



WEBINAR SERIES

Introduction to the International Consortium to Advance Cross-Species Extrapolation

Carlie LaLone
USEPA

Geoff Hodges
Unilever



The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the US EPA

Overview

- Meet the Steering Committee
- What was the motivation behind creating ICACSER?
- What are the primary challenges in extrapolation
- What do we aim to accomplish?
- Who should be involved?
- What are the next steps?



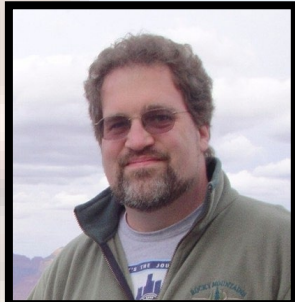
Steering Committee



Carlie LaLone
US EPA



Fiona Sewell
NC3Rs



Steve Edwards
RTI



Patience Browne
OECD



Michelle Embry
HESI

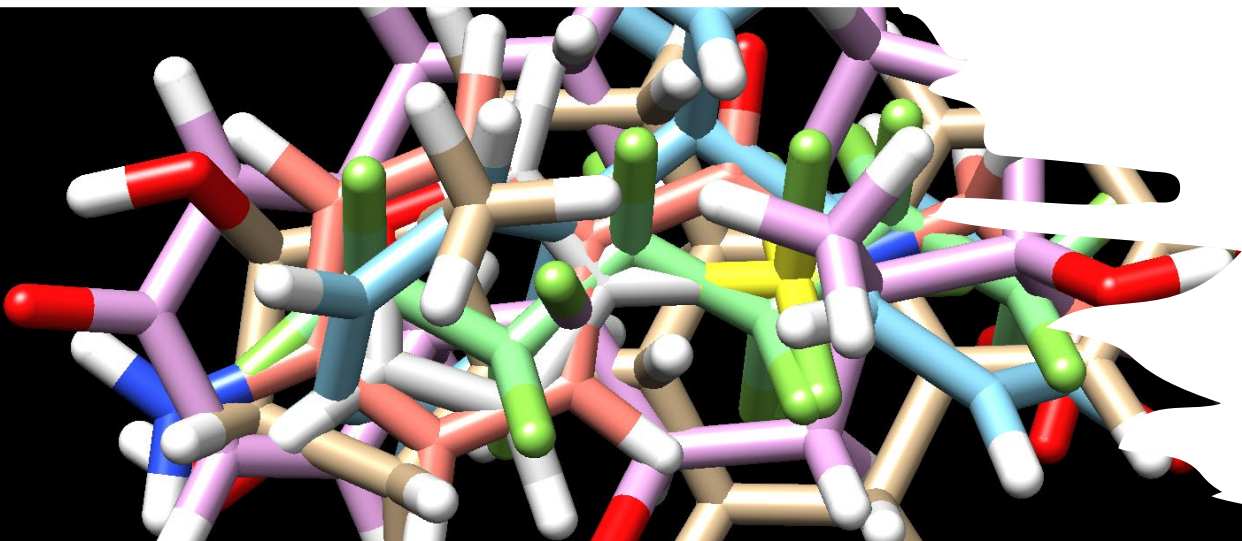
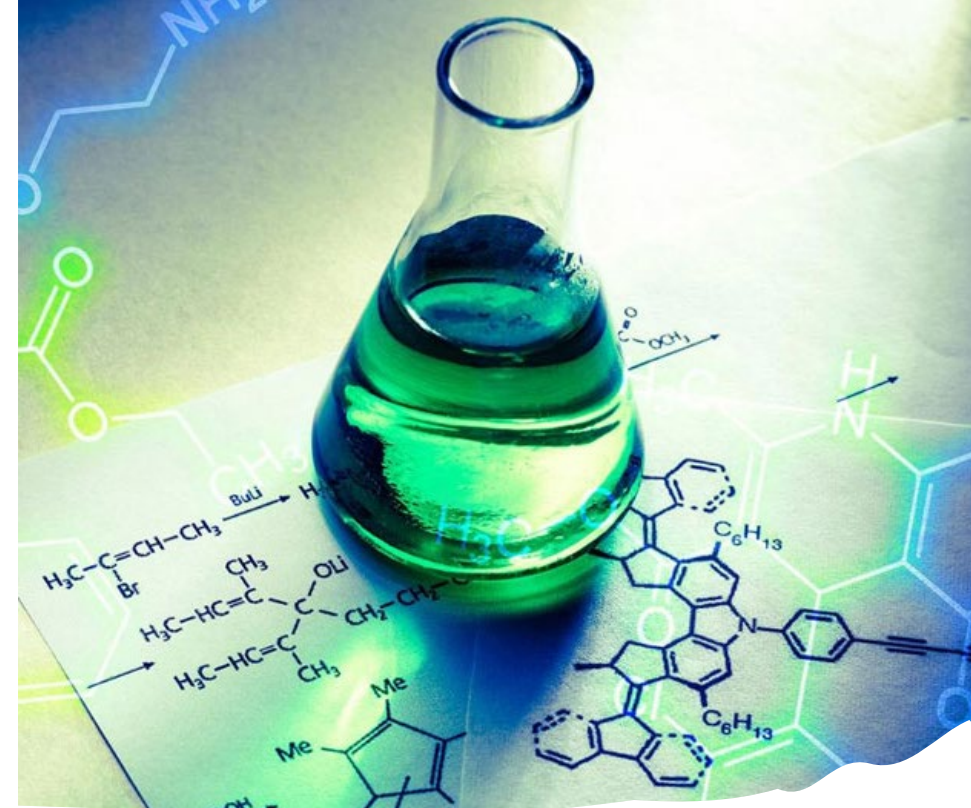


