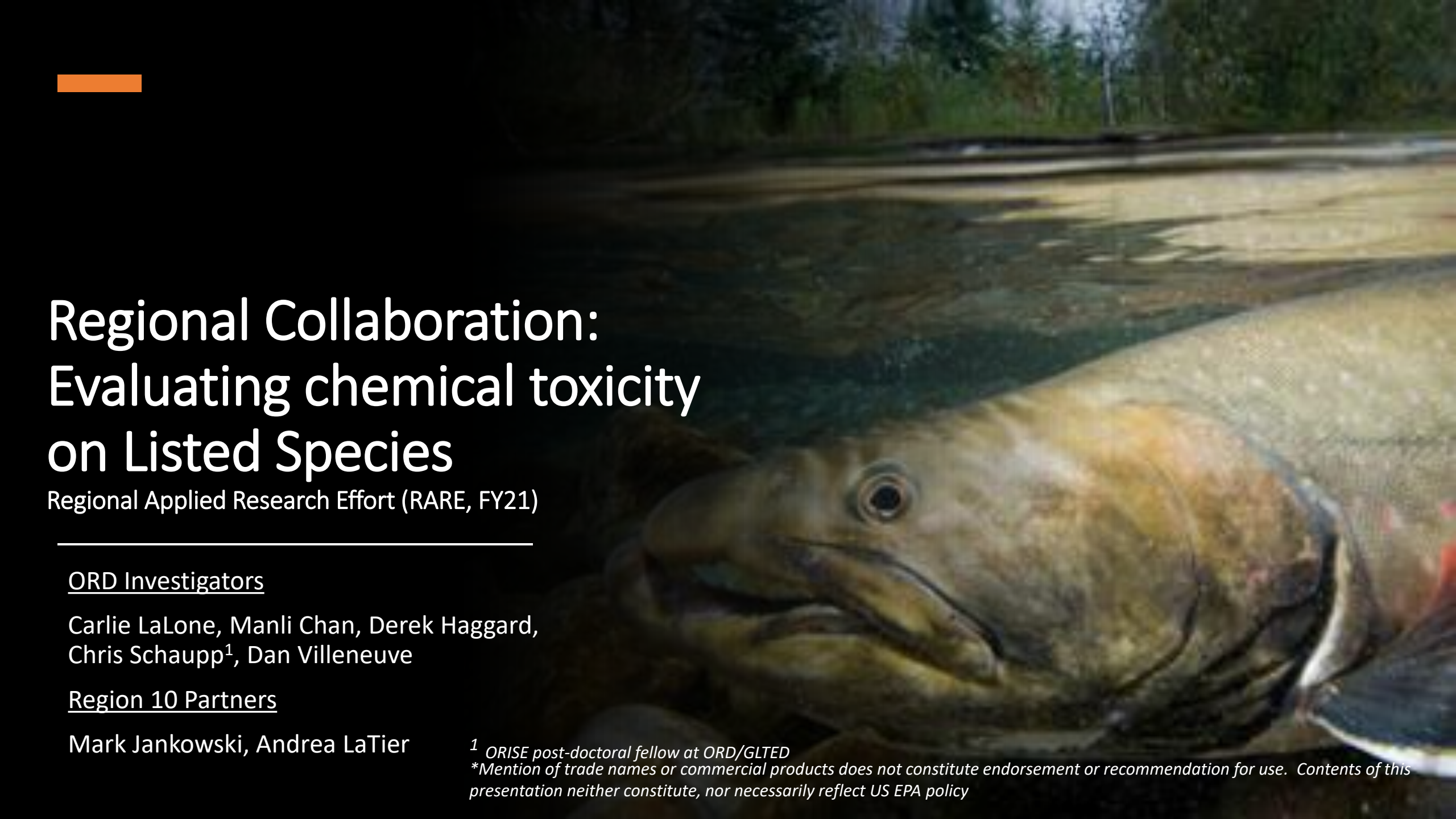

Regional Collaboration: Evaluating chemical toxicity on Listed Species

Regional Applied Research Effort (RARE, FY21)

