Computational Toxicology and Exposure Communities of Practice

Sharing research and promoting collaboration

Thursday, December 12, 11 AM-12 PM ET

Agenda:

- **Introduction: Sammy Hanf**
  Communications Specialist, ORD Center for Computational Toxicology and Exposure
- **Presenter: Sandy Raimondo**
  Senior Research Ecologist, ORD Center for Environmental Measurement and Modeling (CEMM)
- **Q&A**
- **Closing remarks: Sammy Hanf**

Updates to the Web-based Interspecies Correlation Estimation (Web-ICE) application

Sandy Raimondo
Senior Research Ecologist, ORD Center for Environmental Measurement and Modeling (CEMM)

Web-based Interspecies Correlation Estimation (Web-ICE)

Sandy Raimondo

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Office of Research and Development (ORD)

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Computational Toxicology and Exposure Communities of Practice

12 December 2024

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the USEPA

Biodiversity Challenges in Ecological Risk Assessment (ERA)

- Biodiversity is critical for a healthy environment*
  - > 140,000 invertebrates
  - ~ 3,000 species of vertebrates
  - > 18,000 species of plants
  - > 1,300 threatened or endangered
- Sensitivity of a chemical is often tested only on a few surrogate species
- International move to reduce animal testing in favor of New Approach Methodologies (NAMs)

≠

*Estimates for United States

from the gallery of szymek drobniak

How Web-ICE Helps Tackle this Challenge

ICE in ERA

- Populates acute toxicity database with species, genus, and/or family-level sensitivity predictions
- Toxicity estimation for endangered species
- Allows for development of species sensitivity distributions (SSDs)

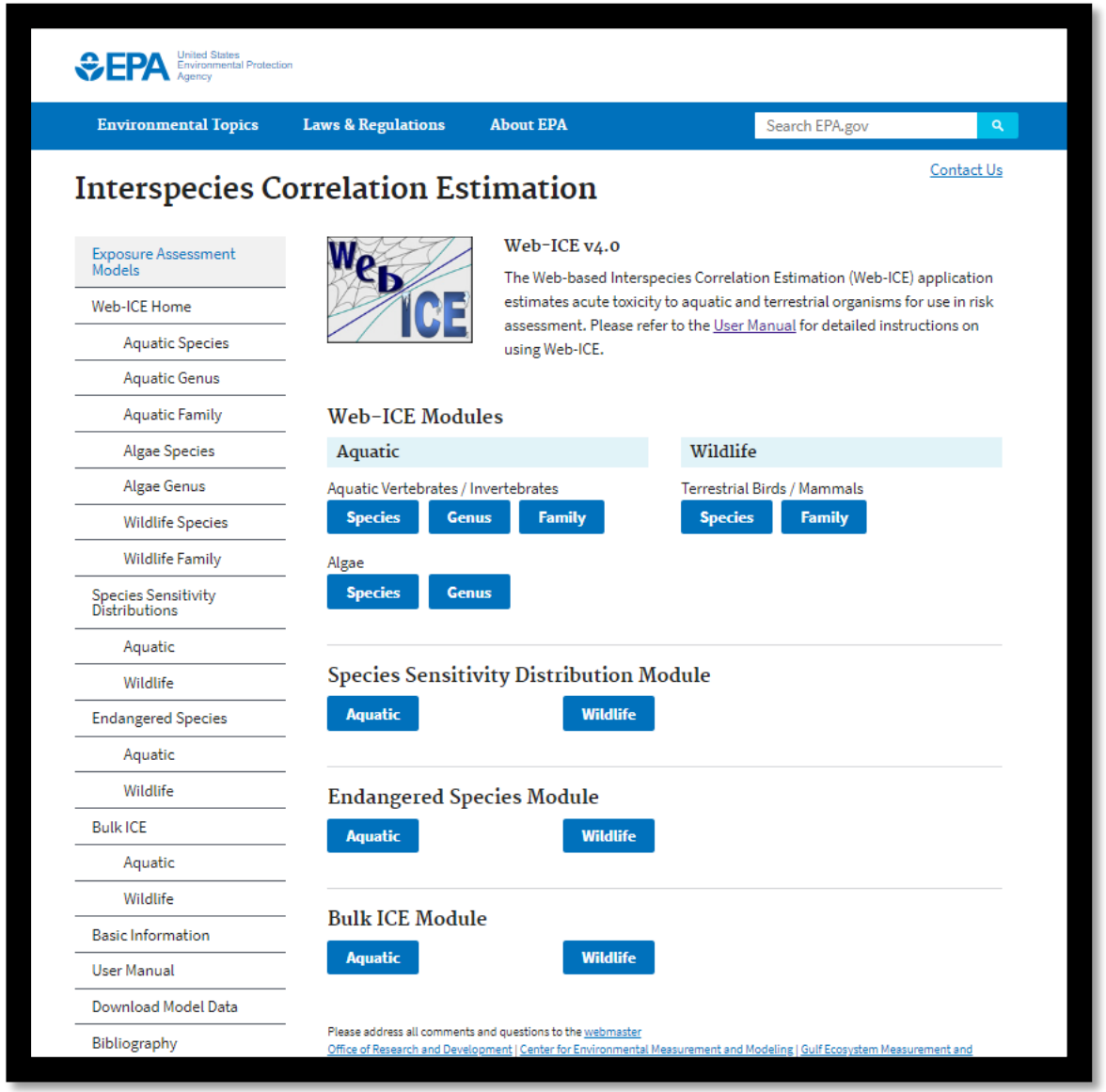
Rainbow trout

Atlantic salmon

What is Web-ICE?

http://www.epa.gov/webice/

- Uses Interspecies Correlation Estimation (ICE) models to estimate acute toxicity from the known toxicity of a surrogate species
- Contains modules to derive acute hazard levels and endangered species toxicity useful to chemical Ecological Risk Assessment (ERA)
- Version 1.0 released 2007
- Version 4.0 released May 2024



Discussion Outline

Technical Basis of ICE models

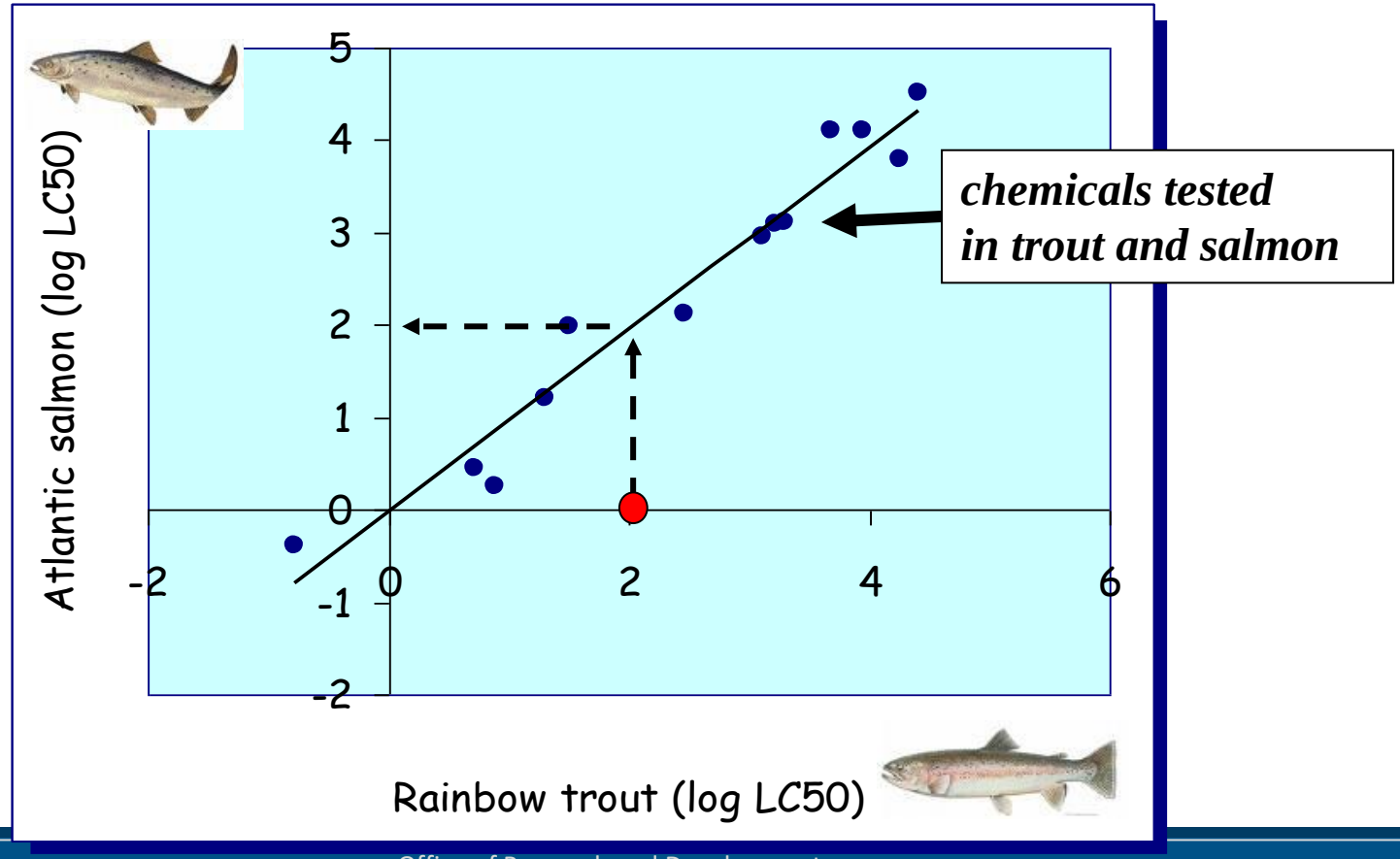
- Database & model development
- Validation and uncertainty analysis (select)
- User guidelines

Applications in EPA

- Aquatic Life Benchmarks
- TSCA chemical evaluation
- Endangered species assessment

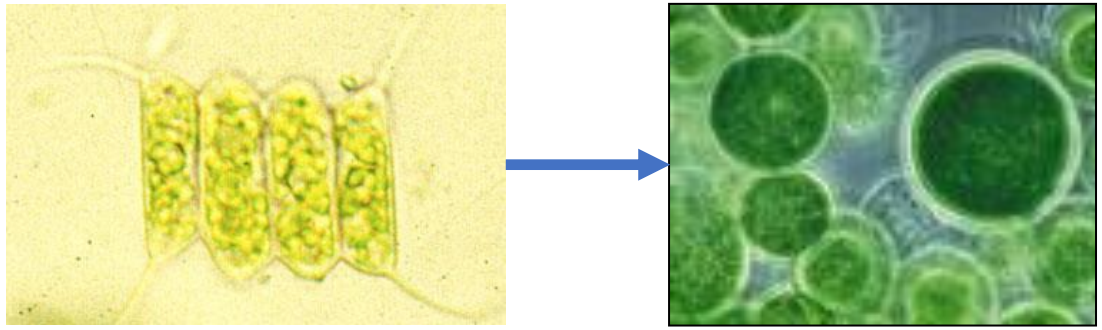
Interspecies Correlation Estimation (ICE) Models

Log-linear models of the relationship between the acute toxicity (LC50/LD50) of chemicals tested in two species.