Nil Basu
McGill University



Geoff Hodges
Unilever

Established: March 2020



Chemicals make up the world around us – necessary for our modern society

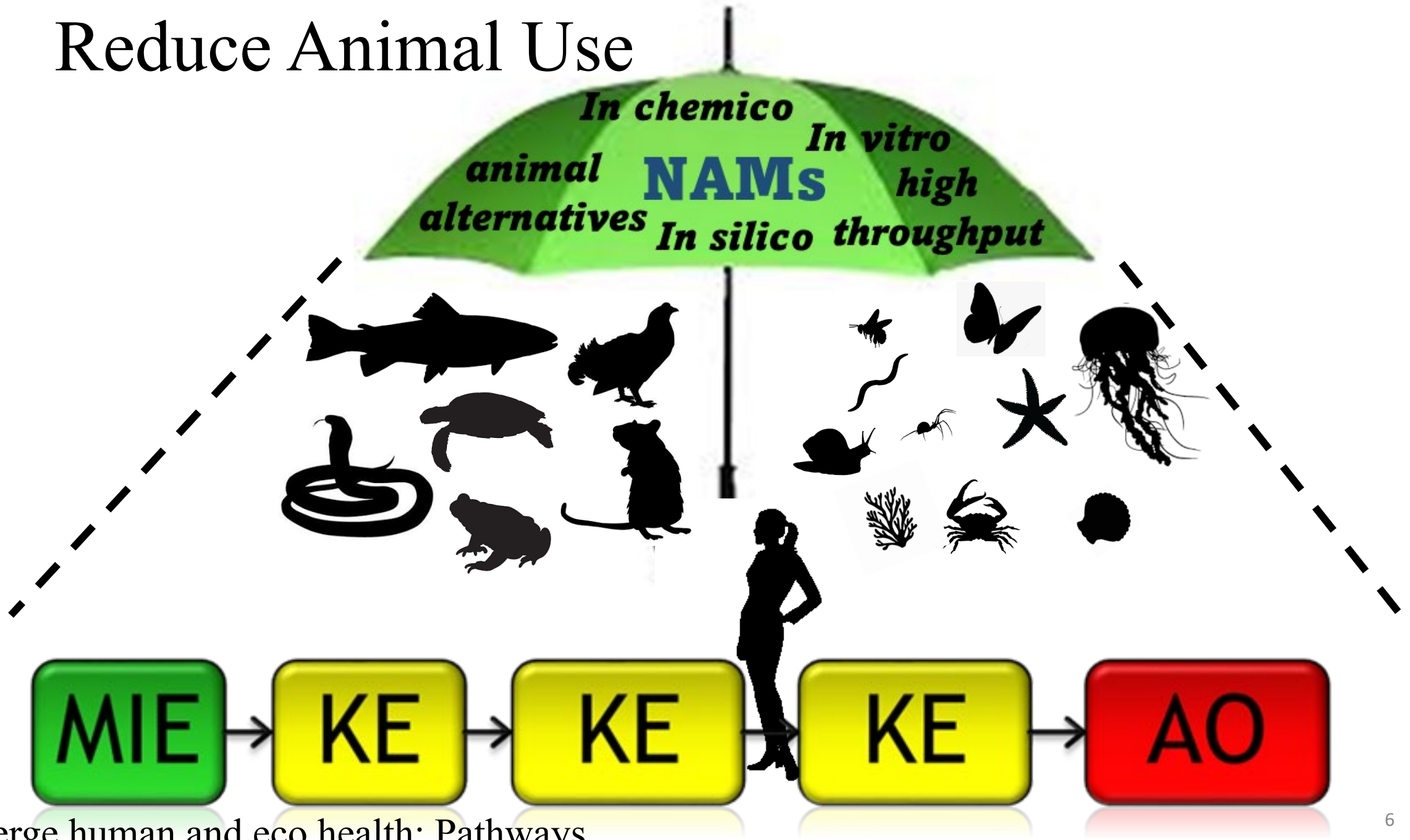
Collectively protect human health and the environment