ORD Investigators

Carlie LaLone, Manli Chan, Derek Haggard, Chris Schaupp[1], Dan Villeneuve

Region 10 Partners

Mark Jankowski, Andrea LaTier

[1] *ORISE post-doctoral fellow at ORD/GLTED*

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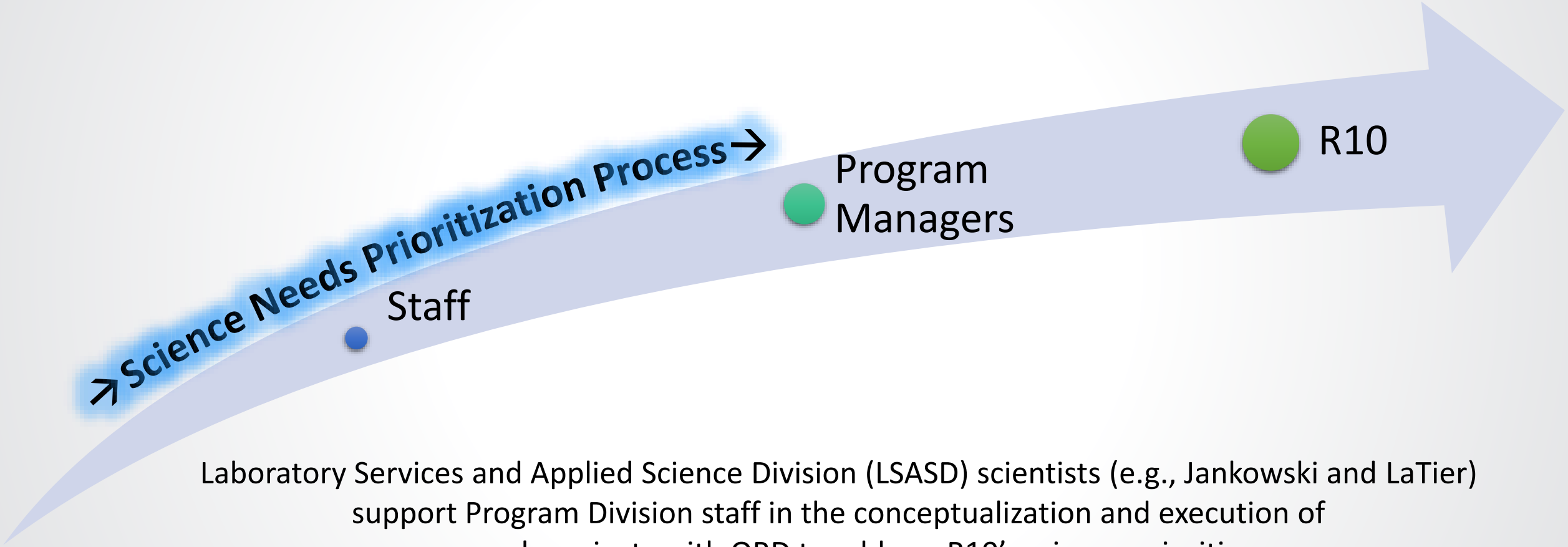
This Project Addresses R10 Science Priorities



Laboratory Services and Applied Science Division (LSASD) scientists (e.g., Jankowski and LaTier) support Program Division staff in the conceptualization and execution of research projects with ORD to address R10's science priorities

This project addresses an **R10 Science Priority** (Orca toxicity benchmark development) + a **WD Program Need** (Efficient BE production) + **LSASD Science Priority** (Integration of NAMs)

