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Maximizing the Utility of Existing Data: Opportunities and Challenges for the Application of Systematic Review in Cross Species Extrapolation

Sara Vliet

Biologist, Scientific Computing and Data Curation Division

Office of Research and Development
Center for Computational Toxicology & Ecology

United States Environmental Protection Agency

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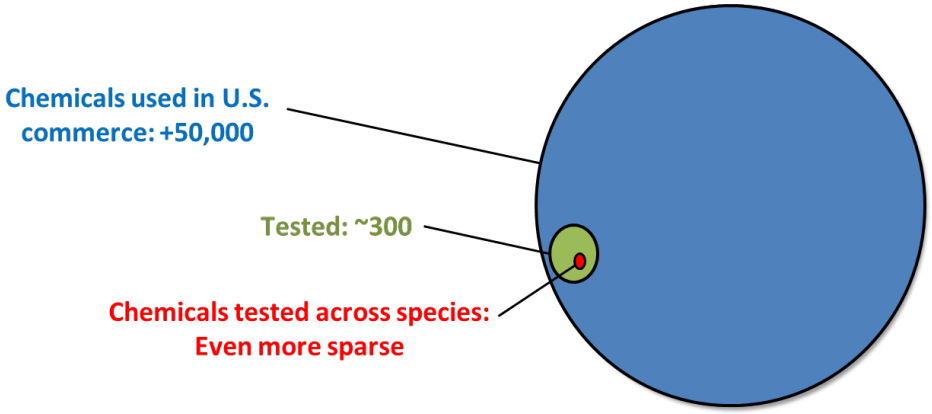
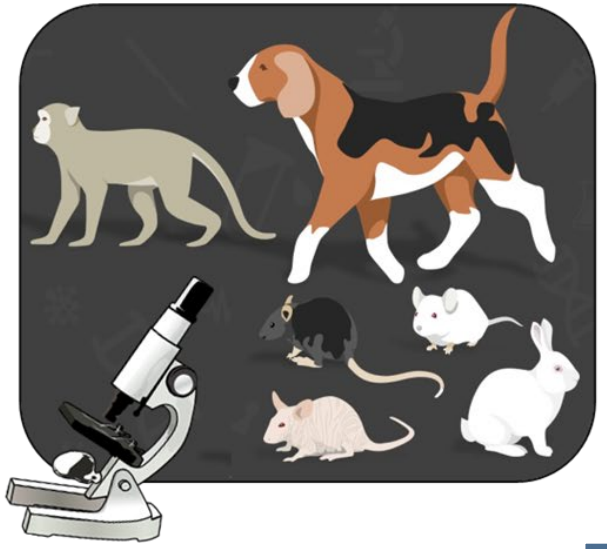
New Approach Methodologies: Moving Away From Animal Testing

- The mission of the EPA is to Protect Human Health and the Environment and the evaluation of ecological and human health risks associated with toxic chemicals represents one of the EPA's primary responsibilities