Motivation for ICACSER

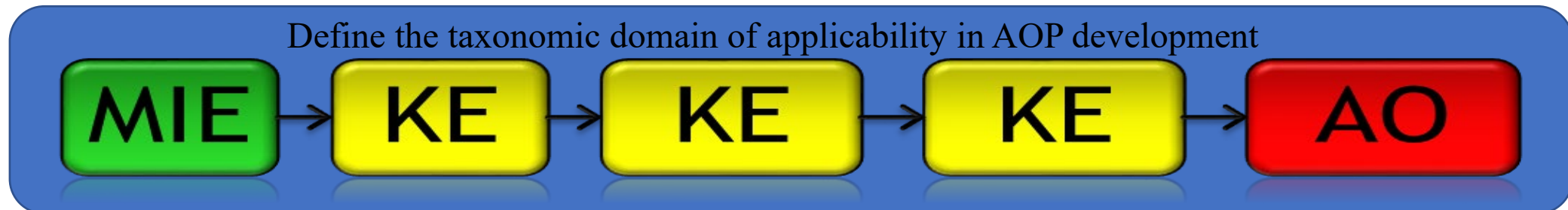
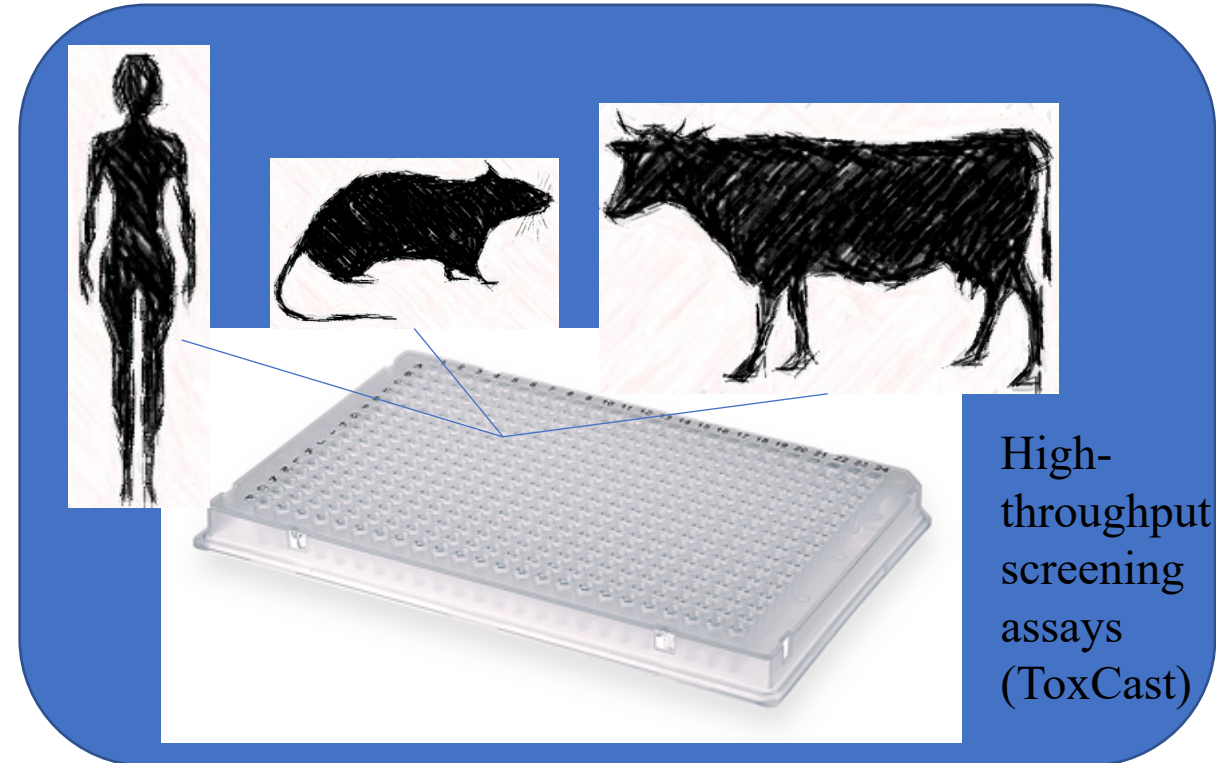
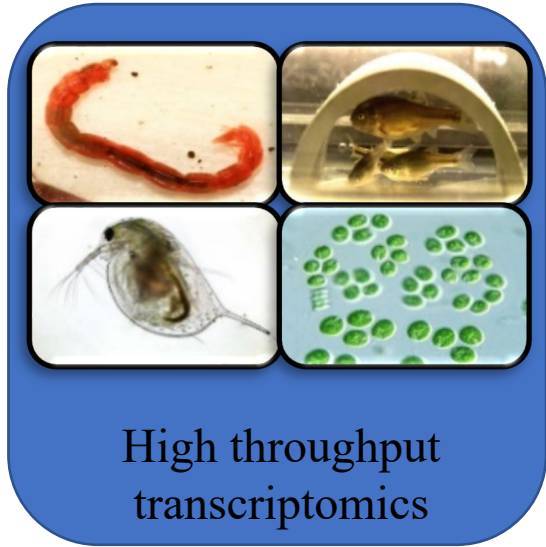