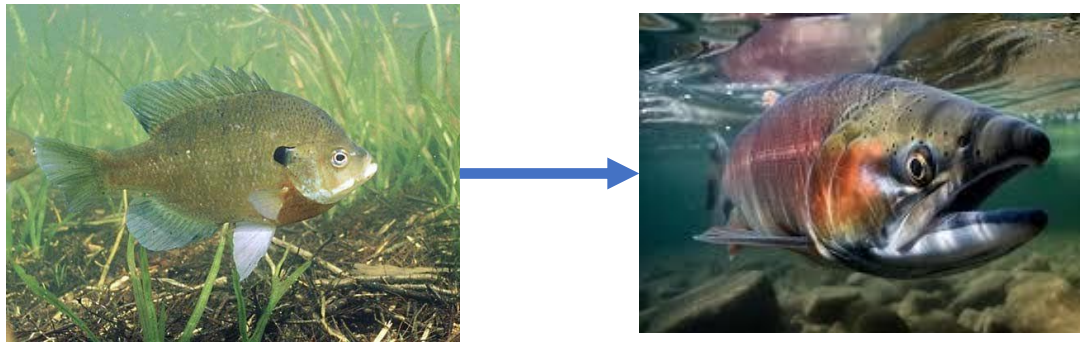


ICE Assumptions

1. ICE models represent the relationship of inherent sensitivity between two species.
   - Conserved across chemicals, mechanisms of action, and ranges of toxicity
   - ICE model data are highly standardized to reduce the variability underlying the model



2. The nature of a contaminant that was tested on the surrogate reflects the nature of the contaminant in the predicted species.
   - i.e., Effect concentration (EC50) or lethal concentration (LC50)
   - Percentage of active ingredient, and formulation/technical grade
   - Unit of toxicity



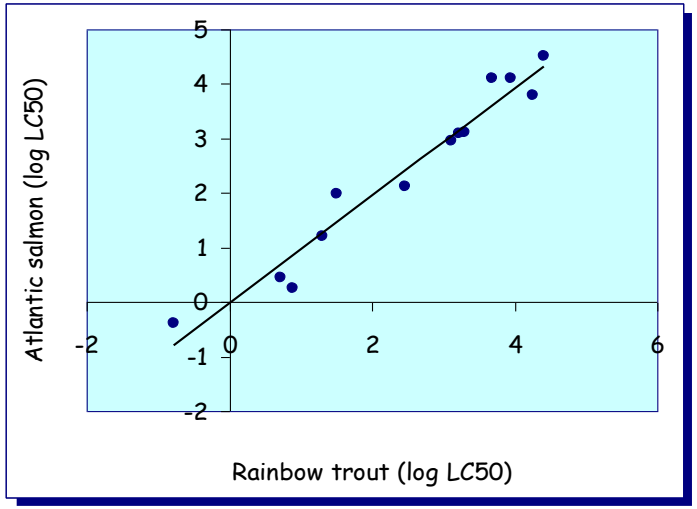
ICE Models – the basics

1. ICE models start with large database of acute toxicity

2. All possible pairings of species by common chemical

3. ICE model = Log-linear least squares regression of common chemicals tested in two species
   - some pairings will not yield any ICE model
   - some models will not be significant (p>0.05)

4. Suite of ICE models dependent on toxicity database



Web-ICE Databases: Aquatic Animals & Plants

Fish, amphibians, & invertebrates

- USEPA Office of Pesticide Programs Ecotoxicity Database
- USEPA Office of Pollution Prevention & Toxics
- USEPA Office of Water Ambient Water Quality Criteria
- ECOTOX (http://cfpub.epa.gov/ecotox/)

Algae & aquatic macrophytes

- ECOTOX (http://cfpub.epa.gov/ecotox/)
- Procter and Gamble (Brill et al. 2016)
- UPDATE IN PROGRESS

cas	species	genus	family	toxicity
50293	Orconectes nais	Orconectes	Cambaridae	0.24
50293	Ictalurus punctatus	Ictalurus	Ictaluridae	7
50293	Orconectes nais	Orconectes	Cambaridae	0.9
50293	Pimephales promelas	Pimephales	Cyprinidae	26
50293	Atherix variegata	Atherix	Athericidae	17
50293	Sander vitreus	Sander	Percidae	2.9
50293	Caecidotea brevicauda	Caecidotea	Asellidae	4
50293	Sander vitreus	Sander	Percidae	4.6
50293	Salmo salar	Salmo	Salmonidae	1.8
50293	Salmo trutta	Salmo	Salmonidae	1.8
50293	Orconectes nais	Orconectes	Cambaridae	0.3
50293	Lepomis macrochirus	Lepomis	Centrarchidae	8.6
50293	Ameiurus melas	Ameiurus	Ictaluridae	4.8
50293	Ictalurus punctatus	Ictalurus	Ictaluridae	22
50293	Ictalurus punctatus	Ictalurus	Ictaluridae	21.5
50293	Notropis blennius	Notropis	Cyprinidae	5.8
50293	Ictalurus punctatus	Ictalurus	Ictaluridae	16
50293	Ictalurus punctatus	Ictalurus	Ictaluridae	6.9
50293	Lepomis cyanellus	Lepomis	Centrarchidae	10.9
50293	Lepomis macrochirus	Lepomis	Centrarchidae	4.3
50293	Lepomis cyanellus	Lepomis	Centrarchidae	6.5
50293	Pteronarcella badia	Pteronarcella	Pteronarcyidae	1.9
50293	Lepomis macrochirus	Lepomis	Centrarchidae	5.8
50293	Lepomis macrochirus	Lepomis	Centrarchidae	6.3
50293	Micropterus salmoides	Micropterus	Centrarchidae	1.5
50293	Lepomis microlophus	Lepomis	Centrarchidae	15
50293	Ameiurus melas	Ameiurus	Ictaluridae	5.1
50293	Oncorhynchus clarkii	Oncorhynchus	Salmonidae	5.5
50293	Oreochromis mossambicus	Oreochromis	Cichlidae	17
50293	none	Tipula	Tipulidae	1.6
50293	Simocephalus serrulatus	Simocephalus	Daphniidae	2.8
50293	Simocephalus serrulatus	Simocephalus	Daphniidae	2.5
50293	Carassius auratus	Carassius	Cyprinidae	14.7
50293	Carassius auratus	Carassius	Cyprinidae	15.5
50293	Ictalurus punctatus	Ictalurus	Ictaluridae	17.3
50293	Esox lucius	Esox	Esocidae	2.7
50293	none	Ephemerella	Ephemerellidae	1.2
50293	Oncorhynchus mykiss	Oncorhynchus	Salmonidae	7.6
50293	Oreochromis mossambicus	Oreochromis	Cichlidae	14
50293	none	Tilapia	Cichlidae	5.1
50293	Oncorhynchus mykiss	Oncorhynchus	Salmonidae	11.4
50293	Oncorhynchus mykiss	Oncorhynchus	Salmonidae	8.7

Data Standardization: Aquatic Animals & Plants

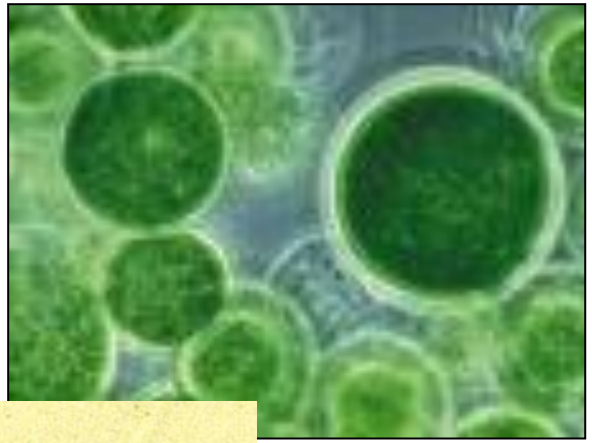
Category	Data Information	Criteria
Chemical	Identity	Reported CAS corresponds to single compound or element, name or structure confirmed
	Compound	Mixtures excluded except for chemical salts and specific congener mixtures[1]
	Purity	Active ingredient $\geq$ 90%
	Name	Synonyms conformed to ICE chemical name
Test Conditions	Test Media	Aquatic (no sediment, dietary, mixed dose or phototoxicity)
	Exposure type	Flow through (F), static (S), or static renewal (R)
	Test Location	Laboratory
Toxicity Value	Concentration	~, > or < excluded
	Element Conversions	Ag, Al, Cu, Cd, Co, Cr(III), Cr(VI), Hg, NH_4, Ni, Pb, Zn

Data Standardization: Aquatic Animals

Component	Information required	Acceptance requirements
Organism	Taxa	Fish, invertebrates, amphibians
	Life stage	Amphibians: embryo and larvae (tadpole) Crabs, crayfish, and lobsters: juvenile and larvae only Fish: juvenile only Zebrafish: embryos or juveniles (separated for models) Insects: immature aquatic lifestages Mollusc: juvenile and spat All other species: all life stages
Endpoint	Exposure duration	24-48 hr: fairy shrimp 48 hr: water fleas, midges, mosquitoes 96 hr: all other species
	Statistic	EC50 or LC50
	Measurement	Mortality or immobility
	Units	µg/L
	Chemical Normalization	Pentachlorophenol, ammonia, metals in accordance with AWQC
Test conditions	Temperature[4]	Species specific ($\pm$ 3°C)
	Dissolved oxygen	> 60%: Static $\leq$ 48 h, static renewal, flow-through > 40%: Static > 48 h
	Salinity	<1 ppt: FW species[5] $\geq$15 ppt: SW species[6]

Data Standardization: Aquatic Plants

Component	Information required	Acceptance requirements
Organism	Taxa	Algae and *Lemna* spp.
		Name & taxonomy verified
Endpoint	Exposure duration	Algae: 72 & 96 h *Lemna* spp: 7 d
	Measurement	Growth or mortality
	Statistic	EC/IC50
	Units	mg/L



Applied to update in progress

Databases & Standardization: Terrestrial Animals

Birds & mammals

- USEPA Office of Pesticide Programs Ecotoxicity Database
- Environment Canada
- Hudson et al. 1984
- Schafer et al. 1983
- Schafer and Bowles 1985
- Schafer and Bowles 2004
- Smith 1987

Data Standardization

- Single, oral dose, acute LD50 (mg/kg)
- Adults only
- Chemical formulation ≥ 90% active ingredient or technical grade

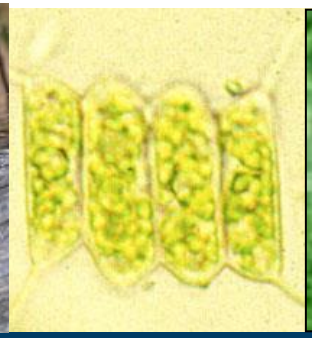
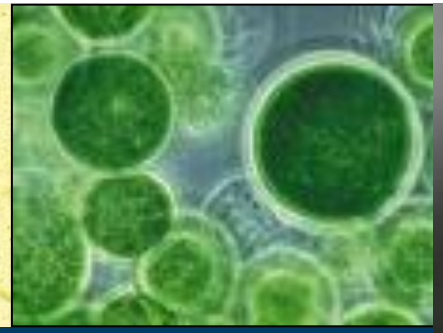
Web-ICE v4.0 Databases & Models