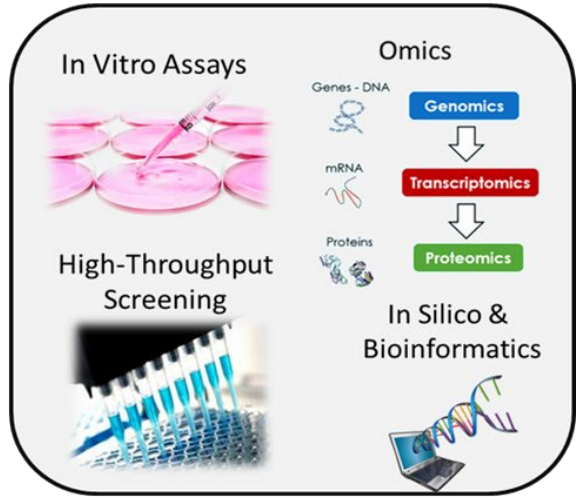


Whole-Animal Models
→ Observe Toxic Outcome



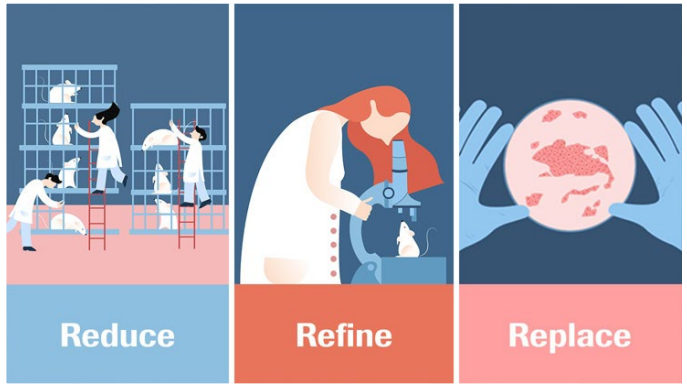
EFFICIENCY

New Approach Methods
→ Identify Biological Target



NAMs come with their own set of challenges (just to name a few)…

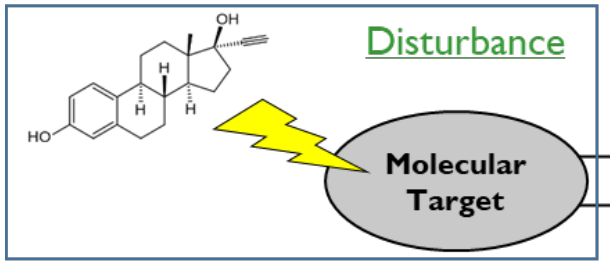
- Uncertainties surrounding biological relevance (metabolism, kinetics, etc.)
- Uncertainties surrounding biological representation (cell-type, species, etc.)
- Uncertainties surrounding biological extrapolation (how well does the molecular/cellular data reflect organism responses?)



Cross Species Extrapolation: A Challenge in New Approach Methodologies

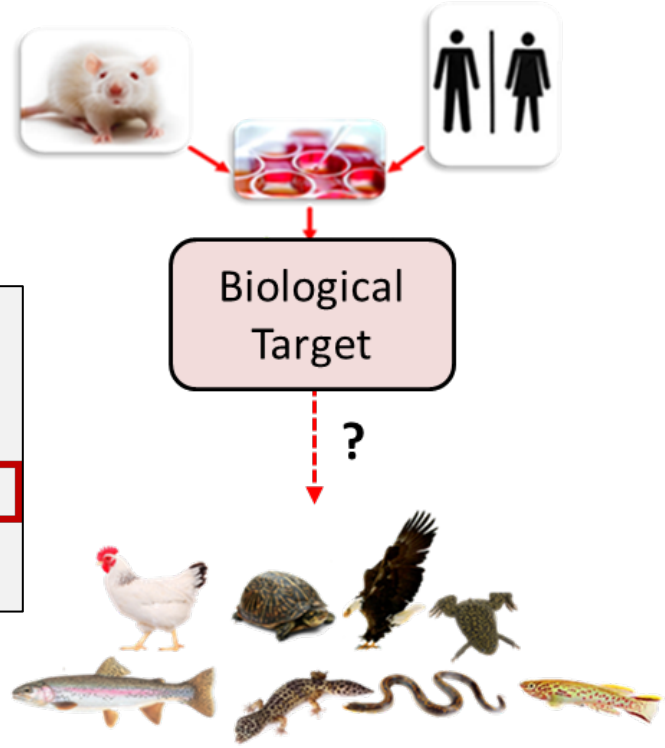
- Within animal testing, the sensitivity of species to a chemical is assumed to be a function of their relatedness, however, how well a model species represents the species of concern is often poorly understood
- This question still applies to many NAMs and the extrapolation of NAMs data from test species (e.g., mammalian cells) to other species of concern is essential

- For NAMs to play useful roles in decision-making, we need to understand how changes at the molecular level in cells and tissues are related to the apical adverse outcomes