- Mutual goals in translating science for regulatory use
- Eliminating or greatly reducing the use of animals in toxicology
- Changing regulatory landscape
 - Greater use of mechanistic, cell-based, and computationally derived information [New approach methods (NAMs)]
- Establish confidence in mechanistic data and provide evidence as to how it relates to apical level changes
 - Aid decision-makers in understanding strengths and weaknesses for application
 - Domain of applicability
- Establish criteria/guidance for use of NAMs

Reduce Animal Use



Need for Advances in Species Extrapolation



Use of model organisms as surrogates representing the diversity of species in the environment

Species Extrapolation



What is it?

- Using existing knowledge about one species to estimate, predict, project, or infer the effect, impact, or trajectory of another species
 - For chemical safety typically dealing with toxicity

Why the need to extrapolate?

- Impractical to generate new data for all species
 - Limited or no toxicological data for the animal or plant species of interest – reliance on surrogate (model organisms)
 - Immense diversity of species in the wild
 - Important challenge for species listed under the Endangered Species Act
- Testing resources are limited
 - Ever-increasing demand to evaluate more chemicals in a timely and sometimes expedited manner
- International interest to reduce animal use
 - Sensitivity of species must be estimated based on scientifically-sound methods of cross-species extrapolation

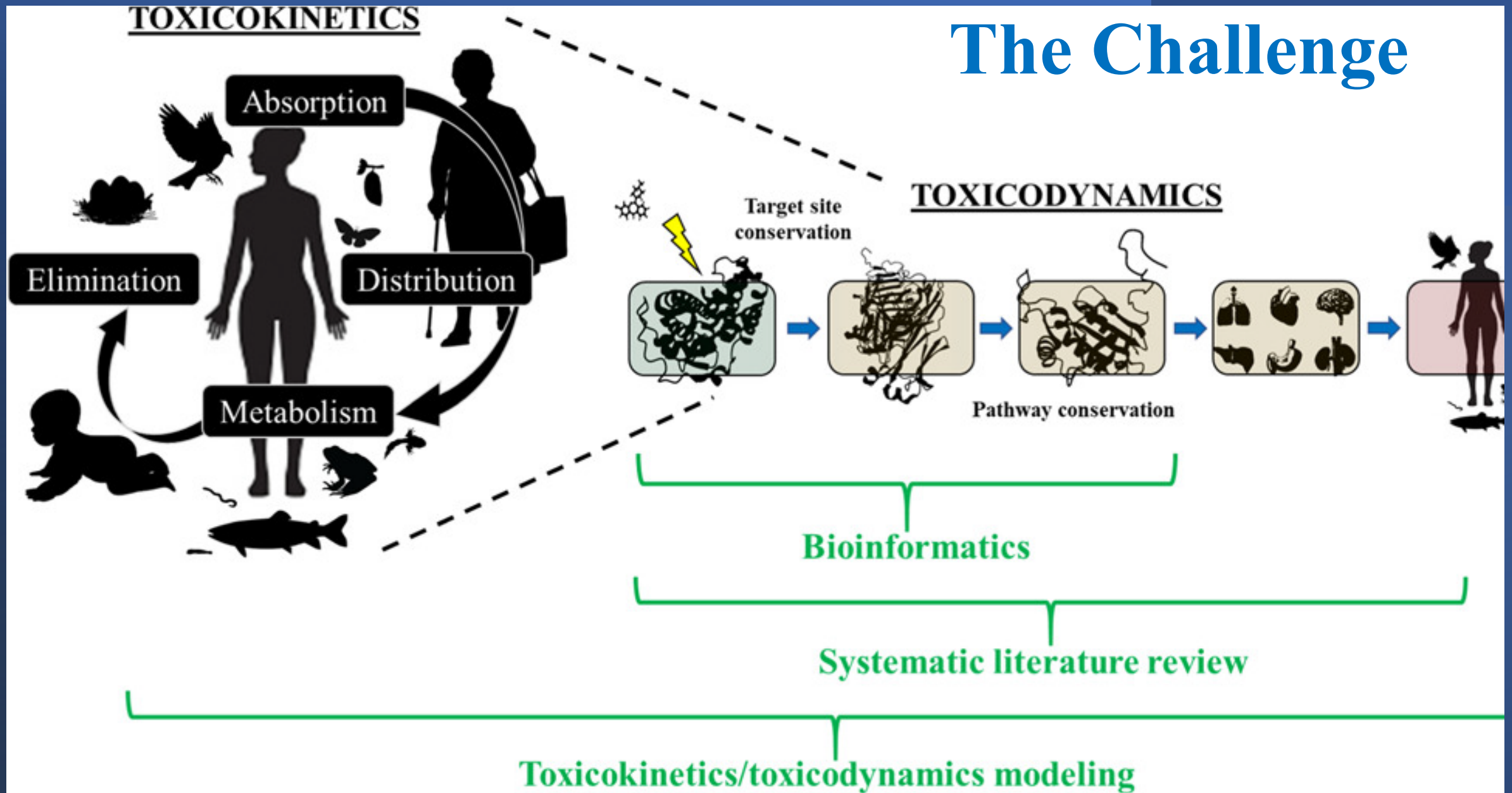


Currently applied methods for extrapolation

- Safety factors to extrapolate from toxicity in laboratory test species to all species representing the taxonomic group in the environment



The Challenge



A part of the solution

Bioinformatics

- Combines mathematics, information science, and biology to answer biological questions
- Developing methodology and analysis tools to explore large volumes of biological data
 - Query, extract, store, organize, systematize, annotate, visualize, mine, and interpret complex data
 - Usually pertains to DNA and amino acid sequences

Let the computers do the work



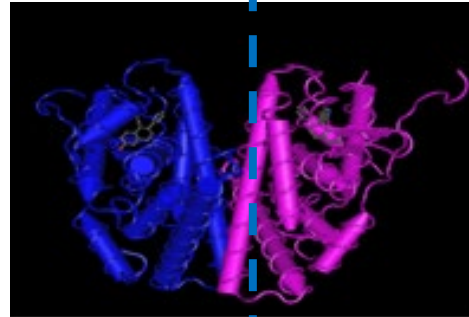
Start simple

Sequence

```
MTMTLHTKASGMALLHQIQGNELEPLNRPQLKIPLERPLGE  
VYLDSSKPAVYNYPEGAAYEFNAAAAANAQVYGQTGLPYG  
PGSEAAAFGSNGLGGFPPLNSVSPSPLMLLHPPQLSPFLQ  
PHGQQVPYYLENESGYTVREAGPPAFYRPNSDNRRQGGR  
ERLASTNDKGSMAVESAKETRYCAVCNDYASGYHYGVWSC  
EGCKAFFKRSIQGHNDYMCNATNQCTIDKNRRKSCQACRLR  
KCYEVGMMKGGIRKDRRGGRMLKHKRQRDDGEGRGEVG  
SAGDMRAANLWPSPLMIKRSKKNSLALSLTADQMVSALLA  
EPPILYSEYDPTRPFSEASMMGLLTNLADRELVHMINWAKV  
PGFVDLTLDQVHLLCAWLEILMIGLVWRSMHPGKLLFA  
PNLLDRNQGKCEGMVEIFDMLLATSSFRMMNLQGEF  
VCLKSIILLNSGVYFLSSTLKSLEEKDHIHRVLDKITDTLIHLM
```



Structure



Function

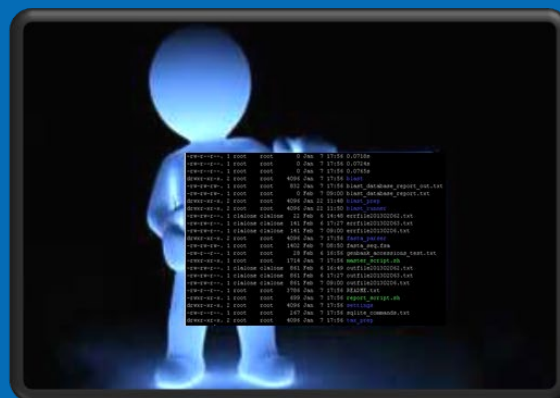
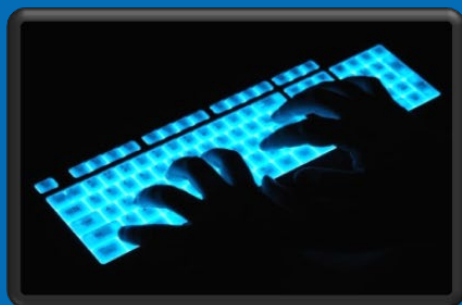


Bioinformatics: Conserved Biology



<https://seqapass.epa.gov/seqapass/>

Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS)