Background: ESA Consultations in R10

- Endangered Species Act, Section 7(a)(2), Interagency Consultation is required when a proposed federal action (any activity that is funded, authorized, or carried out by a federal agency) overlaps listed species range or Designated Critical Habitat
- Robust litigation history in R10 that stimulated Interagency Consultation on Clean Water Act activities:
  - Section 303(c) state water quality standard EPA approval or promulgation actions (heavily litigated)
  - NPDES permit issuance by EPA (no or minimal litigation issues)
- R10 oversees these activities in Washington, Idaho, Oregon, & Alaska
  - Endangered salmonids, southern resident killer whale, birds, amphibians, and more
- When a proposed federal action **May Affect** a species, EPA determines if it is Likely or Not Likely to Adversely Affect (**LAA** or **NLAA**) a species (via a **Biological Evaluation** document, e.g.)
  - Toxicity to each species and other factors are considered
- When action is LAA, NOAA or USFWS produce a **Biological Opinion** to determine if the proposed action will **jeopardize** the continued existence of a species
  - BOs can alter the action in light of the Opinion
- This process can take **years** to complete for each standards or permit action partly due to the species-specific toxicity analyses required

Problem and Need

Problem:

- Substantial Endangered Species Act (ESA) consultation workload within R10 Water Division supporting WQS criteria and National Pollutant Discharge Elimination System (NPDES) permit issuance actions
- Tight regulatory timelines for approving WQS packages and issuing NPDES permits
- Limited toxicity data for many contaminants requiring BE
- Generally using toxicity data derived from surrogate species – relevance can be contentious

Needs:

- Streamlining the development and documentation of hazard assessments for Biological Evaluations (BEs)
- Points of departure (POD) - preferably health protective
    - Unlike most ecological risk assessments, under ESA need to consider adverse effect on individuals of specific species
- Mechanistic understanding and scientific support for surrogacy arguments

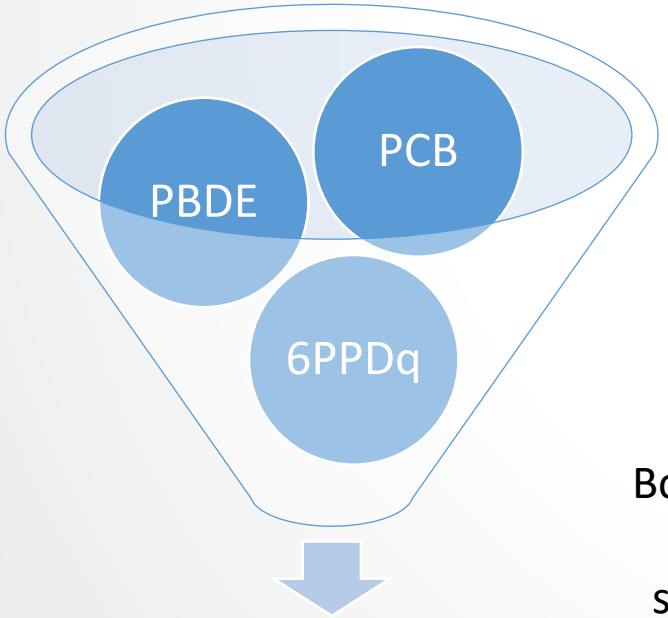
EcoRisk Assessment "Flipped" by ESA

EPA: Chemical Management Oriented Questions

Which chemicals are most toxic to "aquatic life"?
Test many chemicals using model species and standardized approaches

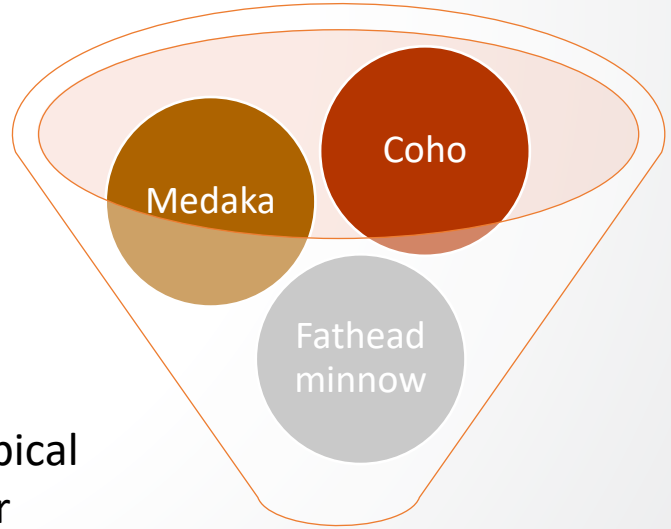
USFWS/NOAA: Resource Management Oriented Question

Which species are adversely affected by 6PPDq?
Test many species to one chemical using realistic exposure scenarios



6PPDq?