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

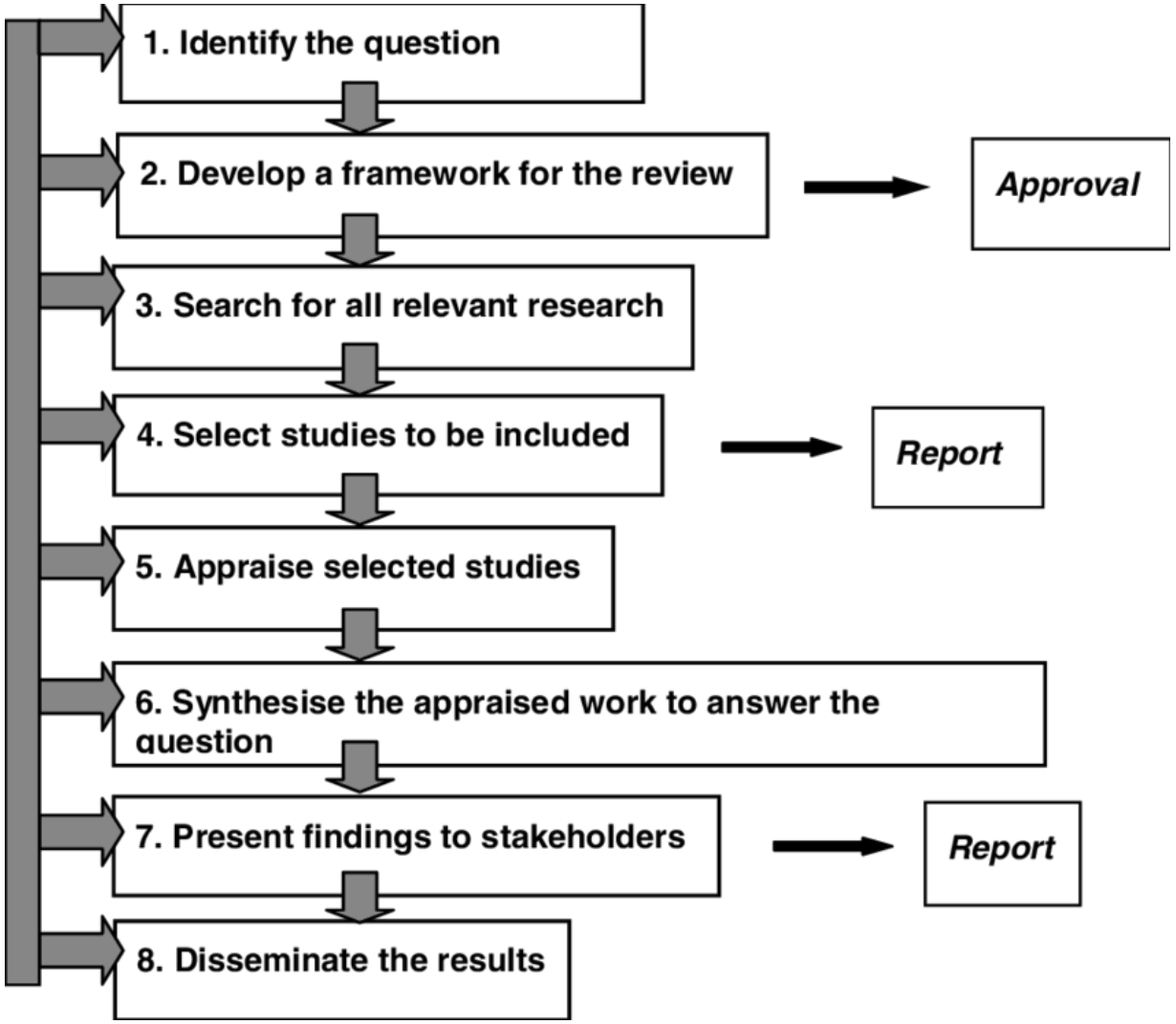
Out of the lab
- Homology modelling
- Molecular docking
- Review of existing evidence
- Etc.



