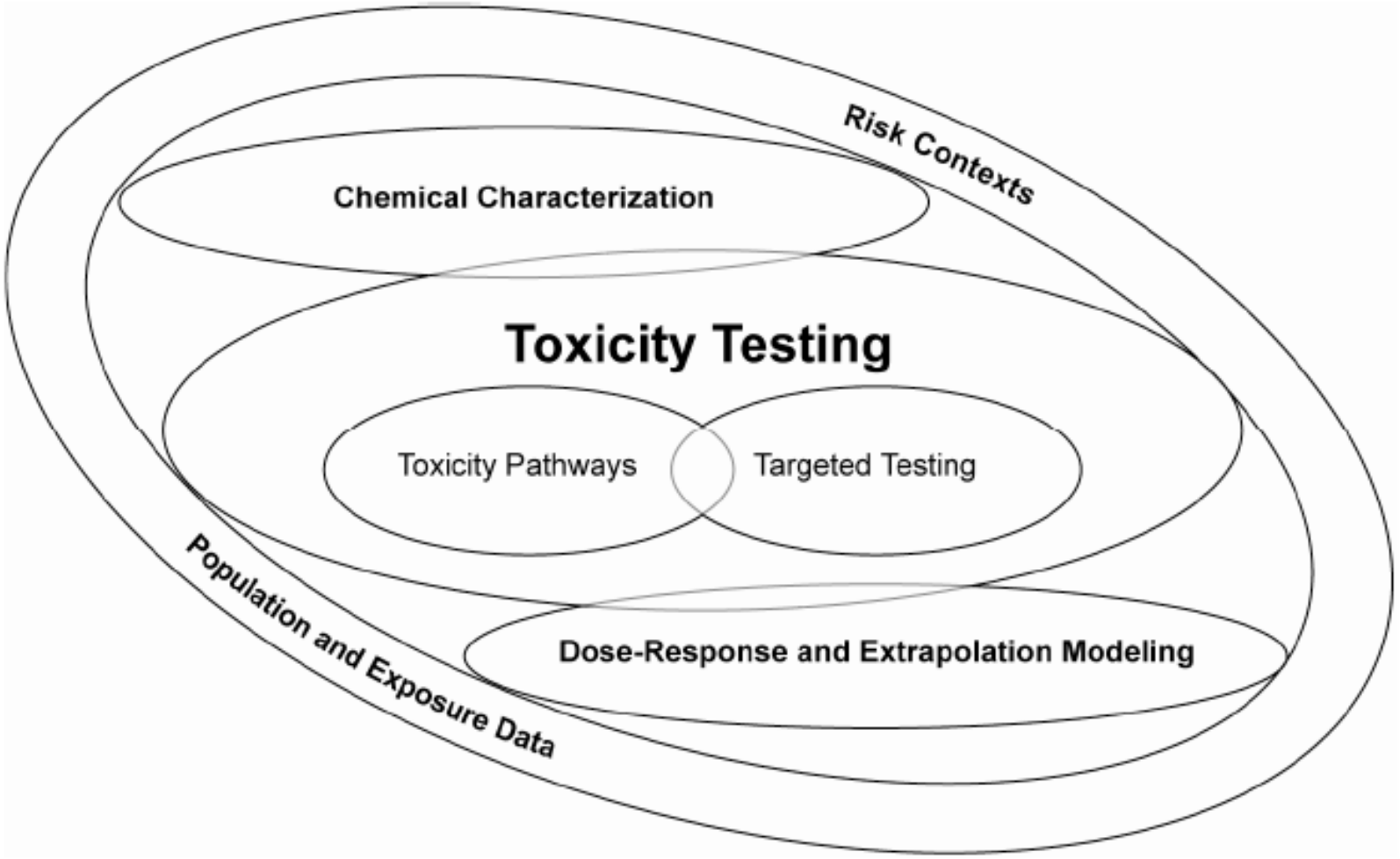
Challenges – Tools

- Outstanding collaborators
  - Universities
    - Medical College of Wisconsin, University of Cincinnati, University of Georgia, University of Massachusetts
  - Other
    - Hamner Institute for Biomedical Sciences
    - LFR Molecular Sciences
- Development of program to insure data quality