- Geometric mean = Species Mean Acute Value (SMAV) by chemical
- Models developed for all species pairs w/ ≥3 shared chemicals
- Only models with $p<0.05$ included

		Attributes		Number of models		
Database	Records	Species	Chemicals	Species	Genus	Family
Aquatic animals	10,737	478	1,708	2,286	1,074	1,363
Algae	1,647	69	457	58	44	0
Wildlife	4,329	156	951	560	0	292

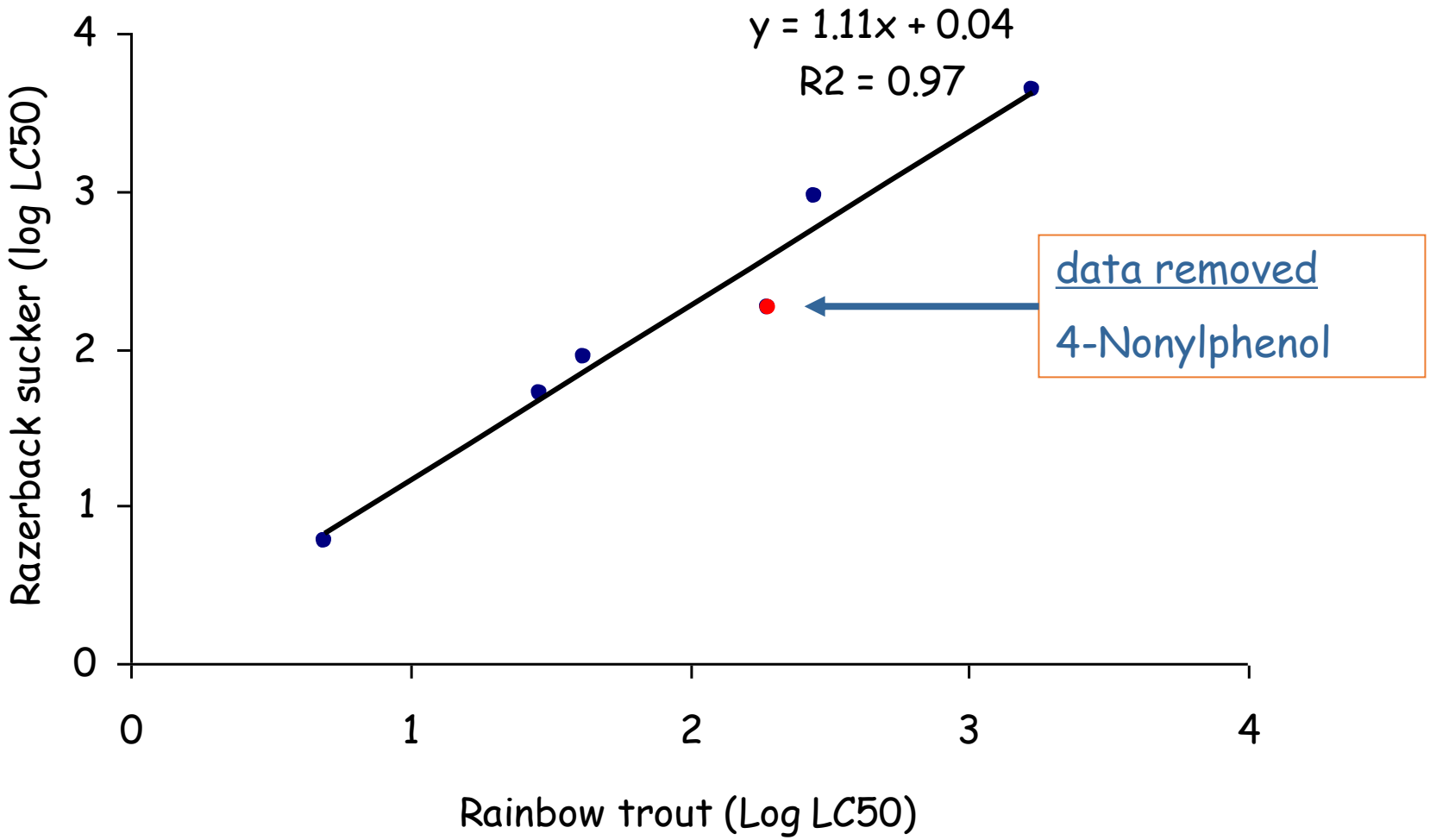
Update in progress



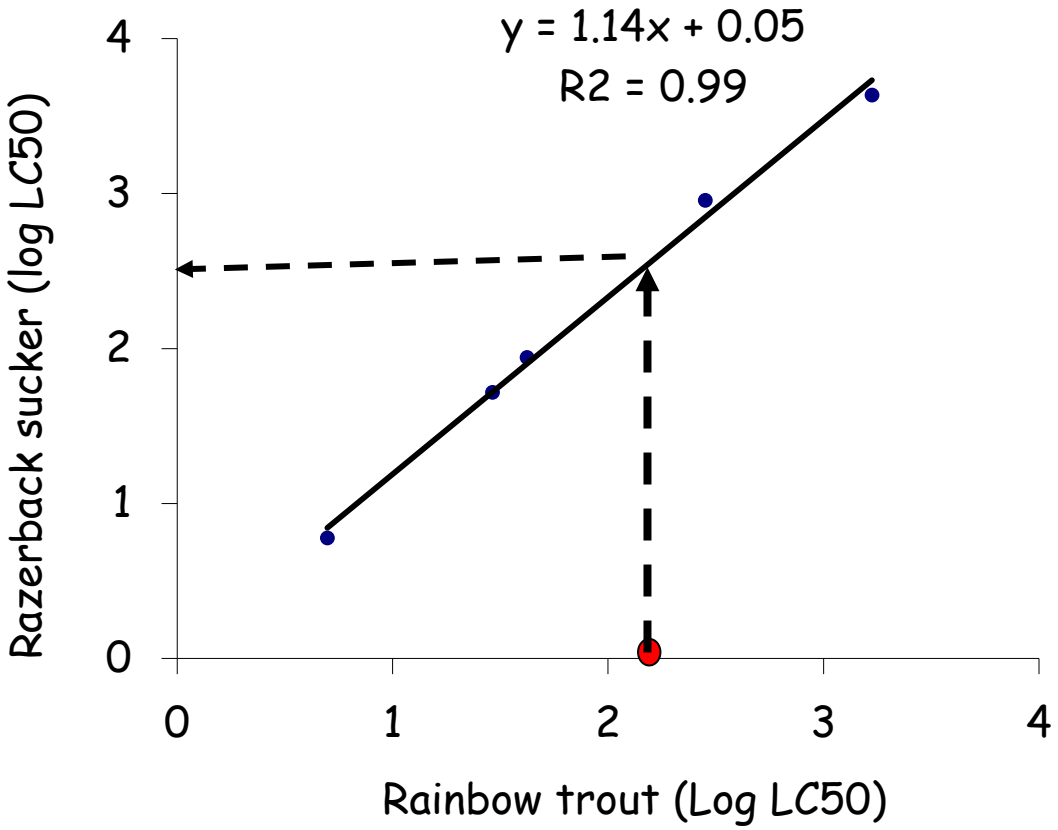




Model Validation: Leave-1-Out

- Models N ≥ 4
- Each data point is removed, one at a time, and the model is rebuilt with remaining data.
- Removed surrogate data are used to estimate removed predicted data from rebuilt model.



Model Validation: Leave-1-Out



data removed

4-Nonylphenol

New model predicted = 436.5 µg/L

Actual value = 182 µg/L

"fold difference" = 2.46

*** "fold diff" is maximum of predicted/actual or actual/predicted

Model Uncertainty Analyses

- Used “fold difference” of cross-validation to identify areas of model uncertainty
  - Analyses with multiple versions showed no tendency for over- or under- prediction

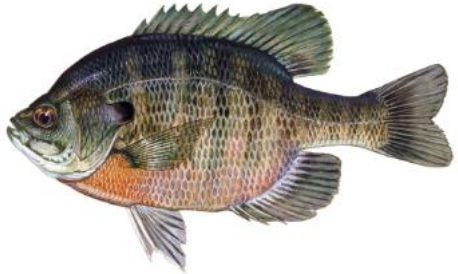
- Species level models
  - Aquatic v4.0: 23,238 data points from 1,954 models
  - Wildlife v1.0: 11,846 data points from 538 models

- Taxonomic relatedness
- Model parameters
- Chemical Mode of Action (MOA)
- Prediction Confidence Intervals (CI)
- Input beyond model domain

Taxonomic Distance

Measure of the taxonomic relatedness of the surrogate and predicted taxa

Surrogate:
Bluegill sunfish
(*Lepomis macrochirus*)



Taxonomic distance	= shared taxonomic level	
1 – genus	Redear sunfish (*Lepomis microlophus*)	
2 – family	Largemouth bass (*Micropterus salmoides*)	
3 – order	Greenthroat darter (*Etheostoma lepidum*)	
4 – class	Rainbow trout (*Oncorhynchus mykiss*)	
5 – phylum	Fowler's toad (*Anaxyrus fowleri*)	
6 – kingdom	*Daphnia magna*	

Uncertainty Analysis: Taxonomic Distance

Aquatic animals v4.0

Shared taxonomic level	Significant models	5-fold	10-fold	20-fold	50-fold	100-fold	> 100-fold
Genus (1)	642	94	99	100	100	100	100
Family (2)	1,412	91	97	99	100	100	100
Order (3)	466	85	95	99	100	100	100
Class (4)	6,424	76	87	92	96	98	100
Phylum (5)	2,838	61	75	84	92	96	100
Kingdom (6)	11,456	55	71	81	90	94	100

Raimondo et al. (2024)