Both are important, but it is typical to use standardized data for species-specific ESA assessments.
"R10 RAPID TOX" helps us do this



Coho

Goal:
Determine which NAMs may work for R10 BEs and how they can be effectively integrated into R10 assessment processes

Objectives:

1. Develop an automated computational pipeline for retrieving PODs. Compare to manual POD identification.
   - *Benefit: streamline R10's ability to rapidly identify, extract, and evaluate PODs from relevant literature and on-line sources*
2. Derive points of departure (POD) from ToxCast data. Compare PODs to traditional toxicity reference values (TRVs) used in previous Region 10 ESA Biological Evaluations. Aid R10 understanding of the confidence and limitations.
   - *Benefit = faster BE/ERA development. Having a POD where we did not previously.*
3. Use ToxCast data to identify mode of toxic action for chemicals of importance to R10, where relevant, and evaluate relevance to listed species (e.g., Orca, salmon).
   - *Benefit = Expand science-based arguments for application, or rejection, of PODs from surrogate species.*

Objective 1

Develop an automated computational pipeline for retrieving PODs.
"R10 RAPID TOX"

Desired capabilities:

1. Initial screen to classify as probable Persistent, Bioaccumulative, Toxic, and/or Volatile

2. Rapidly acquire and filter points of departure (PODs) from public data sources like the ECOTOX knowledgebase, ToxCast, and QSARs

3. Score records based on "preferred" data for the assessment
   - E.g., taxonomic relatedness, study design attributes, analytical verification, etc.

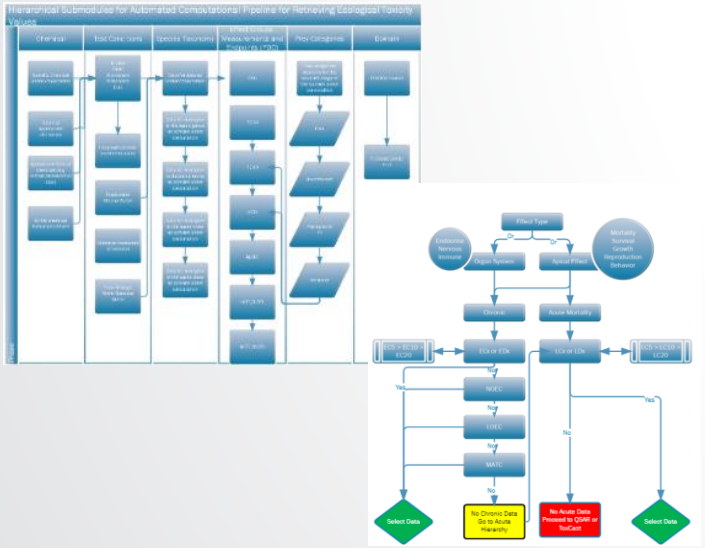
4. Flag whether ToxCast provides evidence for a specific mode of action that should be considered

Approach

R10 scientists developed process flow diagrams

ORD-GLTED identified data-sources and outlined “rules” for data processing, filtering, scoring

ORD-SCDCD created appropriate data mart, computer code, and Qlik sense app to implement



10. For each record (row) in **Data Table S2** that matches a chemical (Preferred name; Cas No; or DTXSID) from Data Table S3 compare “Species Taxonomic Information” from Table S2 to “Subfamily” column (P) in Table S3.
    a. If there is a match, add “Subfamily match” to “Taxon match column” of Table S4 and “5” to “Taxon Score” column of Table S4 and proceed to 11a.
    b. If no, proceed to 11a.