Challenges – Tools

- Read-across Strategy
  - Also known as bridging
    - Applying knowledge from representative pyrethroids that have been studied to others for which database is smaller
  - Reduces testing needs
  - Reduces time, expense, and animal use

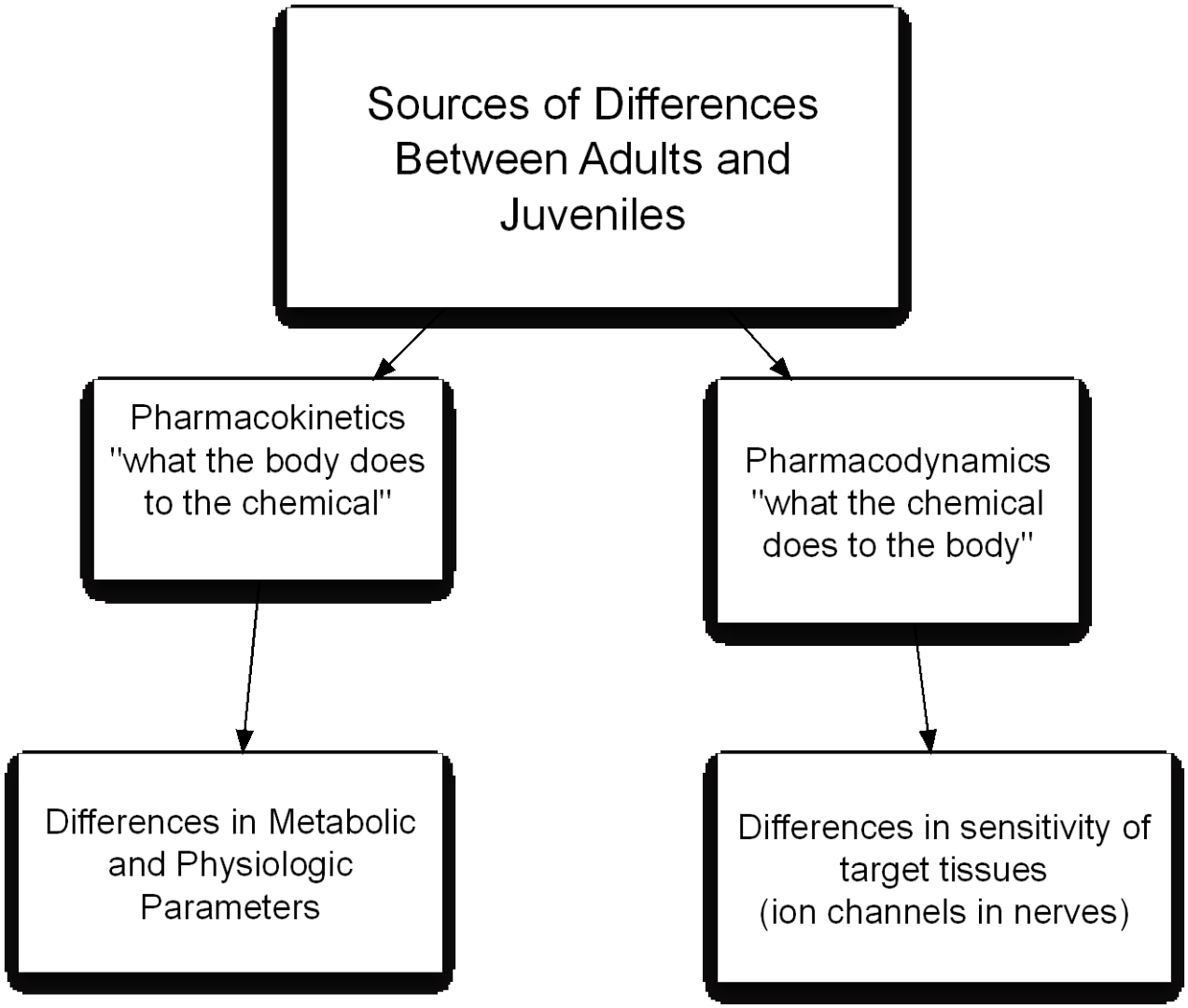
CAPRHA Conceptual Framework
Based on NAS – Toxicology Testing in the 21st Century