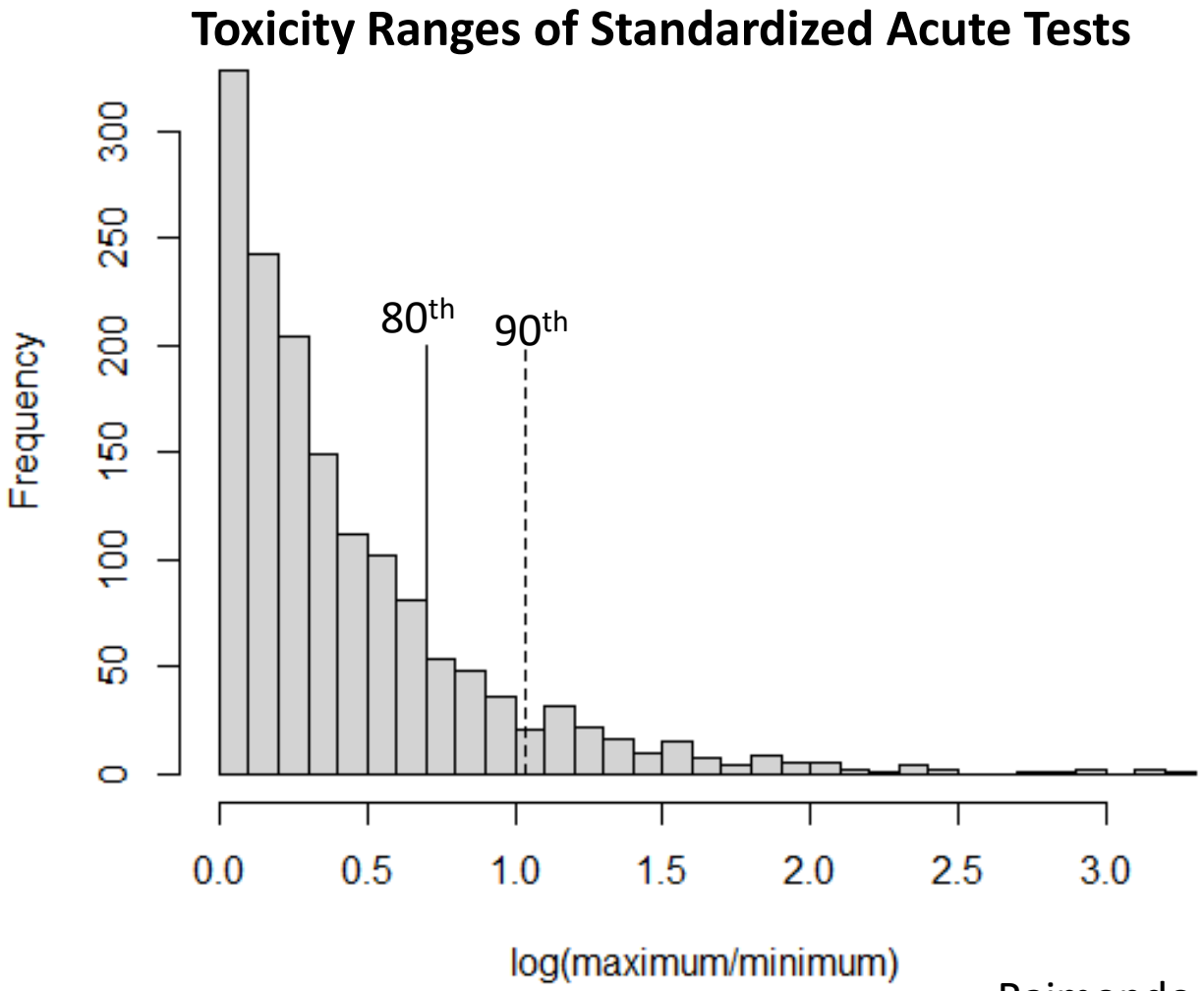
Variability of Standardized Data

Toxicity ranges for species-chemical

- 1,518 species-chemical combinations
- 189 species
- 554 chemicals

- Average acute max/min = 11.6
- 80th percentile = 5
- 90th percentile = 10.8

- No substantial differences when viewed by chemical MOA



Raimondo et al. (2024)

Reproducibility of ICE Validation: 10-fold predictions

ICE Model Assumption # 1:
ICE models represent the relationship of inherent sensitivity between two species that is conserved across chemicals, mechanisms of action, and ranges of toxicity

		Aquatic Animal Species			
		v3.2	v3.3	v4.0	Wildlife
	Year released	2010	2016	2024	2007
	Total N	10,914	17,416	23,238	11,846
Taxonomic Distance	1 – Genus	96	99	99	100
	2 – Family	96	98	97	98
	3 – Order	96	98	95	97
	4 – Class	89	77	87	95
	5 – Phylum	75	76	75	89
	6 – Kingdom	71	70	71	n/a
	Reference	Raimondo et al. (2010)	Willming et al. (2016)	Raimondo et al. (2024)	Raimondo et al. (2007)

Genus & Family Level Models

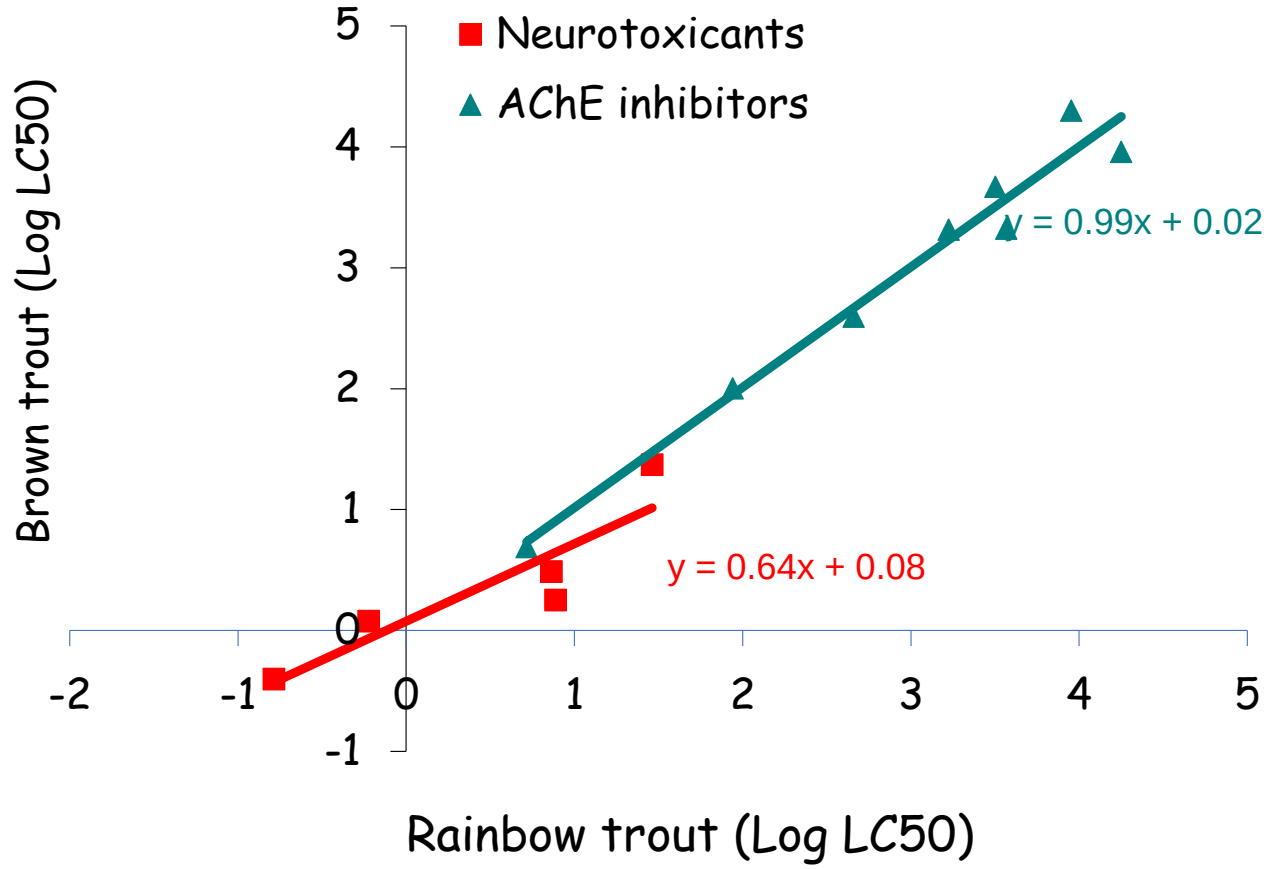
- Predict to genus or family from surrogate species
- Developed for taxa with > 1 species
- SMAV -> Genus or Family Mean Acute Value
- Surrogate species excluded for models with its own genus or family
- Uncertainty analysis by taxonomic distance

Aquatic animals v4.0

		Species	Genus	Family
	Total N	23,238	16,528	19,157
Taxonomic Distance	1 – Genus	99	97	n/a
	2 – Family	97	97	97
	3 – Order	95	90	91
	4 – Class	87	87	87
	5 – Phylum	75	75	74
	6 – Kingdom	71	69	69

MOA-Specific Models

- What role does chemical MOA play in model prediction?
- How do models built with MOA-specific data compare to models built with all data (e.g. all MOAs)?
- Do models built with MOA-specific data predict toxicity more accurately?



Development of MOA-specific models

- MOA assignments based on Barron et al. (2015)
  - 11 broad (e.g., AChE inhibition, narcosis)
  - 23 specific (e.g., carbamate AChE inhibition, nonpolar narcosis)

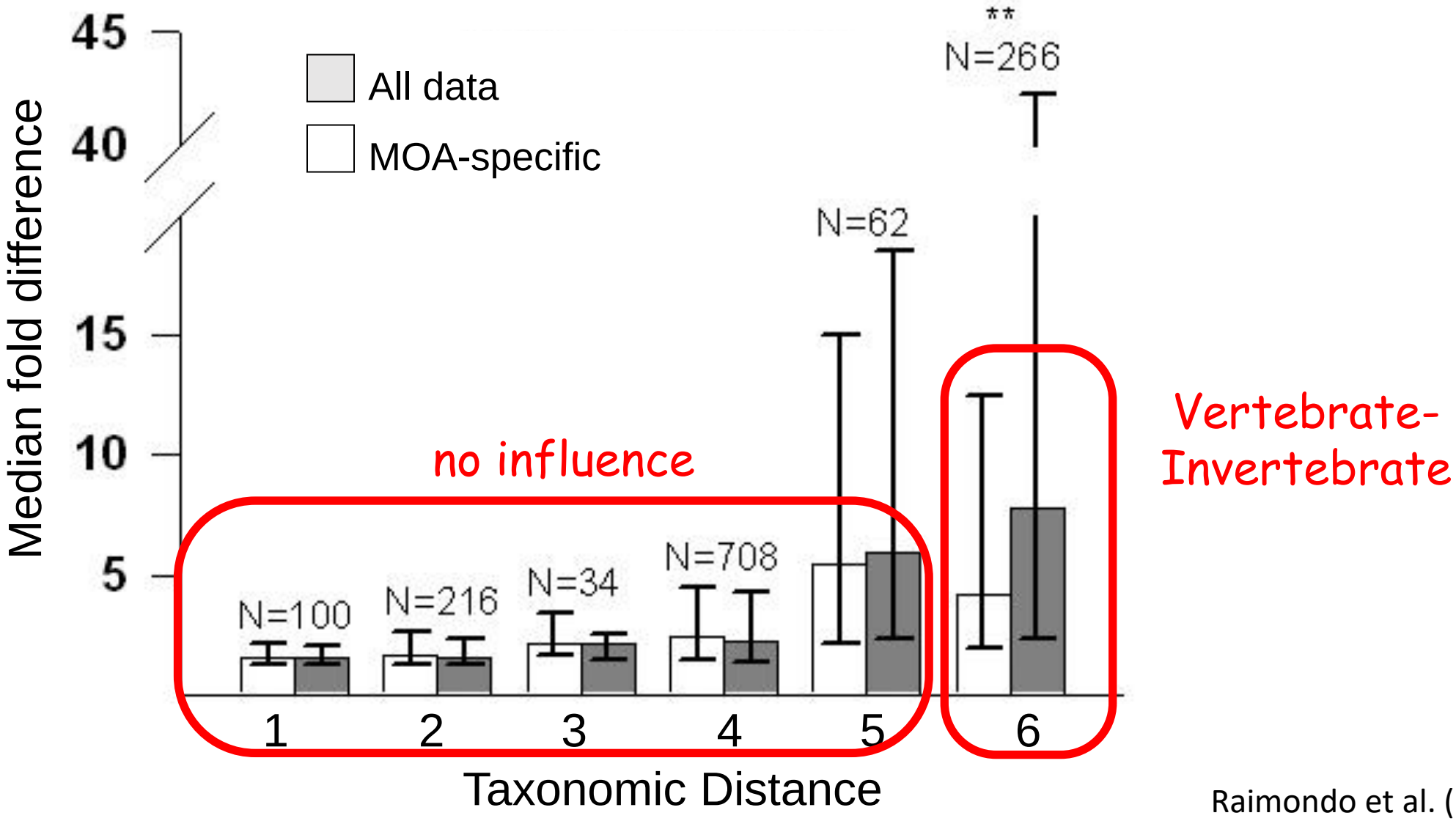
- Broad MOA
  - 7 broad MOAs
  - 494 species level models
  - 46 species