Systematic Review: **Literature review that uses systematic methods to collect secondary data, critically appraise research studies, and synthesize findings.**

- First developed and used heavily within evidence-based medicine and recently applied more broadly to environmental health and cross-species applications
- Treats the searching, collection, and synthesis of existing evidence as a controlled experiment

Center for evidence-based management



Systematic Review in Ecotoxicology

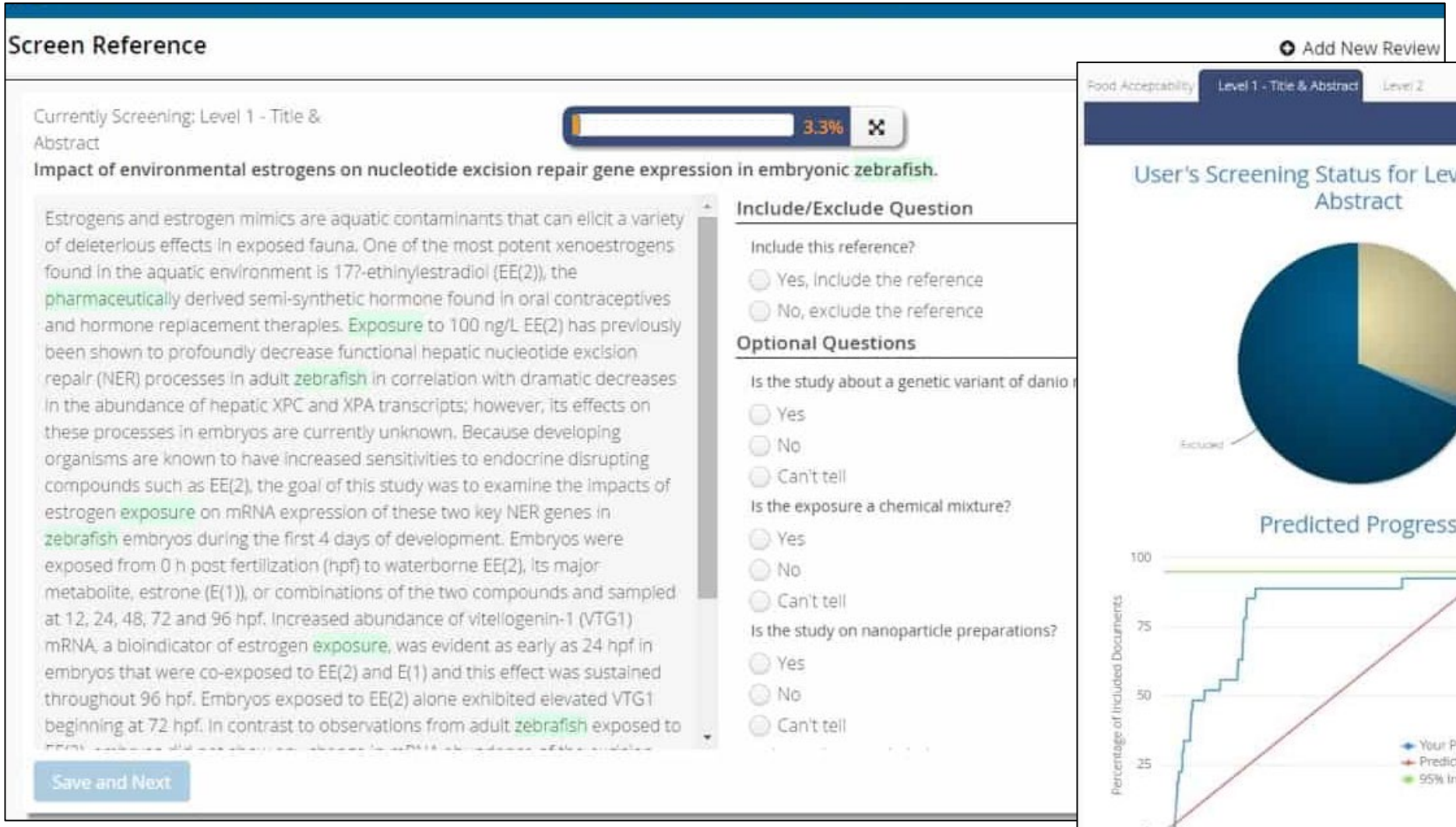
Opportunities & Challenges

- As methods have evolved, a variety of tools have emerged to help manage the systematic review process and help address these challenges