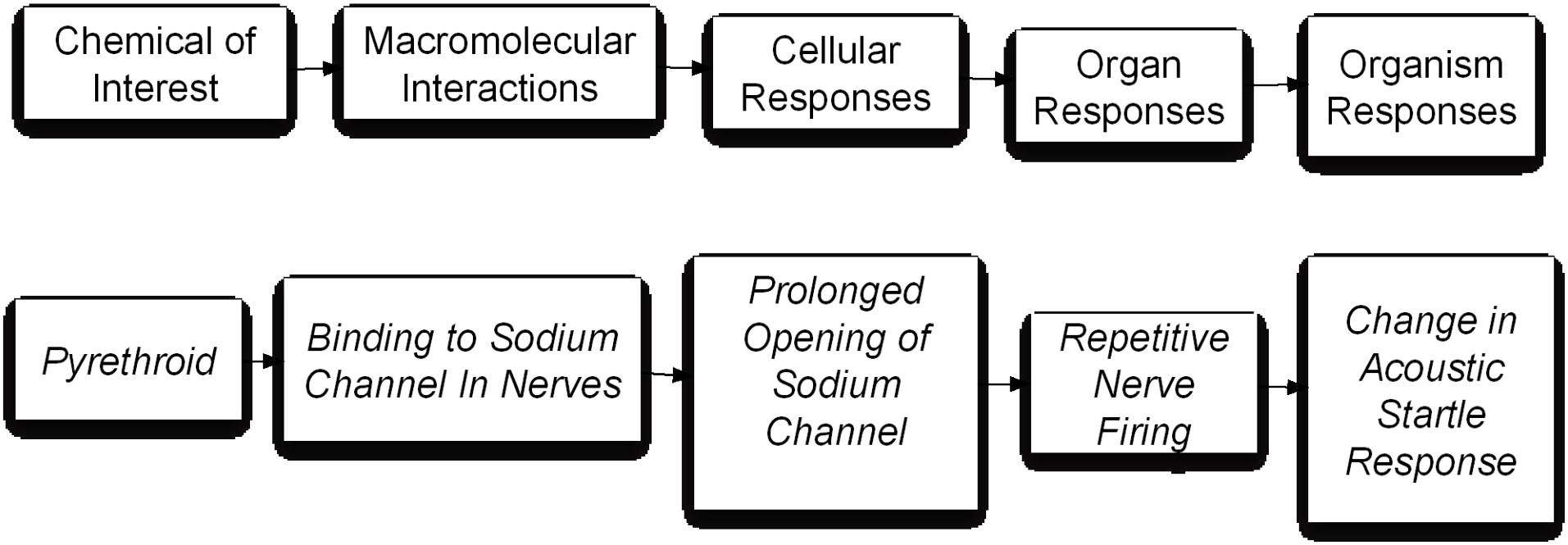
Adverse Outcome Pathway

- Basis for Targeted Testing
  - Linkage between a direct molecular initiating event and adverse outcome at level of biological organization relevant to risk assessment
    (Ankley et al., 2010)
  - Research program designed to address steps along pathway