- Specific MOA
  - 15 specific MOAs
  - 424 species level models
  - 44 species

Analysis

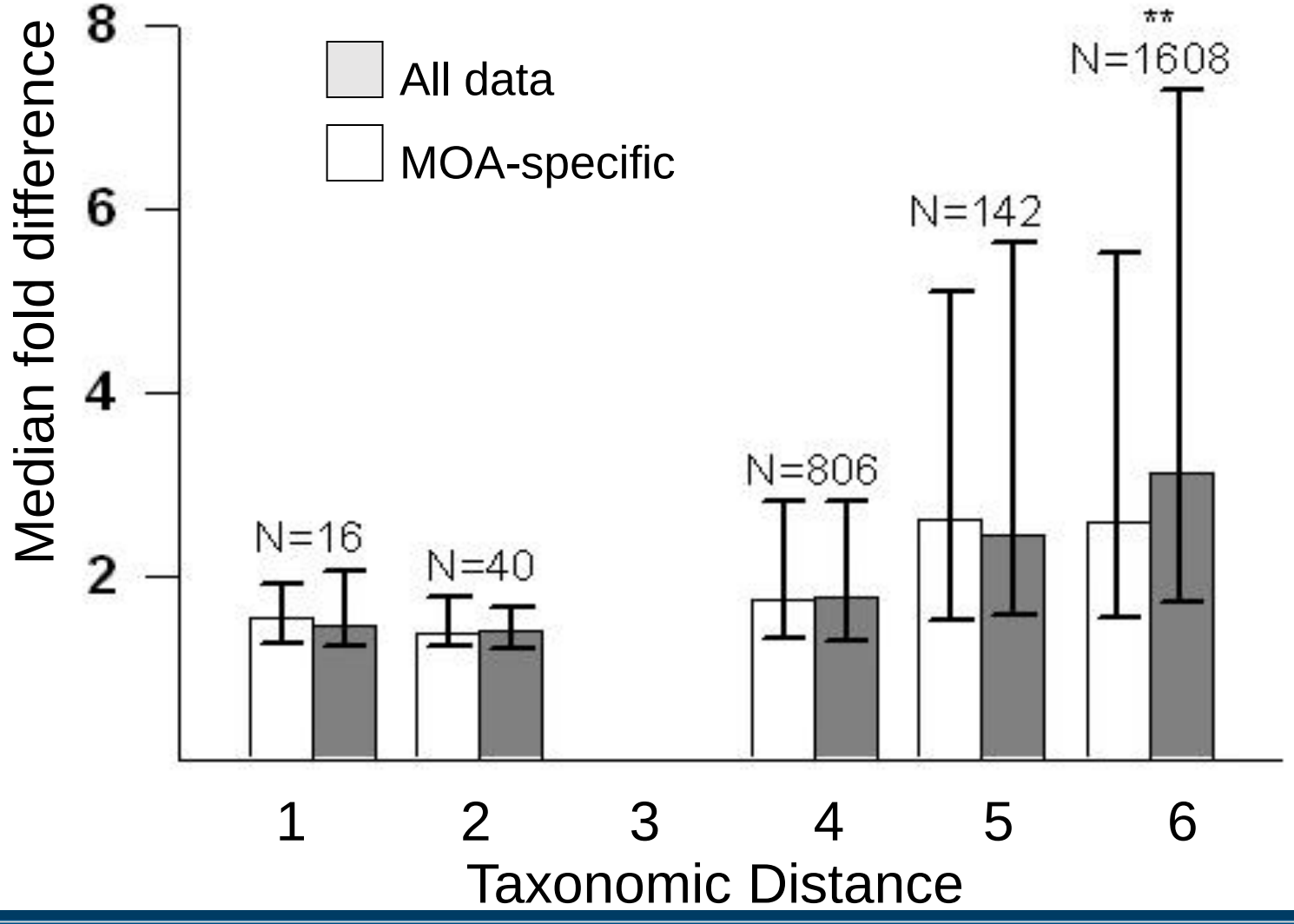
- Cross-validated MOA-specific models with leave-one-out approach
- Compared accuracy of data point predicted by "All data" models to that of MOA-specific models

AChE-Specific vs. “All data” models



Raimondo et al. (2010)

Narcosis vs. “All data” models



Raimondo et al. (2010)

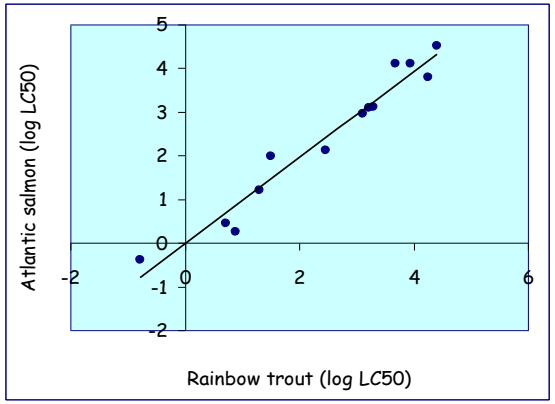
Uncertainty Analysis: Model Parameters

What combination of model parameters result in the most accurate predictions?

- Iterative approach using cross-validated datapoints
- Model parameters randomly selected
- Combination of parameters that resulted in the highest percentage of data points predicted within 5-fold of the actual value

User Guidance – Model Parameters

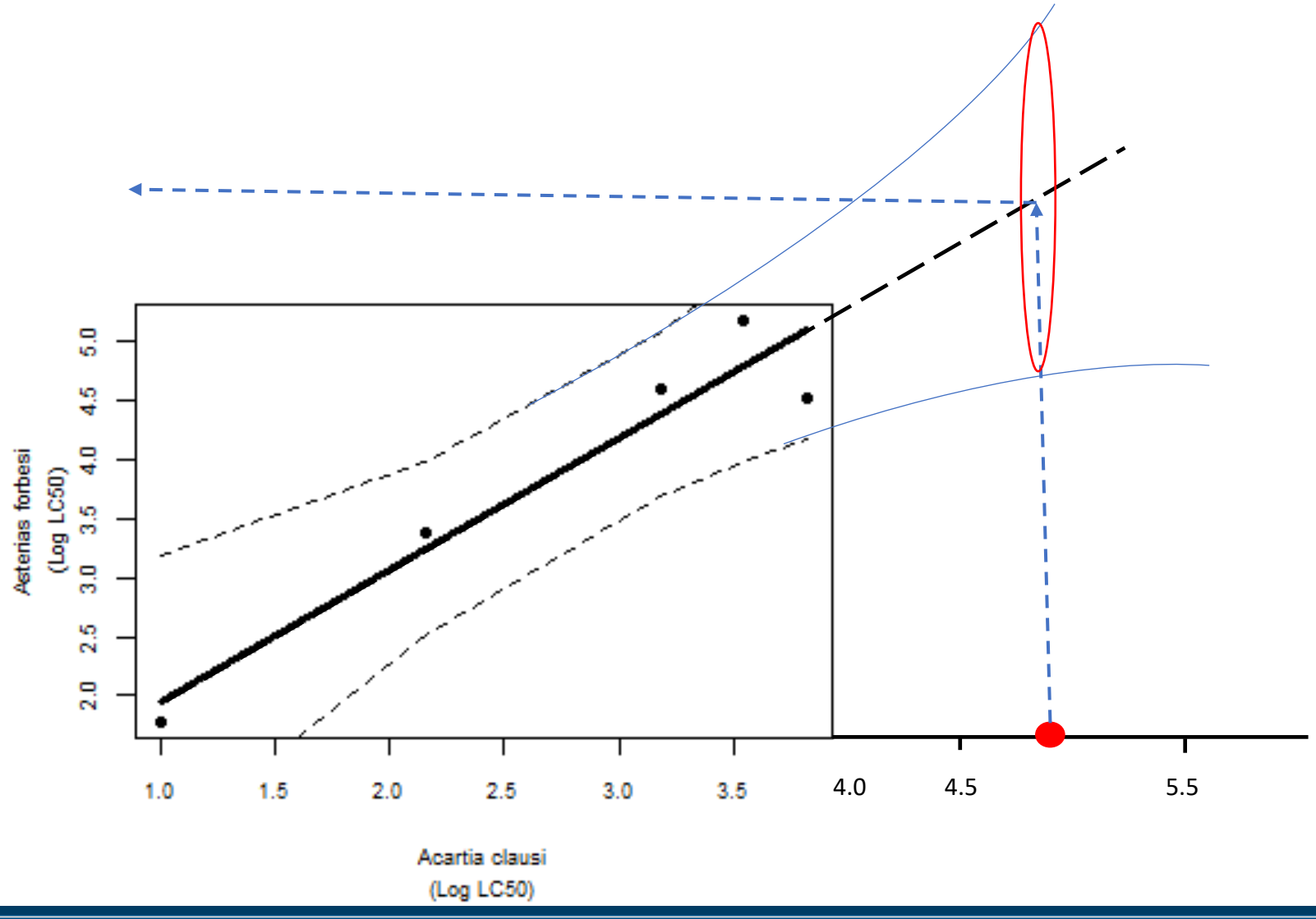
$R^2 \geq 0.6$
Mean Square Error (MSE) ≤ 0.95
Slope 0.6 – 1.4



Willming et al. (2016)

Uncertainty Analysis: Input Beyond Model Domain

- How can we evaluate predictions for input values outside model range?
- CI ranges can be large without correlation to prediction accuracy.