.....continue in this vein through each taxonomic level up to Kingdom, adding scores as listed in the table below

Taxon match	Score
Species	7
Genus	6
Subfamily	5
Family	5
Infraorder	4
Suborder	4
Order	4
Superorder	3
Class	3
Subphylum	2
Phylum	2
Kingdom	1

11. End of sprint 3

NOTE: At the end of this Sprint, Table S4 should be populated with ECOTOX records relevant to each chemical-species pair of interest and labeled as to “Taxon Match” and “Taxon Score”

Sprint 4 – Preferred data type scoring of ECOTOX records

Preferred Endpoint Type

1. Create new column in Table S4 labeled “Effect Type” (Column BJ)
2. Create new column in Table S4 labeled “TOX_STUDY” (Column BK)
3. Create new column in Table S4 labeled “Preferred data score” (BL)
4. For each row in Data Table S4, does “endpoint” (Column S) match any of the following: LCxx (e.g., LC50); LDxx (e.g., LD20); LLxx (e.g., LL50); or LETH (100% mortality)?
    i. If yes, label as “Mortality” in “Effect Type” (column BJ)
    ii. If no, label as “Sublethal” in “Effect Type” (column BJ)
5. For all rows in Data Table S4 labeled as “Mortality” in the “Effect Type” field (Column BJ) enter “Acute” into “TOX_STUDY” column (column BK).
6. For all rows labeled as “Mortality” in the “Effect Type” field (Column BJ)
    a. If “endpoint” column (Column S) is LCxx, LDxx, or LLxx and xx = 1-5, assign score of “5” to “Preferred data score” column (BL); if not go to 6b
    b. If “endpoint” column (Column S) is LCxx, LDxx, or LLxx and xx = 6-10, assign score of “4” to “Preferred data score” column (BL); if not go to 6c
    c. If “endpoint” column (Column S) is LCxx, LDxx, or LLxx and xx = 11-20, assign score of “3”

IT Implementation

Data Hub

Global CCTE data sources

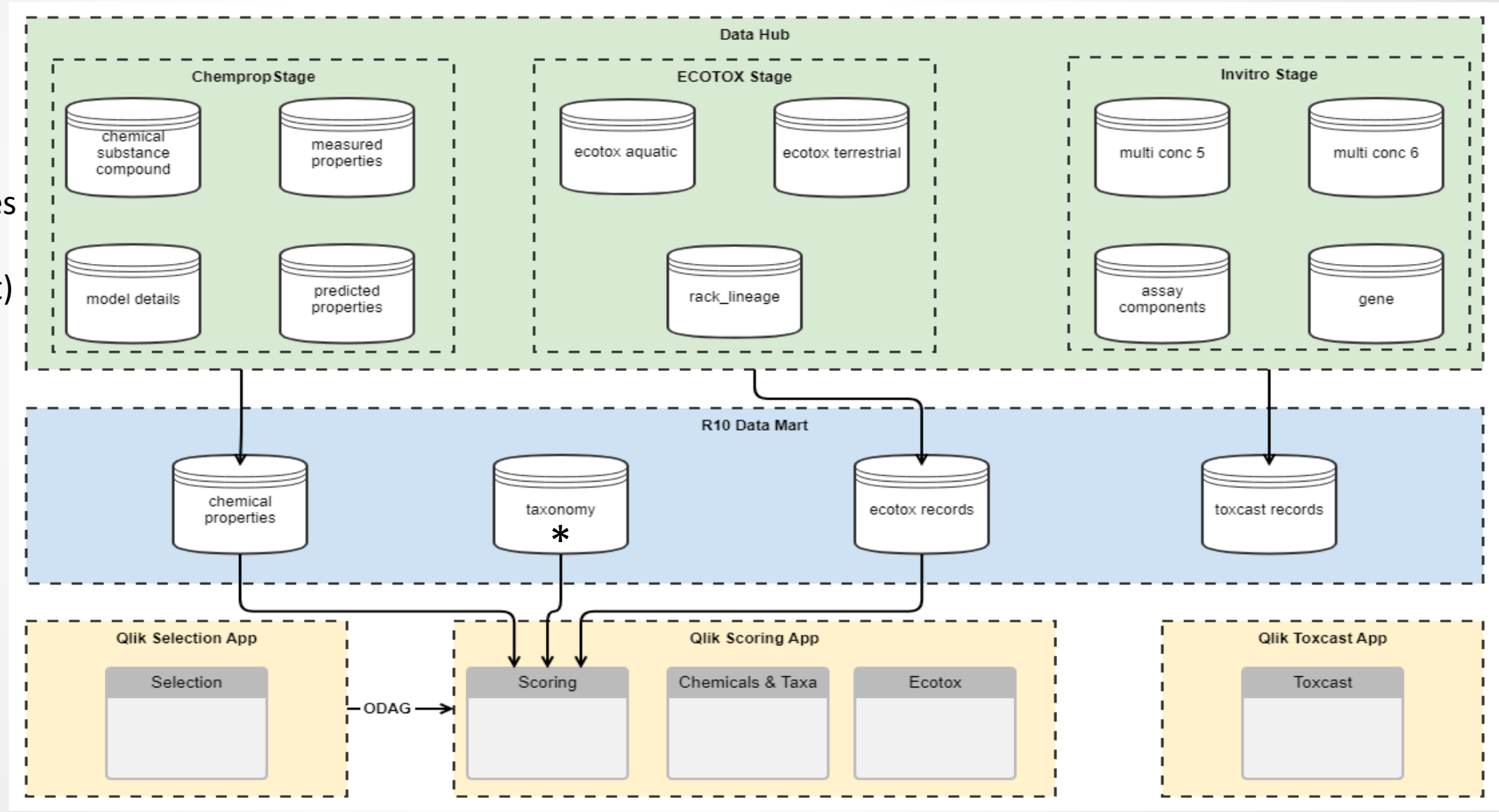
- Chemical properties
- ECOTOX
- In vitro db (ToxCast)