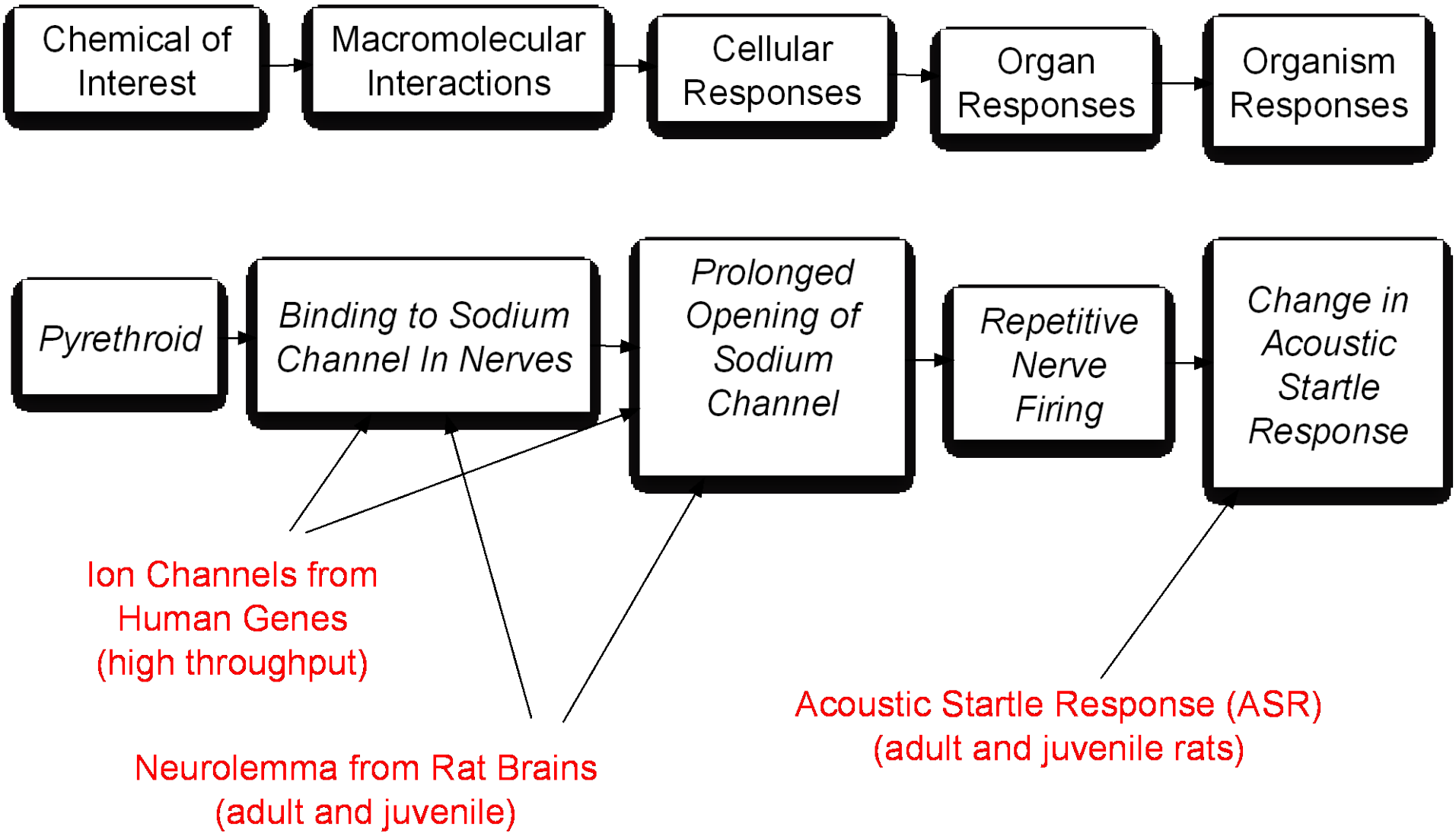
Addressing Age-Related Sensitivity to PYR