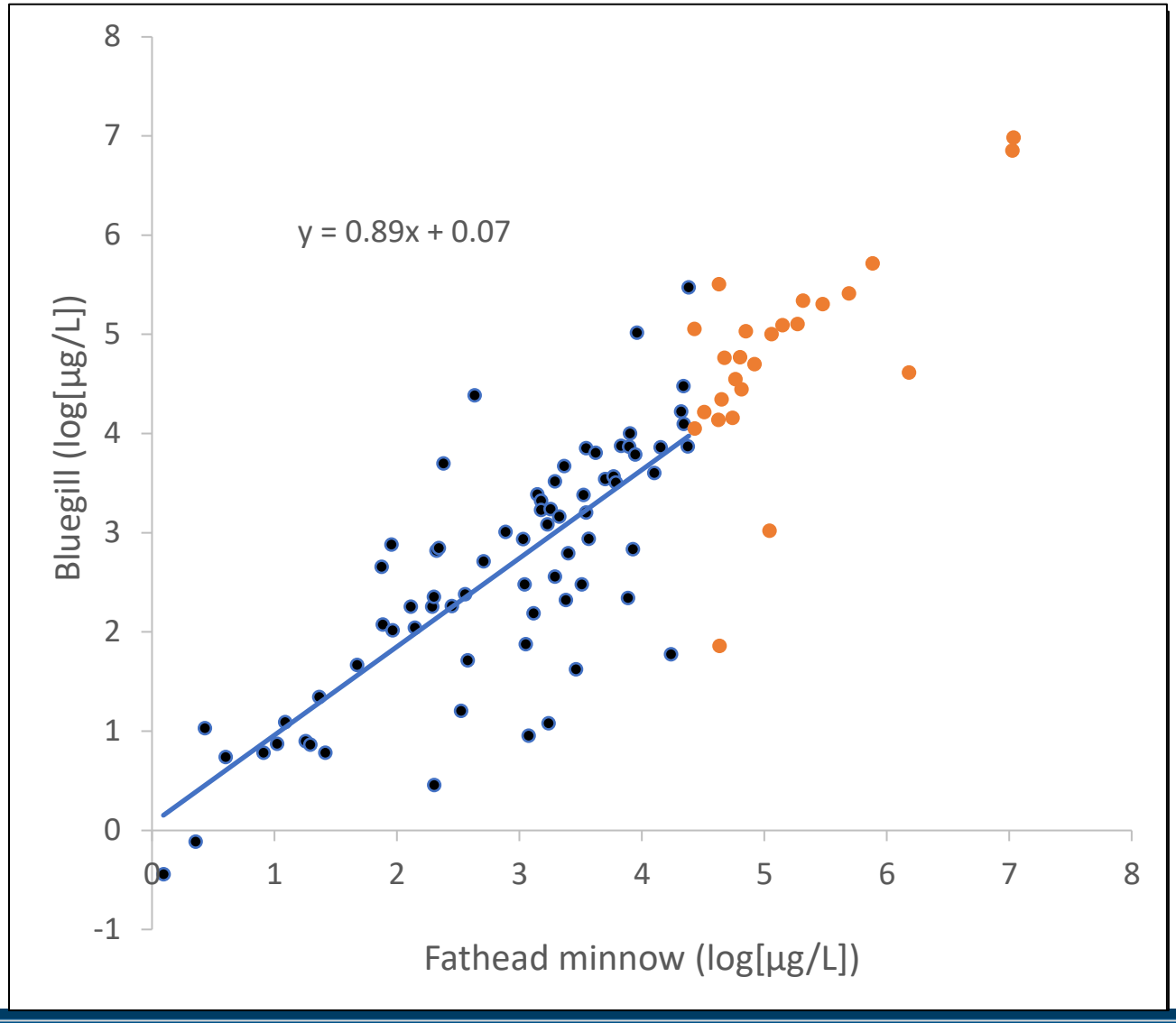


Uncertainty Analysis: Input Beyond Model Domain

- ICE models developed as µg/L
- Input on the "scale" of mg/L

Analysis:

- "Truncated" ICE models for validation of scaled values
  - N>10, tox range > 5 orders magnitude
  - Lower 75th percentile of surrogate values and associated y values
- Validation set:
  - Upper 75th percentile of surrogate data and associated y values
  - Predicted by truncated models
  - Compared to measured value of predicted species



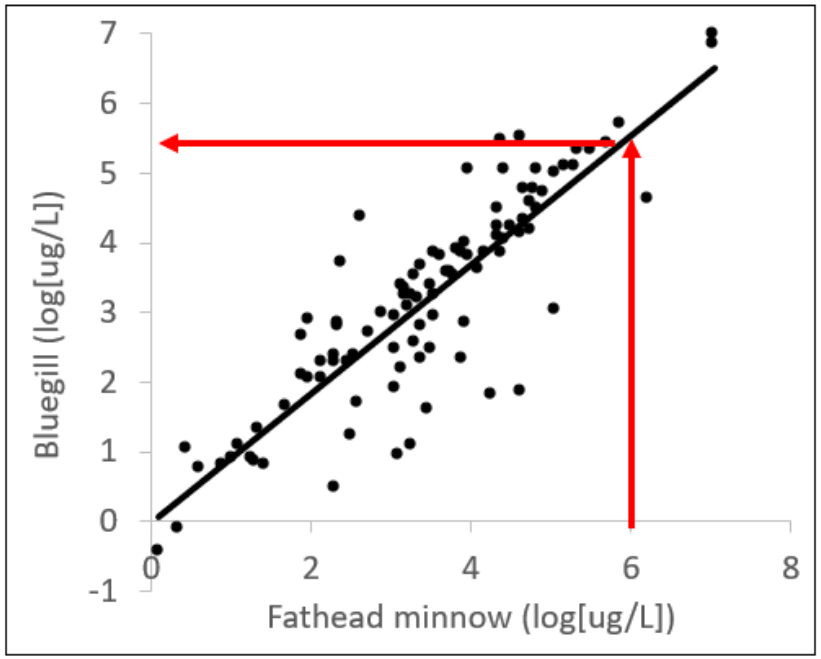
Uncertainty Analysis of “Scaled” Toxicity

3,943 datapoints from 475 species pairs evaluated using:

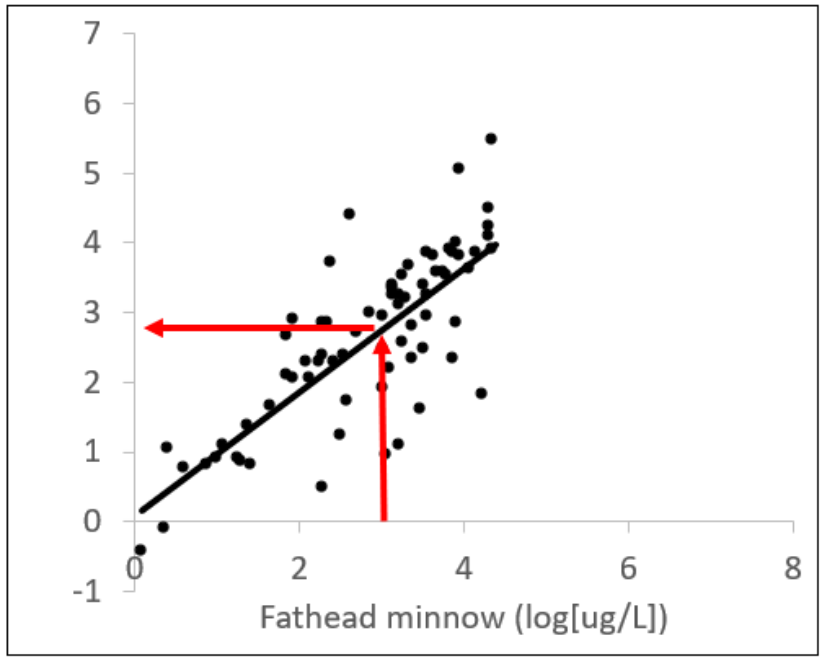
A. Traditional ICE extrapolation
B. Scaled toxicity
C. Extrapolated beyond the model domain

Uncertainty analysis with taxonomic distance and model parameters

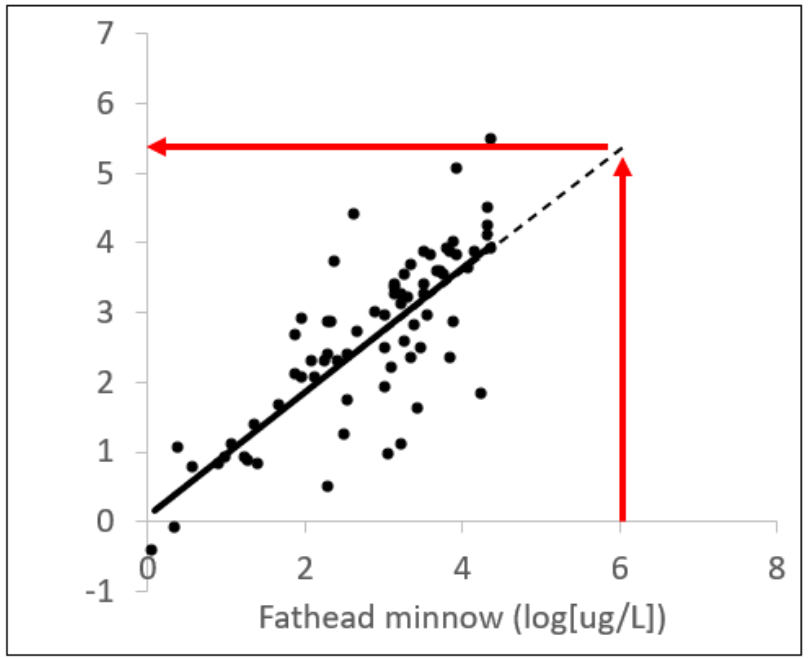
A) Traditional ICE use



B) “Scaled” input value (mg/L)



C) Extrapolated beyond model (µg/L)



Raimondo et al. (2024)

Reproducibility of ICE Validation

ICE Model Assumption # 2:
The nature of a contaminant that was tested on the surrogate reflects the nature of the contaminant in the predicted species.