Data Mart

- Application-specific subset of data
- Additional sources*

Custom Interface

- Query generation
- Visualization
- Export

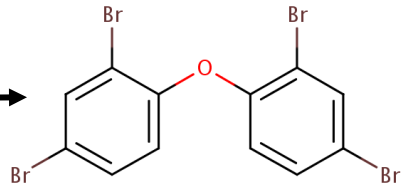


Use of the R10 RapidTox App In Brief

R10 Endangered Species Act Assessment Use Case

- Question: Is a permitted discharge in the vicinity of Piper's Creek adjacent to Puget Sound likely to adversely affect migrating Coho salmon (*Oncorhynchus kisutch*)?
- Contaminant of Potential Concern: 2,2',4,4'-tetrabromodiphenyl ether
- Sub-question: Is the estimated *effluent concentration* > a *toxicity value* relevant to coho salmon?
- App question: what is the lowest relevant + reliable toxicity value useful for this assessment?

Discharge



BDE-47
DTXSID3030056

Photo credit

Enter Query into Qlik selection app

- Chemical(s) – BDE-47
- Specie(s) of interest - Oncorhynchus kisutch
- Habitat (aquatic/terrestrial) - Aquatic

Generate scoring app

- Pulls appropriate data from data mart
- Applies scoring and filtering rules

View Scores and Flags for ECOTOX records

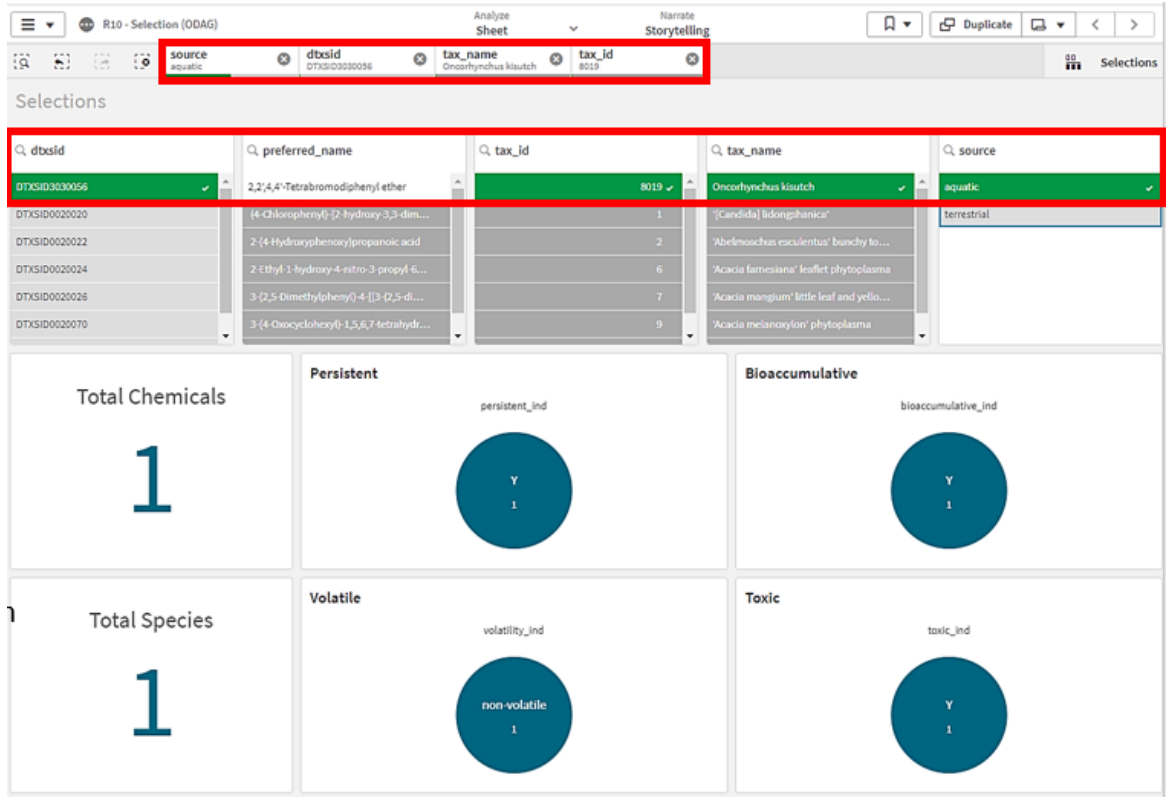
- High level summary information
- Quickly narrow down to the information of greatest interest

NAMs overview

- Alternative PODs based on ToxCast and/or QSAR
- Flag evidence for specific MoA

Drill down into details as appropriate

- Transparent presentation of underlying data
- Data provenance (sources, record ids, references)



Immediately retrieves chemical property information