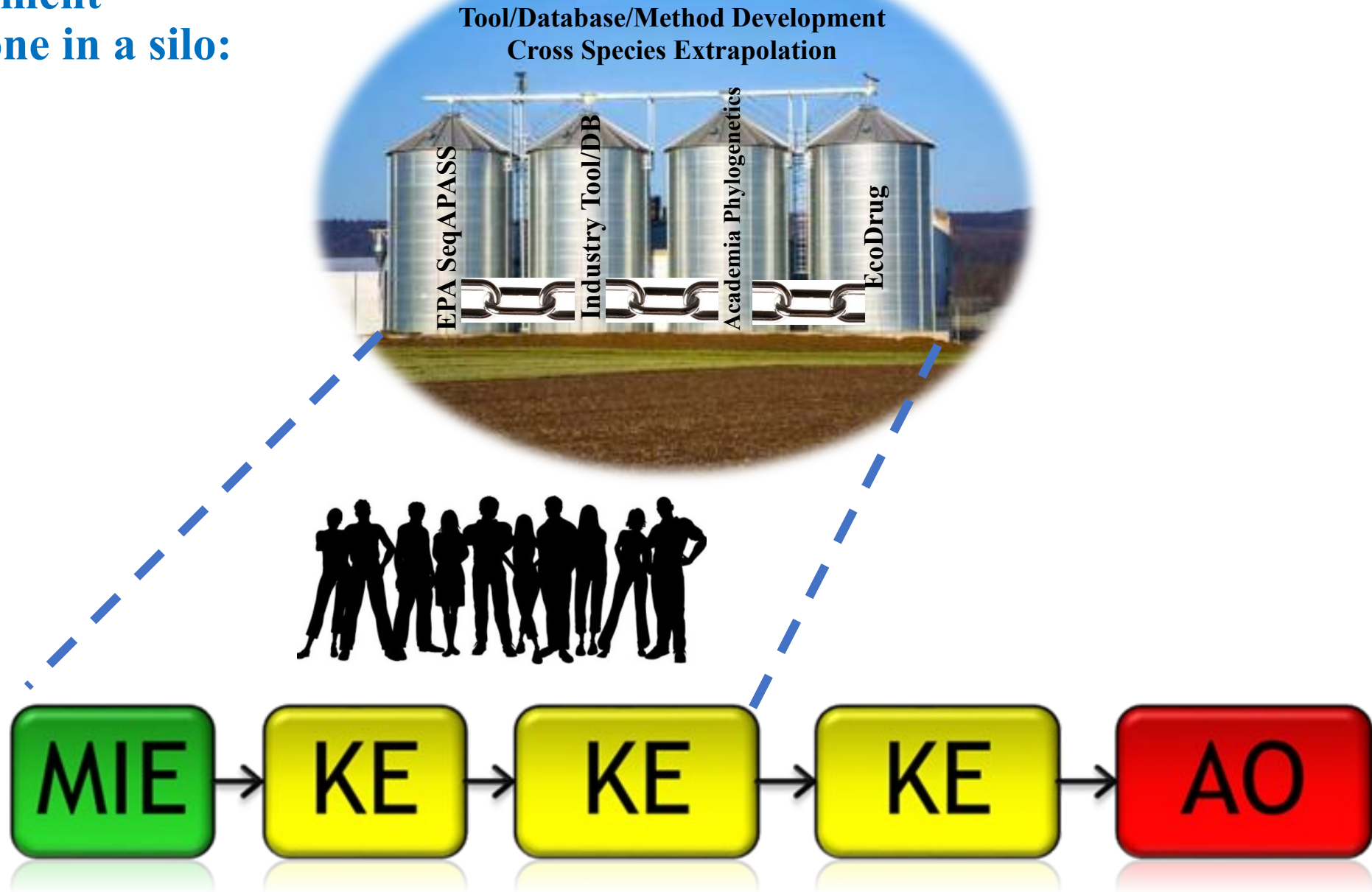


Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS): A Web-Based Tool for Addressing the Challenges of Cross-Species Extrapolation of Chemical Toxicity

Charlie 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^{*}



Tool development cannot be done in a silo:





ICACSER

Vision to Move Forward

What we plan to accomplish

Define the Global Regulatory Landscape and Needs for Extrapolation

- Where is species extrapolation currently applied in regulation?
 - What are the differences in regulations?
- What are the criteria for validation/confirmation/development?
- What are training/communication needs?
- How to engage decision-makers in development from the start?
- Define a roadmap for integration in regulation
 - OECD guideline



Developing a Bioinformatics Toolbox:

The right tools for the job

- Identify available tools/databases/methods
 - Ideally developers join ICACSER
- Define standards for inclusion
- Development for interoperability
- Create case studies to demonstrate applicability
- Engage decision-makers
- Create toolbox and make available for all
 - Workshop(s) to meet objectives