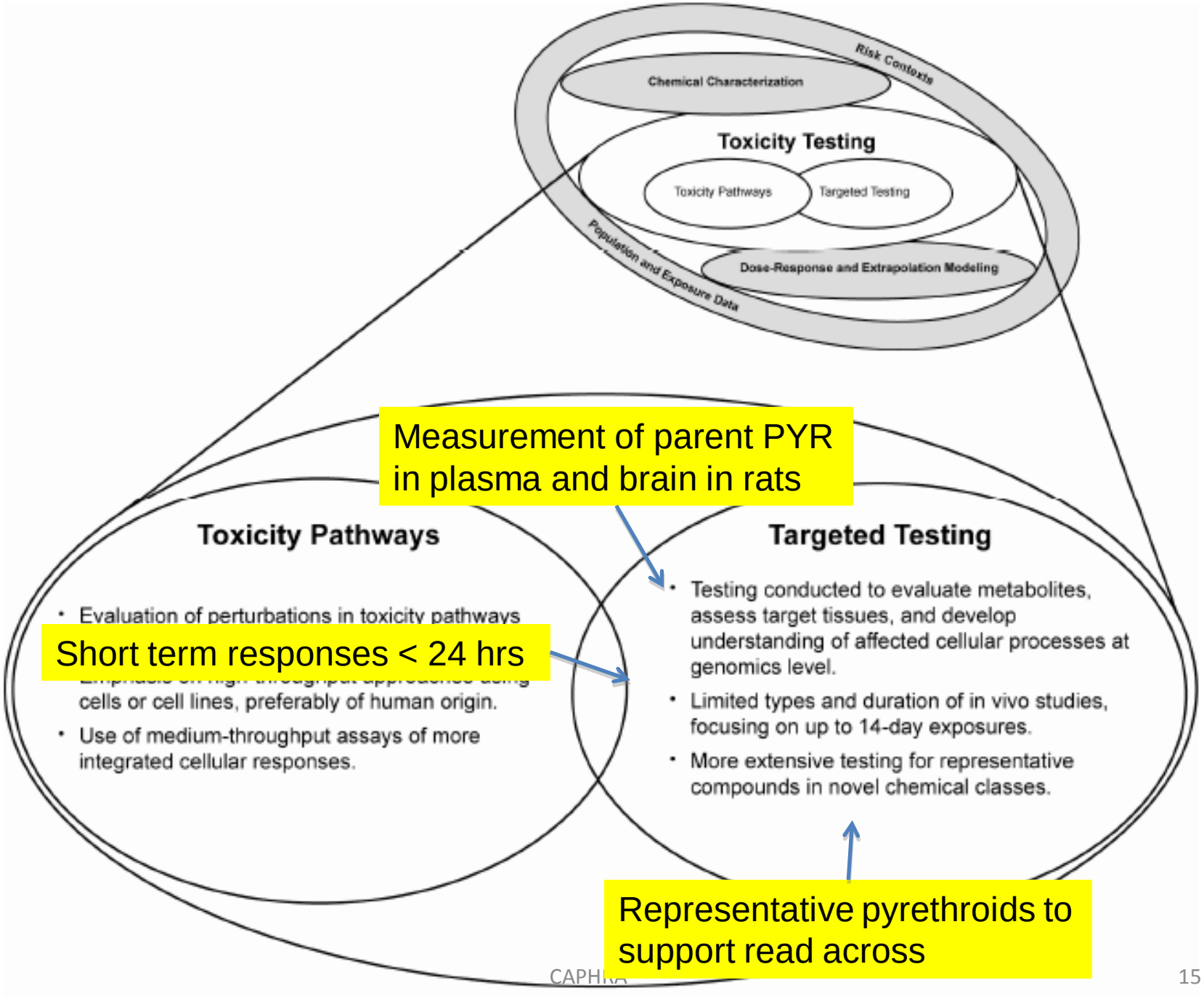


Adverse Outcome Pathway - Targeted Testing



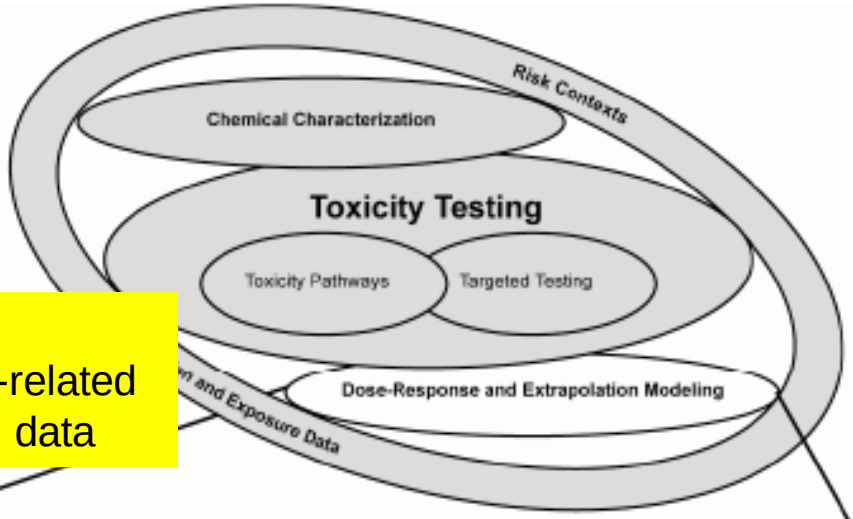
Adverse Outcome Pathway - Targeted Testing