[Checks against “rules”]

- P: ½ life, water, sed, fish
- B: Log Kow, BCF, BAF
- V: Vapor pressure
- T: QSAR (from ToxVal)

Enter Query into Qlik selection app

- Chemical(s) – BDE - 47
- Specie(s) of interest – Oncorhynchus kisutch
- Habitat (aquatic/terrestrial) - Aquatic

Generate scoring app

- Pulls appropriate data from data mart
- Applies scoring and filtering rules

View Scores and Flags for ECOTOX records

- High level summary information
- Quickly narrow down to the information of greatest interest

NAMs overview

- Alternative PODs based on ToxCast and/or QSAR
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Drill down into details as appropriate

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- Data provenance (sources, record ids, references)

Rapid Tox

ecotox_scientific_name	ecotox_common_name	conc1...	Summed Score	effect_type_s...	taxon_...
Gadus morhua	Atlantic Cod	0.00023	4.4285714285714	1	class
Gadus morhua	Atlantic Cod	0.00023	4.4285714285714	1	class
Skeletonema costatum	Diatom	0.016	4.2619047619048	1	superkingdom
Gadus morhua	Atlantic Cod	0.00023	4.1904761904762	0.33333333333333	class
Gadus morhua	Atlantic Cod	0.00023	4.1904761904762	0.33333333333333	class
Gadus morhua	Atlantic Cod	0.00023	4.1904761904762	0.33333333333333	class
Gadus morhua	Atlantic Cod	0.00023	4.1904761904762	0.33333333333333	class
Danio rerio	Zebra Danio	0.01457385	4.1190476190476	1	class
Skeletonema costatum	Diatom	0.028	4.1190476190476	1	superkingdom