Taxonomic distance	N[1]	A. Traditional	B. Scaled	C. Extrapolated	All x-validated v4.0[2]
1 – Genus	114	99	99	98	99
2 – Family	268	99	98	98	97
3 – Order	46	96	100	95	95
4 – Class	1136	93	90	91	87
5 – Phylum	312	80	79	77	75
6 - Kingdom	1107	79	75	75	71

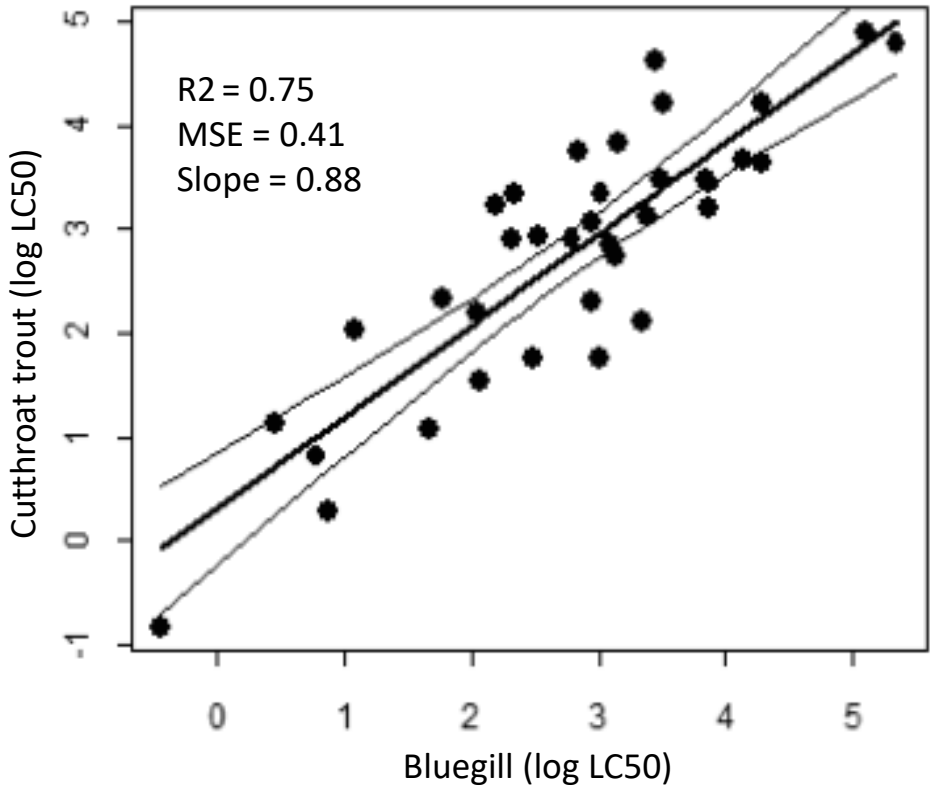
[1] Only includes models with slope 0.66 – 1.33
[2] 23,238 datapoints from all v4.0 models (previously shown)

User Guidance for Robust Predictions

Model parameters

- $R^2 \geq 0.6$
- Mean Square Error ≤ 0.95
- Slope: 0.6 – 1.4; 0.66 – 1.33 for scaled values/input beyond model domain
- Confidence intervals w/in 2-orders of magnitude

Use geometric mean of multiple predictions



Example Applications in USEPA

1. Water Quality Benchmarks
   - EPA Office of Water under CWA
   - Water quality benchmarks for PFAS

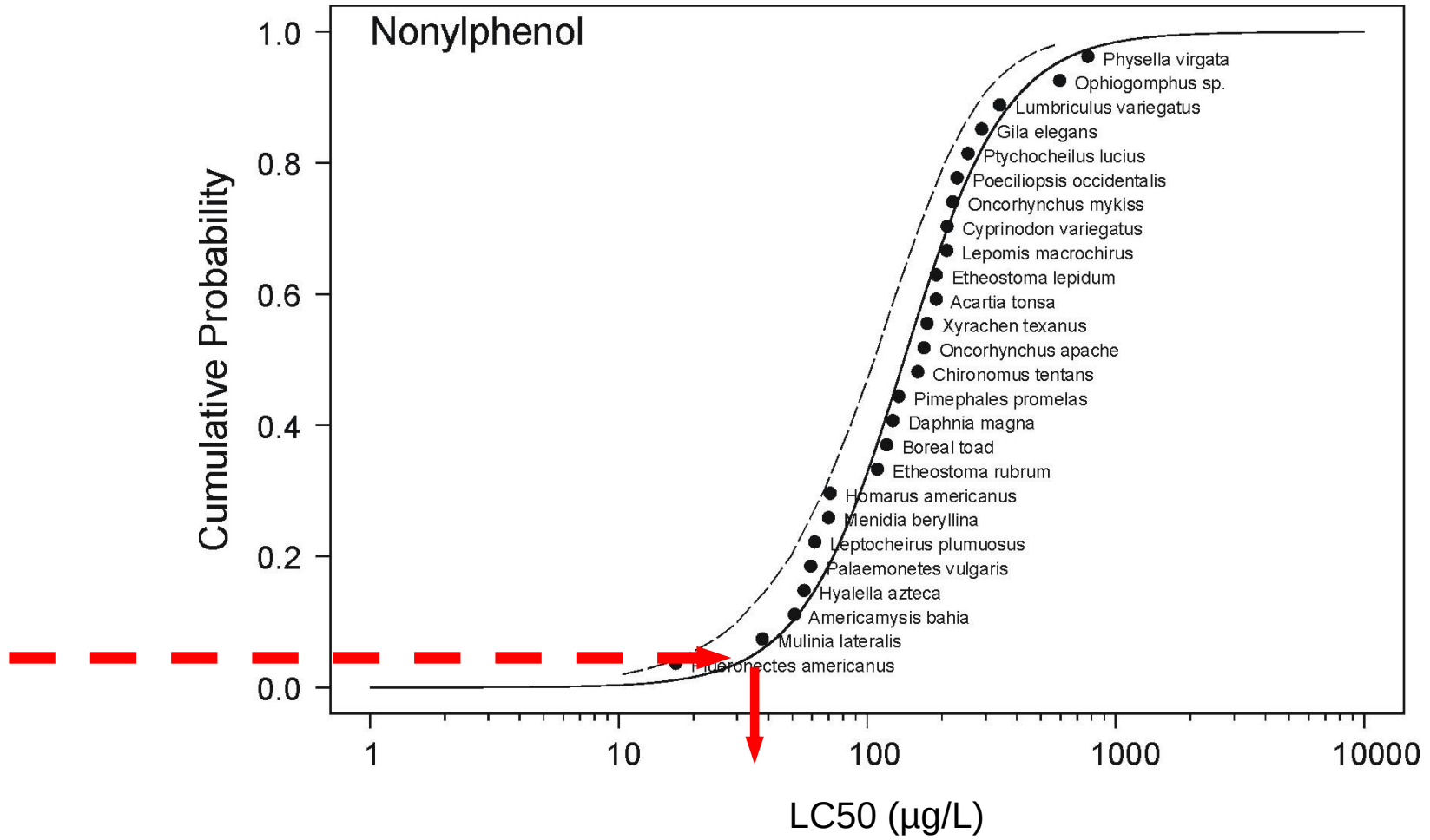
2. Chemical Evaluation under Toxic Substances Control Act
   - Office of Pollution Prevention and Toxics under TSCA
   - Chemicals with varying amount of data

3. Endangered Species Assessment
   - Region 10 under ESA and CWA
   - Biological evaluation for State Water Quality Standards

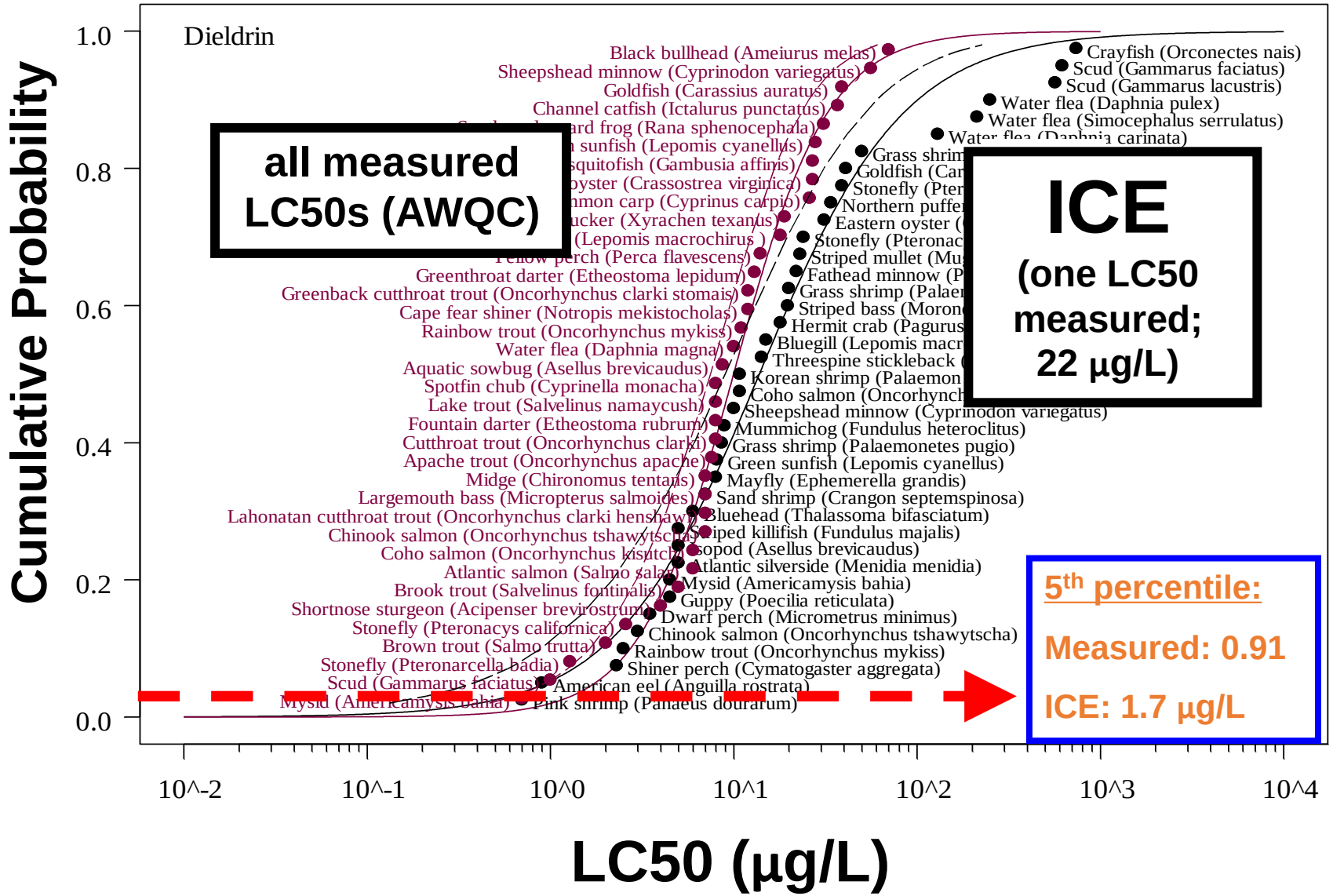
Species Sensitivity Distributions (SSDs)

Cumulative probability distribution of species sensitivity

- Widely used in ERA to determine hazard level
- Data rich requirements
- Hazard level of the 5th percentile considered protective of 95% of represented species/taxa



ICE and Measured SSDs



Aquatic Life Benchmarks for PFAS

https://www.epa.gov/wqc/pfas-and-aquatic-life

EPA United States Environmental Protection Agency

PFAS and Aquatic Life

As part of the U.S. Environmental Protection Agency's commitment to safeguard the environment from per- and polyfluoroalkyl substances (PFAS), the agency uses its Clean Water Act authorities to develop recommended water quality criteria and information benchmarks to help states and authorized Tribes protect aquatic ecosystems from several PFAS.