- The use of existing data reduces the need for further animal testing
- The use of systematic methods promote increased transparency, objectivity, consistency, and reproducibility of information
- Strengthened confidence in risk assessments
- Reduces the influence of reviewer bias and error in the evaluation process

- Harmonized data collection
  - What data fields are being collected during the review?
  - What type of language is being used to describe this data?
- Standardized Techniques
  - What methods are being used to search the literature?
  - What type of QC/QA is being conducted?
- Need for flexibility
  - Ecotoxicology is diverse, approaches will need to be similarly flexible
  - SR may not always be necessary, what are you trying to achieve?
- Resource Requirements
  - Cost, time, expertise, training, etc.

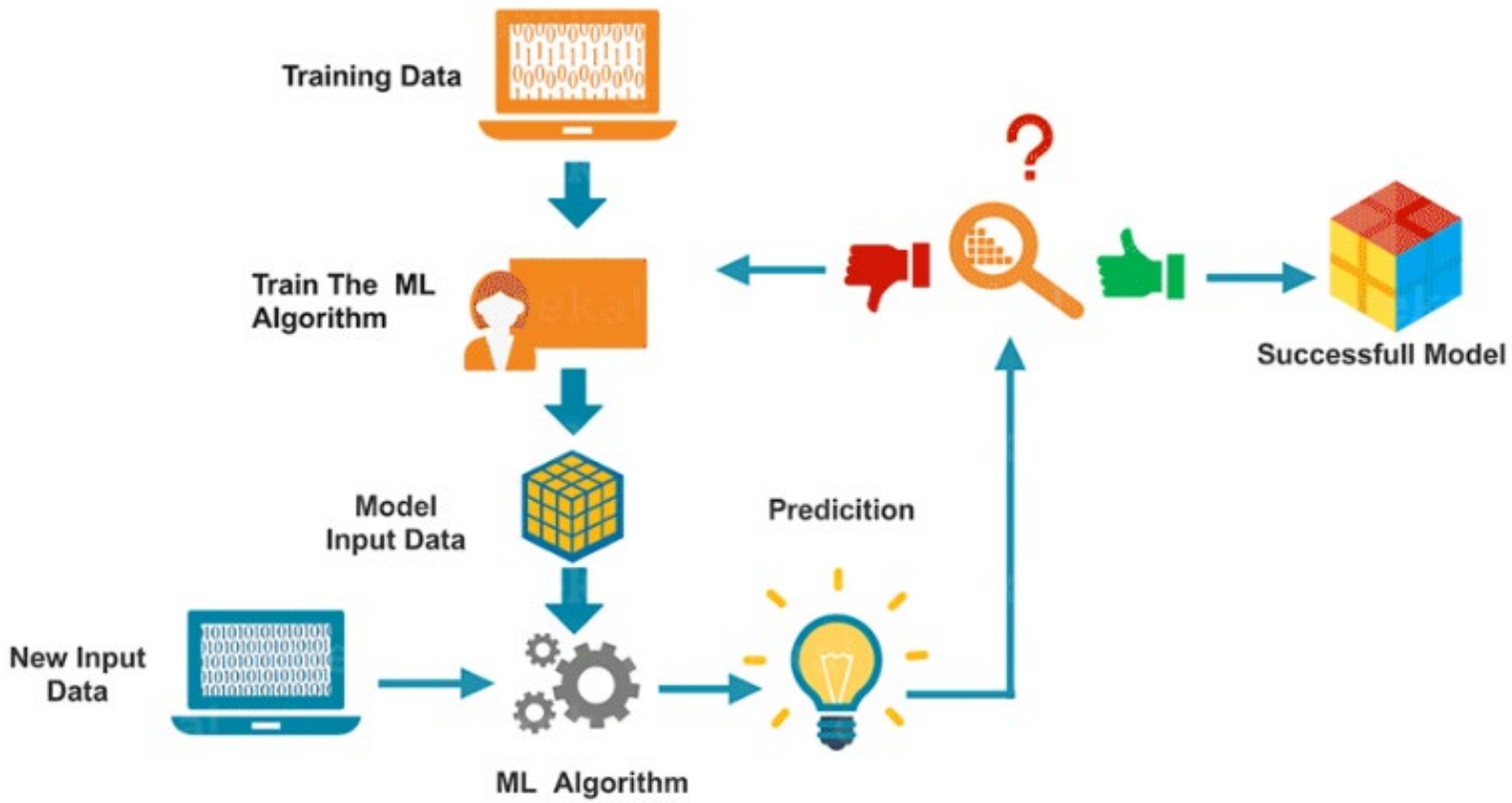
Tools of the Trade: Systematic Review Software