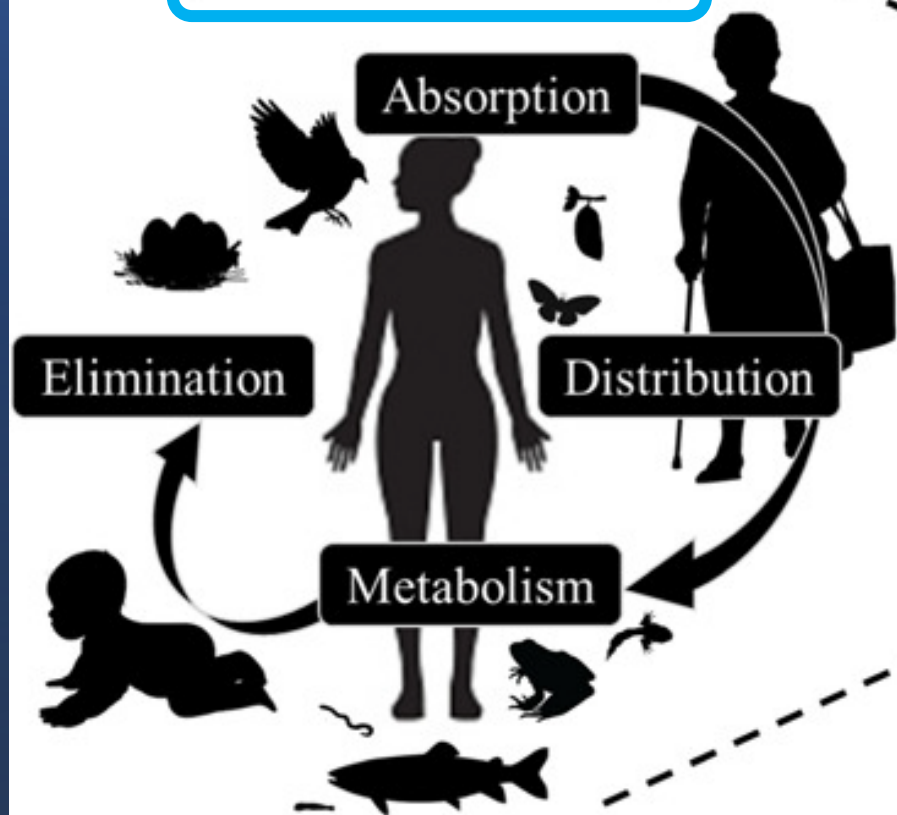


Communicate a Shared Scientific Vision



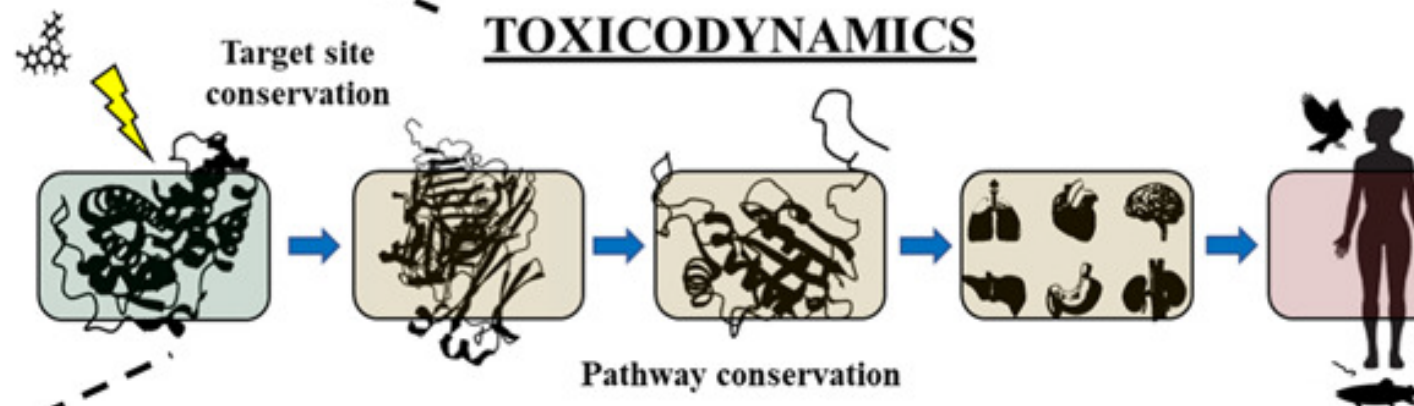
- Develop and provide training
- Communicate Bioinformatics Pipeline – Using the toolbox
 - Publications,
 - Sessions/meetings/workshops