Risk Contexts
Chemical Characterization
Toxicity Testing
Toxicity Pathways
Targeted Testing
Dose-Response and Extrapolation Modeling
Population and Exposure Data
Measurement of parent PYR in plasma and brain in rats
Toxicity Pathways
Evaluation of perturbations in toxicity pathways
Short term responses < 24 hrs
cells or cell lines, preferably of human origin.
Use of medium-throughput assays of more integrated cellular responses.
Targeted Testing
Testing conducted to evaluate metabolites, assess target tissues, and develop understanding of affected cellular processes at genomics level.
Limited types and duration of in vivo studies, focusing on up to 14-day exposures.
More extensive testing for representative compounds in novel chemical classes.
Representative pyrethroids to support read across

PBPK modeling to predict parent PYR in plasma and brain in juvenile humans

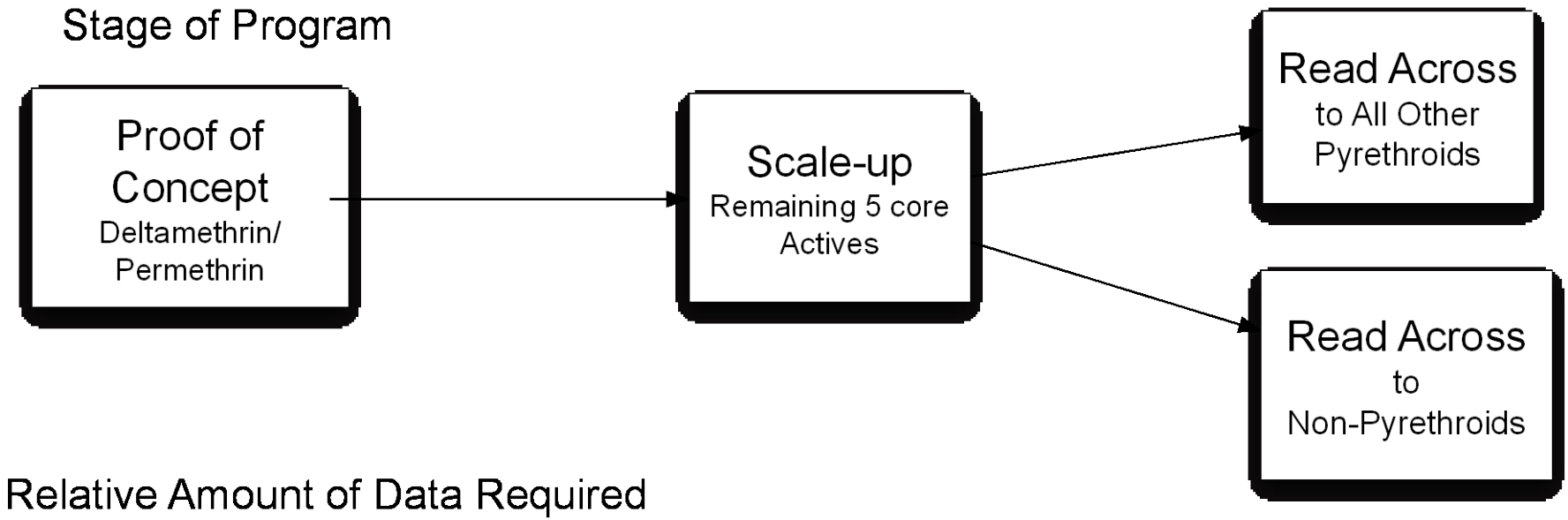
Collection of age and species-related parameterization data