Tools of the Trade: Machine Learning

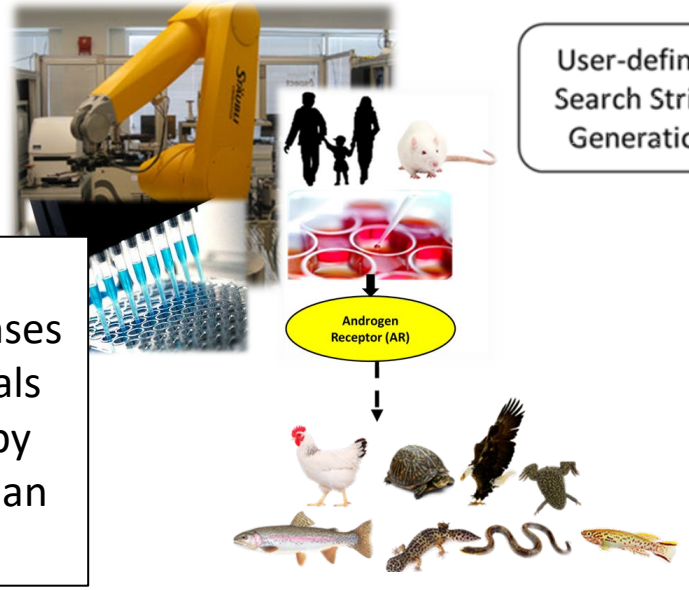
Machine learning can help reduce the human screening burden by predicting and prioritizing relevant references

- Algorithms are also being explored as a potential “second reviewer” or to completely replace human screening
- Applications are being developed to extract information from scientific text, tables, and figures
- Different data/reporting formats and lack of standardization proves challenging
- In general, these methods can be time savers, but all have some limitations, and do not eliminate the need for expert input