TOXICOKINETICS



Expand Focus Beyond Bioinformatics

TOXICODYNAMICS



Bioinformatics

Systematic literature review

Toxicokinetics/toxicodynamics modeling

Progress and Next Steps



- Create Steering Committee ✓
- Develop initial mission statement and define objectives ✓
- Define relationships with appropriate professional societies ✓
- Publish article describing the Consortium ✓
- Create website for ICASCER ✓
- Introduce topics at SETAC and SOT professional meetings ✓
- Develop invited participant list ✓
- Develop a webinar series to introduce tasks more broadly
 - Self nomination of presenters
- Kickoff teams to work on tasks
 - Invite or Self nomination
 - Develop meeting schedules for Task Teams and ICACSER

SETAC Hosted Webinar Series

1. **Introduction to the International Consortium to Advance Cross Species Extrapolation in Regulation (ICACSER)**
2. Extrapolation in the Current Regulatory Landscape
3. The Adverse Outcome Pathway Framework to Capture Knowledge Across Species
4. Needs for Advances in Species Extrapolation; use of biomedical data/knowledge for chemical safety
5. Vision for bioinformatics in decision-making
6. Linking Tools through a Bioinformatics Toolbox: Case examples

Who should be involved

- The consortium aims to **incorporate a diversity of expertise** that represent the **tripartite** nature of the challenges faced in species extrapolation. Participants will be **those motivated to advance this area of science** in a collaborative and **inclusive manner**. It is anticipated that participants will be representatives from government (researchers, regulators, policy-makers), academia, industry, non-government organizations, communicators and social scientists.

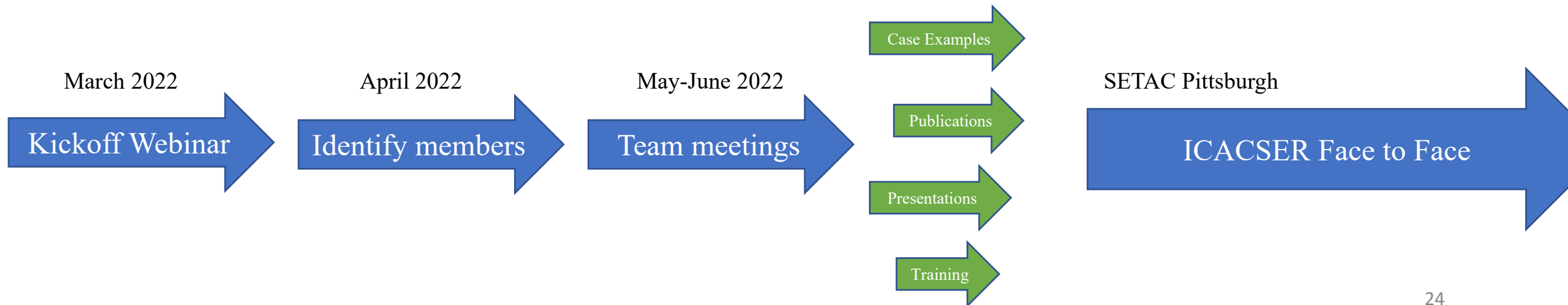


Members: Invitations and self-identified interest

Teams:

- Define the global regulatory landscape/need
- Develop a bioinformatics toolbox
- Communicate a shared scientific vision

Time line
Webinar
Invitations
Kickoff teams
Training – SETA
Course



What motivates you?

- Is your research so exciting that you can't wait to get to the office in the morning to get to work?
- Are you passionate about evaluating the risk of chemicals and protecting the environment?
- Do you enjoy taking on difficult scientific challenges?
- Do you find it rewarding to ensure that quality science reaches the hands of regulators?
- Are you most productive in your research working with other motivated individuals with a variety of expertise?

Resources for ICACSER

- Join ICACSER by emailing:
 - LaLone.Carlie@epa.gov
 - Geoff.Hodges@unilever.com
- Publication:
 - LaLone, C.A., Basu, N., Browne, P., Edwards, S.W., Embry, M., Sewell, F. and Hodges, G., 2021. International Consortium to Advance Cross-Species Extrapolation of the Effects of Chemicals in Regulatory Toxicology. Environmental Toxicology and Chemistry <https://doi.org/10.1002/etc.5214>
- SETAC Websites:
 - <https://www.setac.org/general/custom.asp?page=scixspecies>
- Professional meeting sessions:
 - May 2022 SETAC EU *Computational new approach methods (NAMs) supporting regulatory decision making for chemical safety*
 - March 2022 SOT Roundtable *Cross Species Extrapolation: opportunities in a 21st century regulatory non-animal testing world*
 - November 2021 SETAC NA SciCon4 *Bioinformatics to inform cross species extrapolations in regulatory toxicology: What tools are available?*
 - May 2021 SETAC EU SciCon2 *Cross Species Extrapolation: opportunities in a 21st century regulatory non-animal testing world*