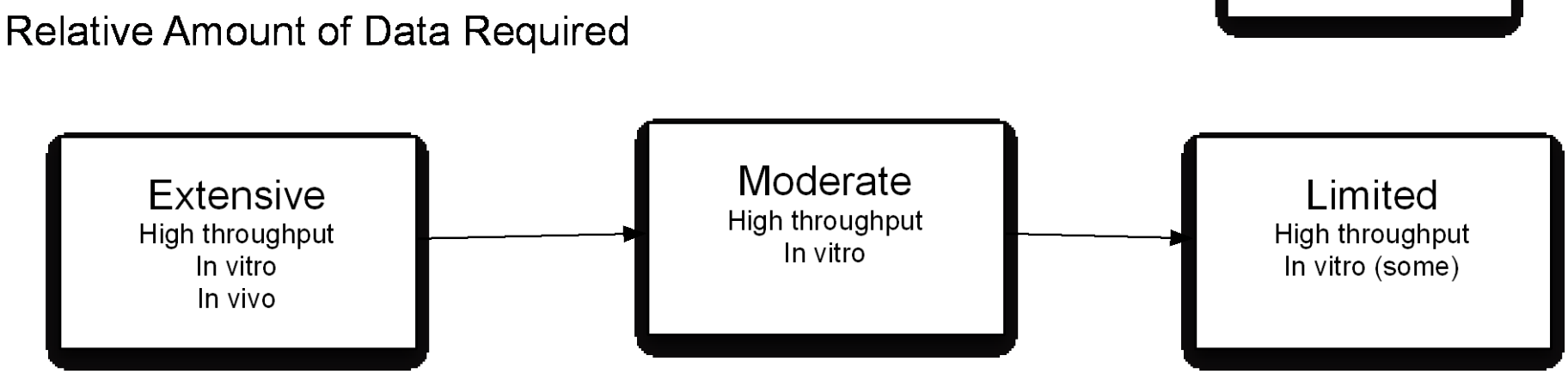


Dose-Response and Extrapolation Modeling

- Empirical dose-response models will be developed on the basis of data from in vitro, mechanistically based assays.
- Physiologically based pharmacokinetic (PBPK) models will equate tissue-media concentrations from toxicty tests with tissue doses expected in humans.
- Dose-response models for toxicity pathways will reliably predict concentrations expected to cause measurable precursor-effect responses.
- PBPK and toxicity-pathway models will identify biomarkers of susceptibility for sensitive subpopulations.

Data Development to Support Read Across (Bridging) for Pyrethroids and Non-pyrethroids





Ensuring Data Quality
Spirit of Good Laboratory Practices (GLPs)

- Overall Goal
  - Make sure that that study information is sufficiently documented so that the study can be "re-built" based on the collected raw data
- Realities
  - Not practical to conduct exploratory development and non-standard research studies under GLPs

Ensuring Data Quality
Spirit of Good Laboratory Practices (GLPs)

- Solution – Streamlined, pragmatic approach
  - Applies to academic collaborators
- Essential Elements
  - Standard operating procedures (SOPs)
  - Careful recordkeeping
  - Protocols – guide the studies
  - Data audit at study conclusion

Ensuring Data Quality
Spirit of Good Laboratory Practices (GLPs)

- CAPHRA Leadership in effort
  - Sponsoring a symposium at the 2013 American Chemical Society Meeting
  - “Spirit of GLP”
  - EPA, CA, academia

Ensuring Data Quality
Transparency and Peer Review

- Scientific Presentations
  - 2011 - American Chemical Society (ACS) – 1
  - 2012 - Society of Toxicology (SOT) – 5
  - 2013 – SOT – 6
    - International Congress on Toxicology – 2
    - ACS – 4
- Peer Reviewed Publications
  - 7-10 anticipated

Progress

- High throughput Assays – nearly complete
- *In vitro* assays for parameterization
  - Excellent progress with rat tissue
  - Human liver tissue assays underway
- *In vivo* assays
  - Neurotoxicity – underway
  - Pharmacokinetics – almost finished for deltamethrin
- PBPK Modeling
  - Rat adult and juvenile model in place
  - Parameterization proceeding
- Future

Discussion