- Aquatic Life Criteria - Perfluorooctanoic Acid (PFOA)
- Aquatic Life Criteria - Perfluorooctane Sulfonate (PFOS)
- Clean Water Act Aquatic Life Benchmarks for PFAS

WQC Minimum Data Requirements (MDRs)

	Freshwater	Saltwater
A	The family Salmonidae	Family in the phylum Chordata
B	A second family of Osteichthyes[1] preferably a commercially or recreationally important warmwater species	Family in the phylum Chordata
C	A third family in the phylum Chordata[2]	Either the Mysidae or Penaeidae family
D	A planktonic crustacean	Family in a phylum other than Arthropoda or Chordata
E	A benthic crustacean	Family in a phylum other than Chordata
F	An insect	Family in a phylum other than Chordata
G	A family in a phylum other than Arthropoda[3] or Chordata	Family in a phylum other than Chordata
H	A family in any order of insect or any phylum not already represented	Any other family

[1] Bony fish; [2] Vertebrates and relatives; [3]Invertebrates with exoskeleton

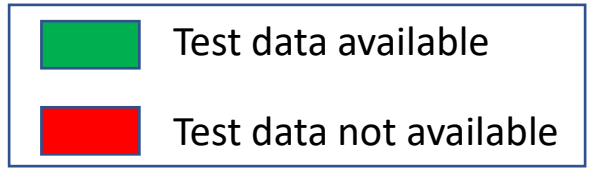
Fulfilling the MDRs for PFAS Chemicals

2024 Aquatic Life Benchmarks for Perfluorooctanoic Acid (PFOA)

Link: https://www.epa.gov/wqc/aquatic-life-criteria-perfluorooctanoic-acid-pfoa

	Freshwater
A	The family Salmonidae
B	A second family in the Osteichthyes, preferably a commercially or recreationally important warmwater species
C	A third family in the phylum Chordata
D	A planktonic crustacean
E	A benthic crustacean
F	An insect
G	A family in a phylum other than Arthropoda or Chordata
H	A family in any order of insect or any phylum not already represented

	Saltwater
A	Family in the phylum Chordata
B	Family in the phylum Chordata
C	Either the Mysidae or Penaeidae family
D	Family in a phylum other than Arthropoda or Chordata
E	Family in a phylum other than Chordata
F	Family in a phylum other than Chordata
G	Family in a phylum other than Chordata
H	Any other family



Fulfilling the MDRs for PFAS Chemicals

MDR	Freshwater Surrogates
A	Rainbow trout
B	Bluegill
	Fathead minnow
	Zebrafish
C	Bullfrog
	African clawed frog
D	Water flea
G	Fatmucket

Saltwater Surrogate

C	Mysid

Saltwater Predicted	
Leon springs pupfish	A
Sheepshead minnow	
Inland silverside	B
Atlantic silverside	
Tidewater silverside	
Additional mysid shrimp	C
Eastern oyster	D
Amphipod	E
Pink shrimp	F
Copepod	G
Thicklip mullet	H

TSCA Chemical Evaluation

https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-tris2-chloroethyl-phosphate-tcep

EPA United States Environmental Protection Agency

Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP)

In September 2024, EPA released the final risk evaluation for tris(2-chloroethyl) phosphate (TCEP).

Find other information about other chemicals undergoing risk evaluations under TSCA.

On this page:

- Risk Evaluation Findings

General Information for Tris(2-chloroethyl) Phosphate (TCEP)

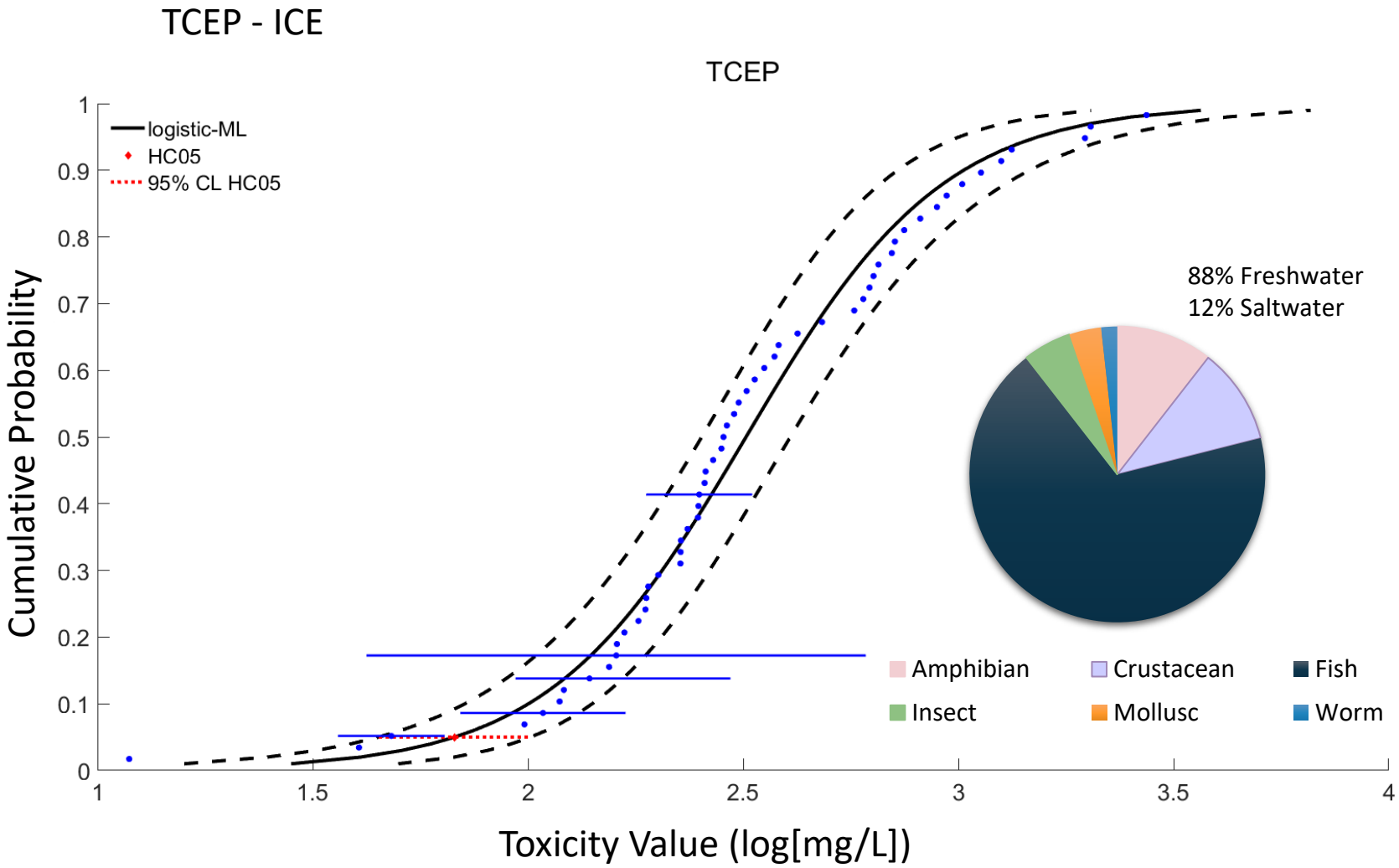
Chemical Group: Flame Retardant

CASRN: 115-96-8

TCEP ICE Application

- Two surrogate fish species
  - Zebrafish = 118 mg/L
  - Rainbow trout = 249 mg/L
- 62 species ICE predictions

"EPA assessed the impact of TCEP on aquatic and terrestrial species and found that TCEP poses unreasonable risk to aquatic species like fish and aquatic invertebrates."



Endangered Species Assessments

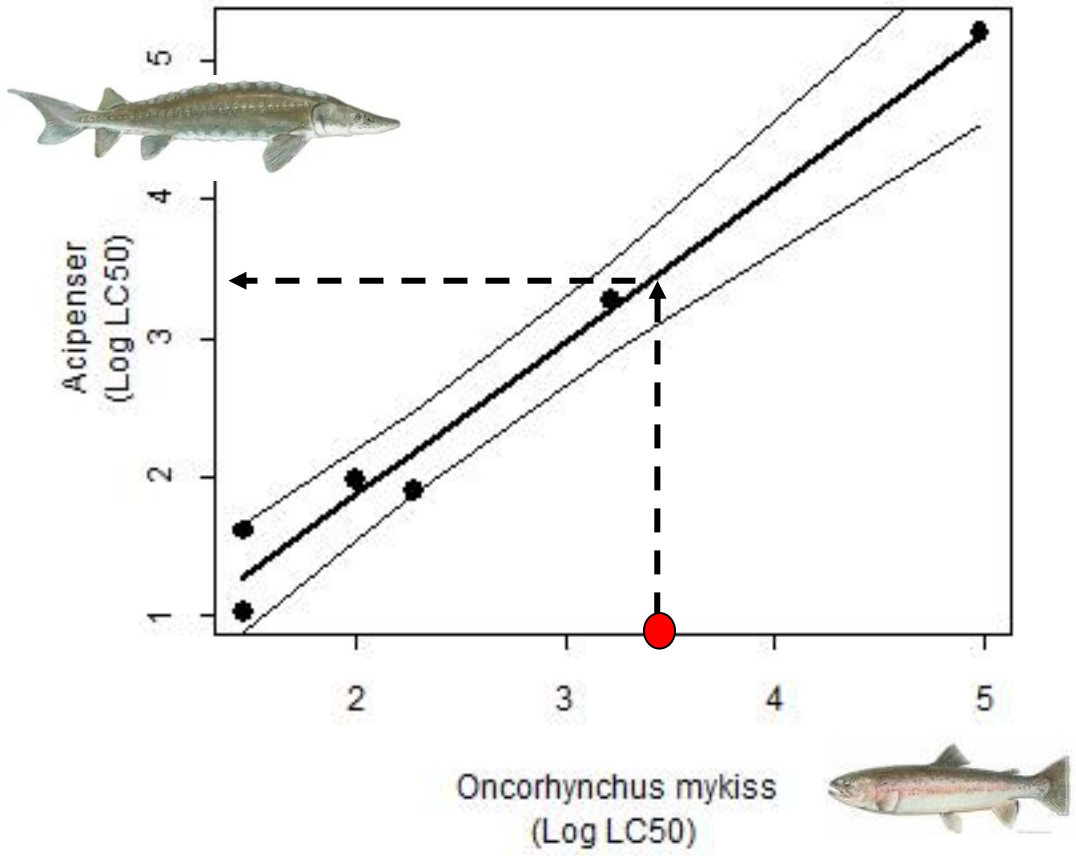
- Under ESA, federal actions cannot jeopardize listed species
  - Pesticide and chemical registration
  - Water quality criteria
- ERAs must focus on endangered species when they may co-occur with federal action
- Biological Evaluation to approve State Water Quality Standards
  - Link: https://gaftp.epa.gov/region10/ORAI/Revised_BE/Main_010220_clean.pdf

Effects of Al on Green Sturgeon

- Al toxicity data were not available for any species within the Order Acipenseriformes
- 15 surrogate species were available to predict to the genus *Acipenser* in Web-ICE v3.3
- The Rainbow trout-to-*Acipenser* ICE model was selected based on model guidance
  - Rainbow trout acute value = 3,312 µg/L
  - *Acipenser* GMAV of 3,593 µg/L (normalized conditions)

GMAV/adjustment factor = LC05
GMAV/ACR/adjustment factor = EC05

- Conclusions based on this value*:
  - Green sturgeon LC05 was less than the Criterion Maximum Concentration in 16.34% of waters, suggesting low level effects.
  - Green sturgeon EC05 was always greater than the Criterion Continuous Concentration, indicating the criterion was protective.



Questions?

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www.epa.gov/webice