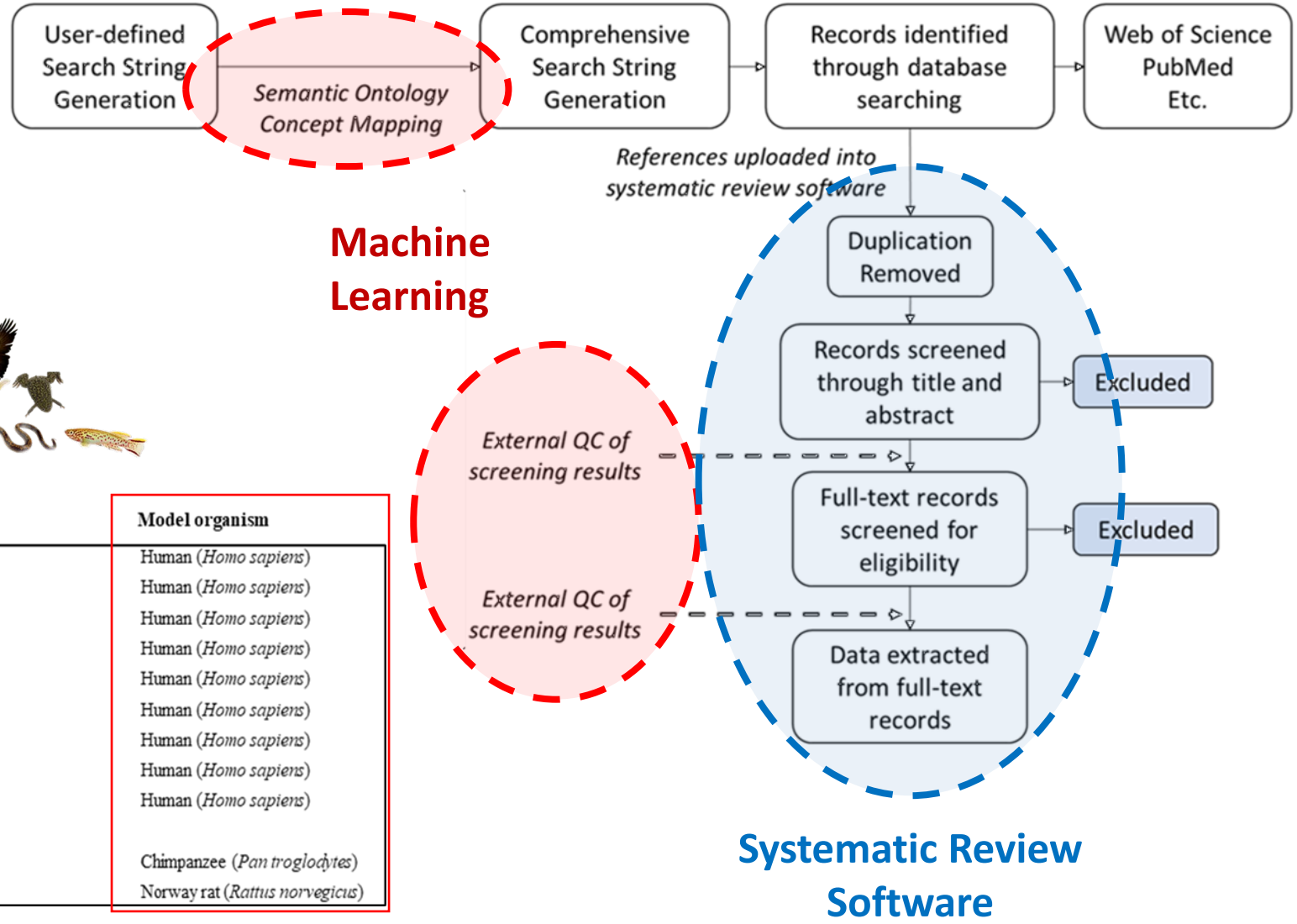


Case Example: How can we apply Systematic Review Methods to Cross-Species Extrapolation?

In non-mammalian vertebrates, are responses to androgenic chemicals able to be predicted by responses in mammalian test systems?

