Predictive Approaches for Cross-Species Extrapolation in Ecotoxicology

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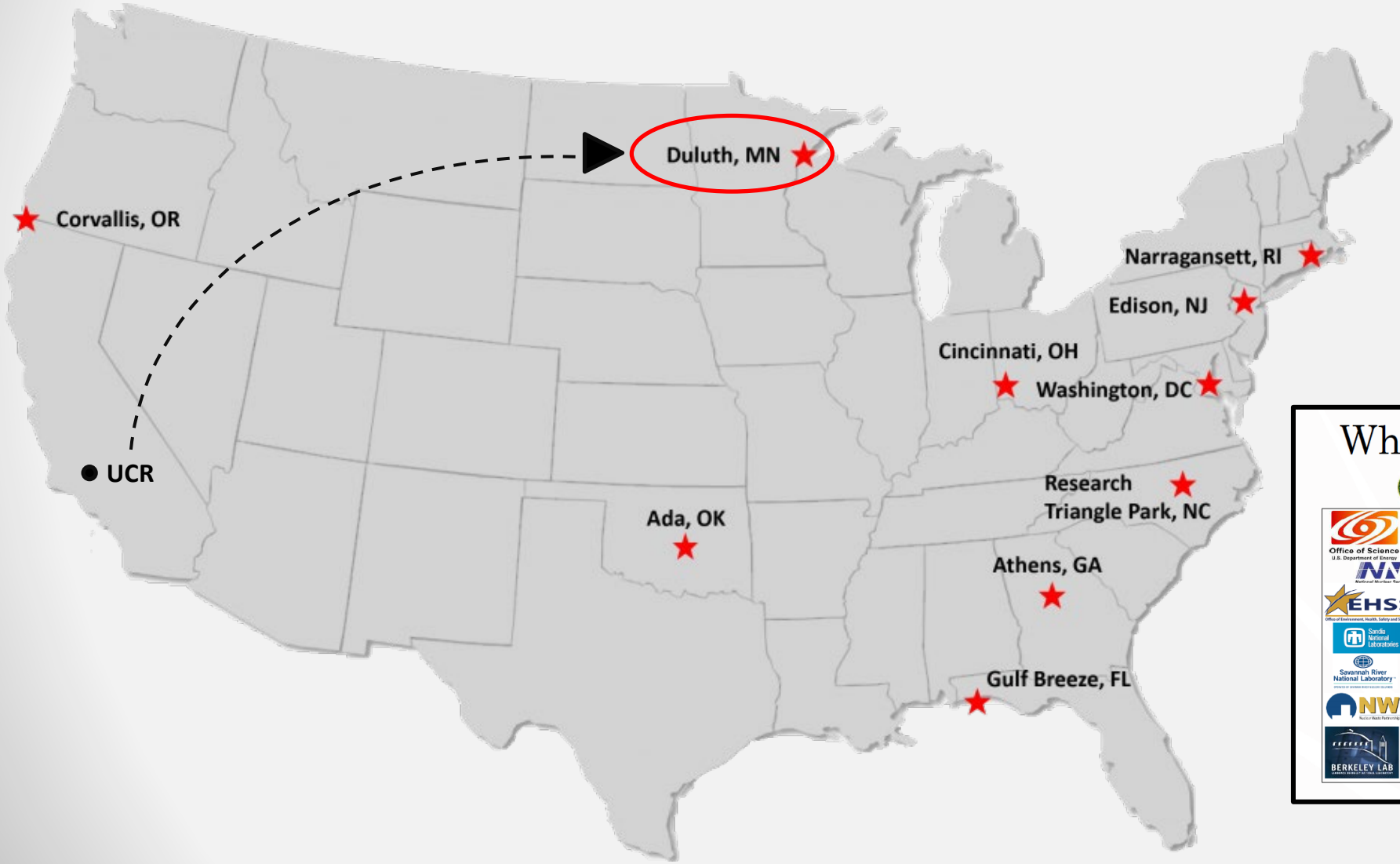
Office of Research and Development (ORD)

Conducts the research for EPA that provides the foundation for credible decision-making.



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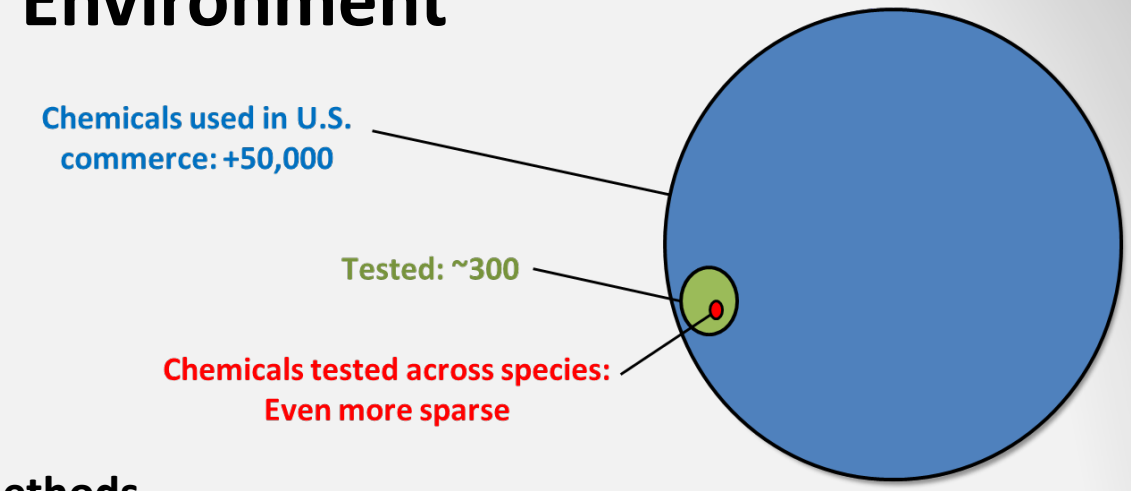
EPA: Protecting Human Health and the Environment

- Ensure that chemicals are safe and evaluate ecological and human health risks associated with toxic chemicals