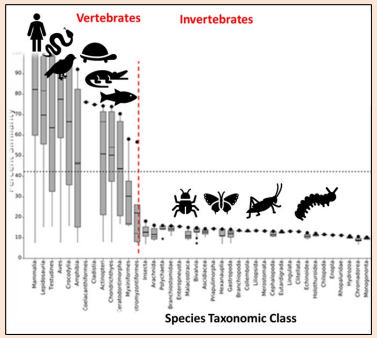


Assay Name	Assay Target	Model organism
ATG_TRANS	Androgen receptor, AR	Human (*Homo sapiens*)
NVS_NR_hAR	Androgen receptor, AR	Human (*Homo sapiens*)
OT_AR_ARELUC_AG_1440	Androgen receptor, AR	Human (*Homo sapiens*)
OT_AR_ARSRC1_0480	Androgen receptor, AR	Human (*Homo sapiens*)
OT_AR_ARSRC1_0960	Androgen receptor, AR	Human (*Homo sapiens*)
TOX21_AR_BLA_Agonist	Androgen receptor, AR	Human (*Homo sapiens*)
TOX21_AR_BLA_Antagonist	Androgen receptor, AR	Human (*Homo sapiens*)
TOX21_AR_LUC_MDAKB2_Agonist	Androgen receptor, AR	Human (*Homo sapiens*)
TOX21_AR_LUC_MDAKB2_Antagonist	Androgen receptor, AR	Human (*Homo sapiens*)
NVS_NR_cAR	Androgen receptor, AR	Chimpanzee (*Pan troglodytes*)
NVS_NR_rAR	Androgen receptor, AR	Norway rat (*Rattus norvegicus*)



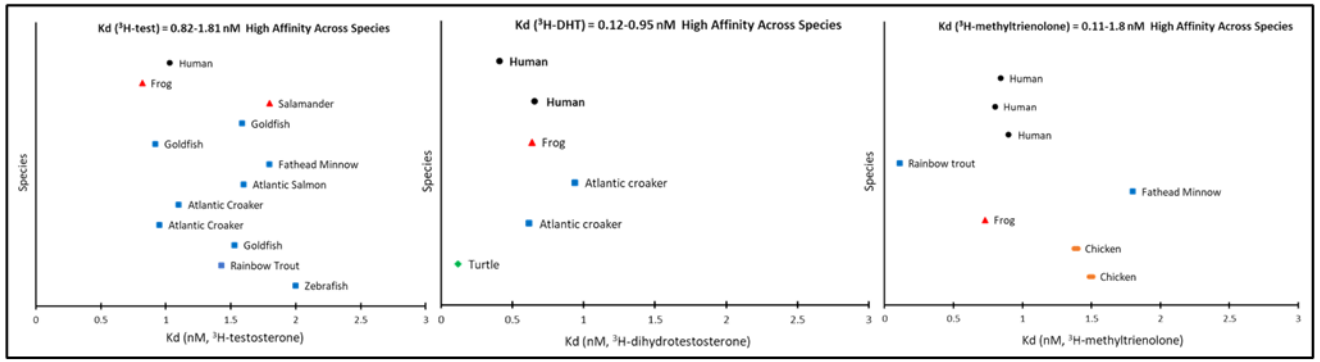
Case Example: How can we apply Systematic Review Methods to Cross-Species Extrapolation?

Computational Predictions of AR Conservation



US EPA SeqAPASS Tool

Systematic Evaluation of In Vitro Cross-Species Data



Systematic Evaluation of In Vivo Cross-Species Data

Chemical	Observations by Vertebrate Class			
	Fish	Reptile	Amphibian	Bird
Testosterone (endogenous androgen)	• Female development of male sex traits	• Female development of male sex traits • Male-biased populations (Skewed sex-ratios)	• Male-biased populations (Skewed sex-ratios)	• Female development of male sex traits • Increase in male behaviors
Methyltestosterone (synthetic androgen)	• Female development of male sex traits • Reduced gonadosomatic index (GSI)	• Female development of male sex traits • Male-biased populations (Skewed sex-ratios)	• Male-biased populations (Skewed sex-ratios)	• Reduced egg laying in females
17ß-trenbolone (environmental androgen)	• Female development of male sex traits • Reduced circulating E2 and vitellogenin levels	• Female development of male sex traits • Male-biased populations (Skewed sex-ratios)	• Female development of male sex traits • Male-biased populations (Skewed sex-ratios)	• Female development of male sex traits • Male-biased populations (Skewed sex-ratios)

Weight of Evidence for AR Conservation Across Species

- Apply pathway to other targets of interest
- Repeat process to account for new information
- Inform future computational predictions

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Thank you!

Vliet.Sara@epa.gov