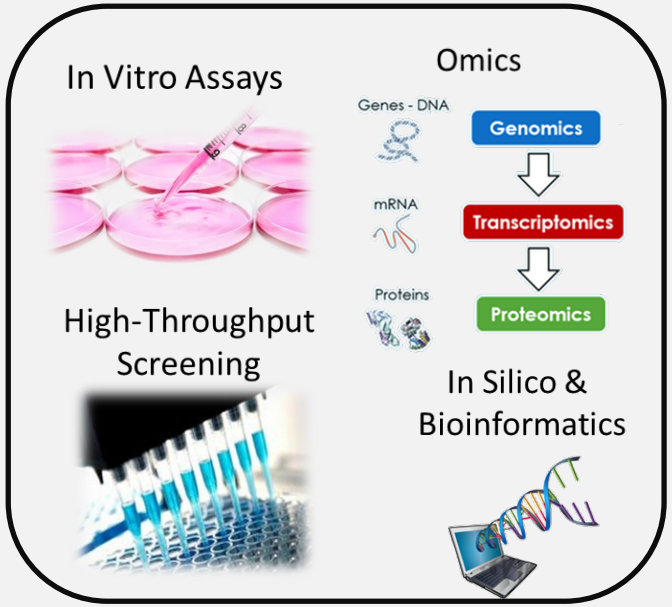
Whole-Animal Models

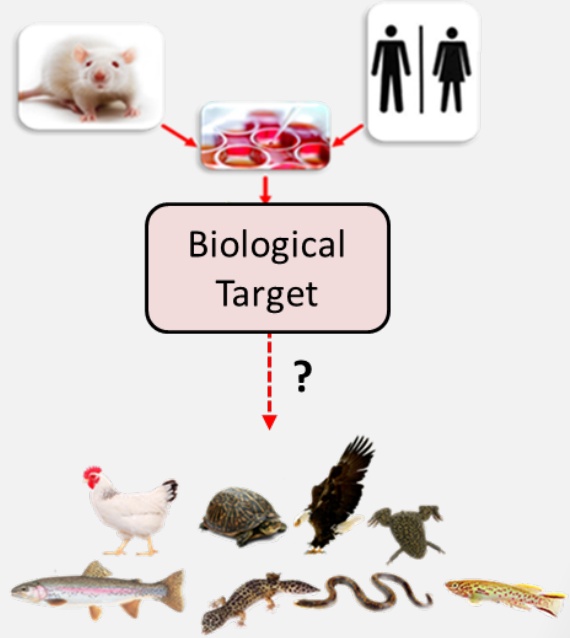
→ Observe Toxic Outcome

- Reduced Animal Use
- Reduced Cost
- Increased Throughput

New Approach Methods

→ Identify Biological Target



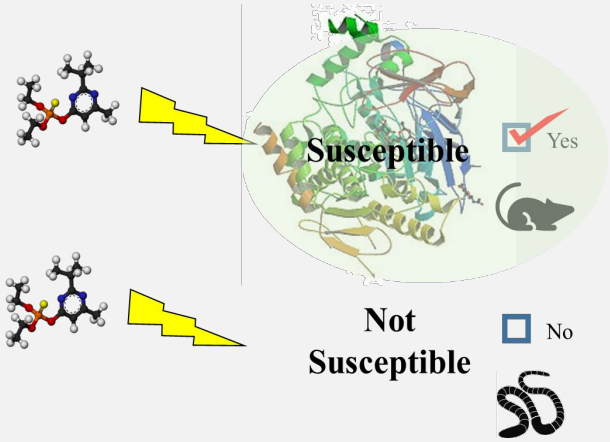


Are results in test species (e.g. mammals) representative of species we want to protect (e.g. non-mammalian vertebrates)?

Assessing Chemical Sensitivity Across Species

Factors that make a species sensitive

- Exposure
- Dose
- ADME
- Target receptor availability
- Life stage
- Life history
- etc.

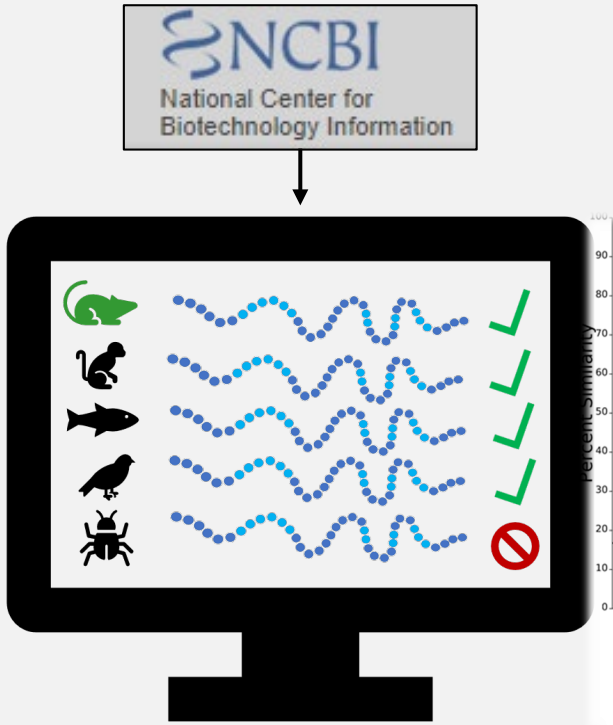


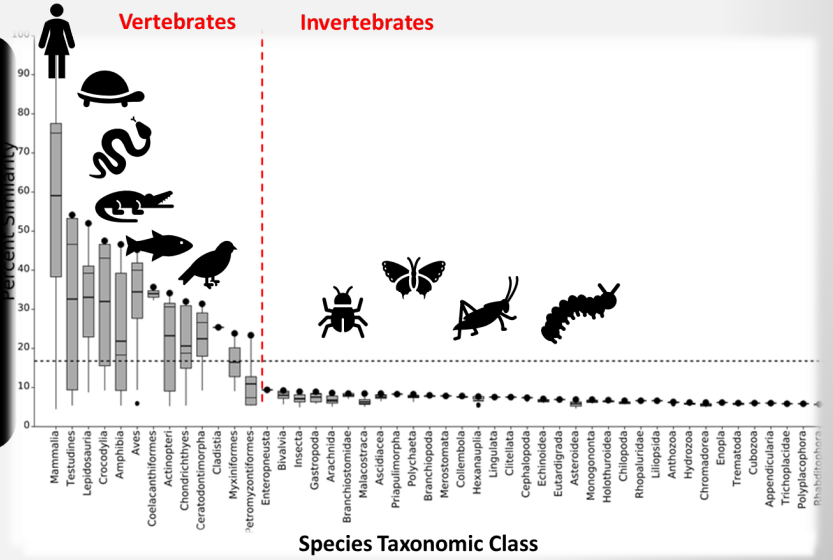
- Is the known chemical target available in a species for a chemical to act upon?
- If a chemical is interacting with a protein target in one species (zebrafish, mouse, human, etc.) can we predict it to interact with a similar in other species?
  - **Evaluation of protein similarity across species can provide a measure of target conservation and predictions of cross-species sensitivity**

Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS): A Web-Based Tool for Addressing the Challenges of Cross-Species Extrapolation of Chemical Toxicity

Carlie A. LaLone,*[,1] Daniel L. Villeneuve,* David Lyons,[†] Henry W. Helgen,[‡] Serina L. Robinson,[§,2] Joseph A. Swintek,[¶] Travis W. Saari,* and Gerald T. Ankley*

- Free, online tool
- Uses publicly available data to rapidly compare protein sequences across thousands of diverse species





Moving Towards Validation

For In Silico tools to be used in a regulatory context it is **essential** to understand how computational predictions relate to empirical data across species

Validation

In the lab

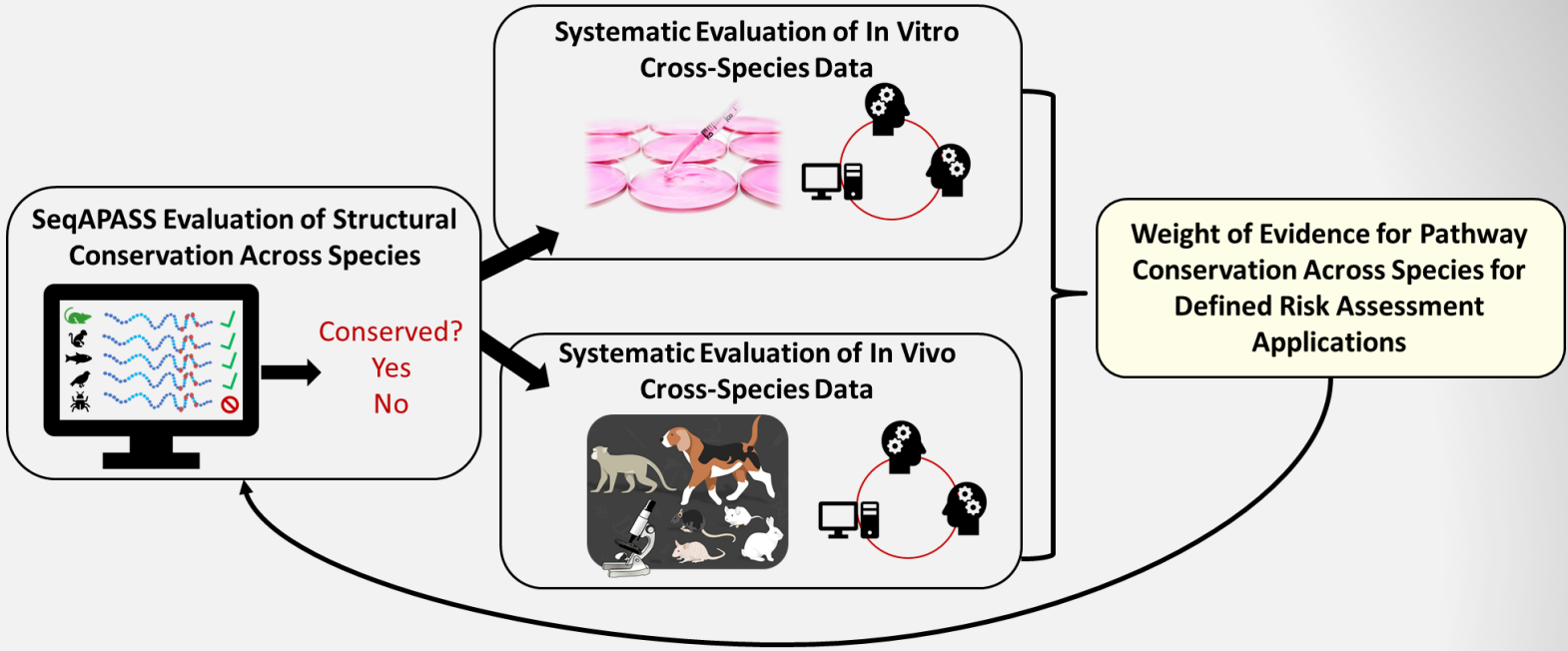
- Cross species In vitro studies
- Cross species In vivo studies
- Chemical proteomics
- Etc.

Out of the lab

- Molecular modeling & docking
- Review of existing evidence
- Etc.

We are currently working across these areas to evaluate and refine computational predictions of cross-species sensitivity

Example: Systematic Review of Existing Data



- Evaluate and refine computational predictions
- Apply pathway to other targets of interest
- Repeat process to account for the emergence of new information

Applications of SeqAPASS in Ecotoxicology

- Extrapolate high throughput screening data
- Extrapolate biological pathway knowledge across species
- Predict relative intrinsic susceptibility
- Generate research hypotheses
- Prioritize testing efforts

Thanks!

Any questions?

SeqAPASS v4.0

https://seqapass.epa.gov/seqapass/

Anyone can use SeqAPASS to help inform their own research questions! If you are interested in using SeqAPASS we are happy to help!

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