Scoring Categories	Examples [*high to low preference score*]
Taxonomic match	Species, genus, family, order, class…..
Effect type	Apical, neuro-endocrine-immune, lower order
POD type	More protective (e.g., LC10, vs. LC50) > score
Exposure type	Flow through, renewal, static…..
Control type	Multiple controls, concurrent control, historical control…
Exposure verification	Measured, nominal only
Summed Score	**Sum of each scoring category (normalized to max score possible in category) – max. = 6**

Enter Query into Qlik selection app

- Chemical(s) – **BDE - 47**
- Specie(s) of interest – **Oncorhynchus kisutch**
- Habitat (aquatic/terrestrial) - **Aquatic**

Generate scoring app

- Pulls appropriate data from data mart
- Applies scoring and filtering rules

View Scores and Flags for ECOTOX records

- High level summary information
- Quickly narrow down to the information of greatest interest

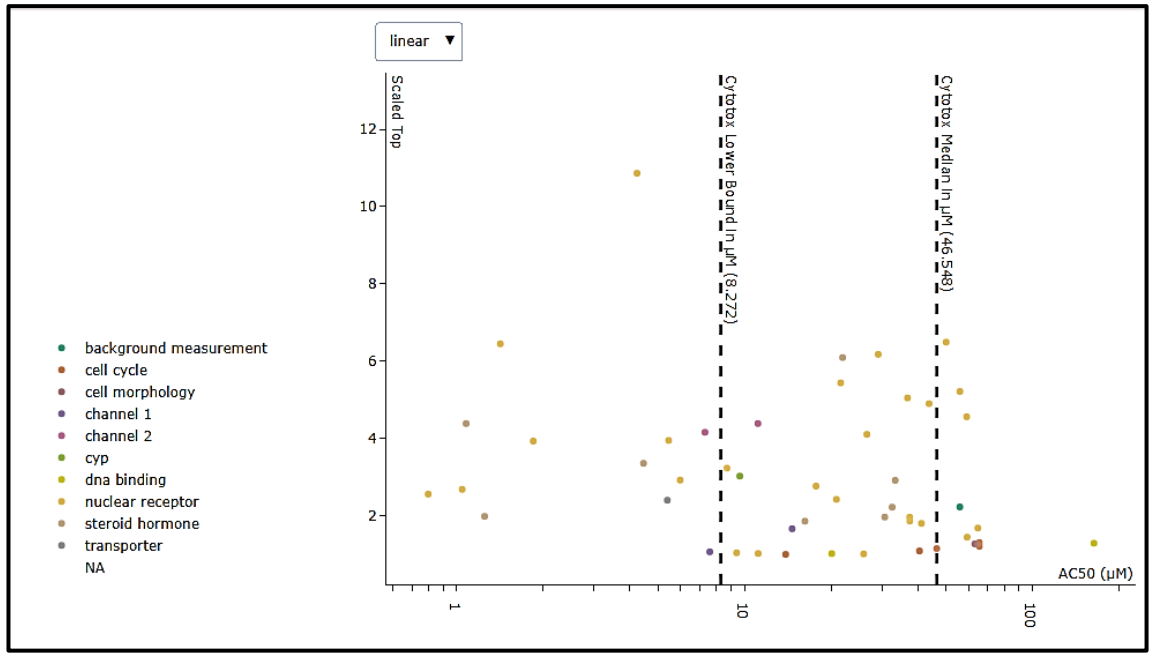
NAMs overview

- Alternative PODs based on ToxCast and/or QSAR
- Flag evidence for specific MoA

Drill down into details as appropriate

- Transparent presentation of underlying data
- Data provenance (sources, record ids, references)

ToxCast Bioactivity Summary



**For illustrative purposes – not specific to BDE-47*

- Alternative POD(s) for data limited scenarios:
  - ACC5 = 5th centile of all ACC < cytotoxic burst
  - Min QSAR POD

- Mechanistic inference flag:
  - ACC5 < 3-fold cytotoxic burst
  - Mech_rank: For each "hit" how far below cytotoxic burst

Enter Query into Qlik selection app

- Chemical(s) – BDE - 47
- Specie(s) of interest – Oncorhynchus kisutch
- Habitat (aquatic/terrestrial) - Aquatic

Generate scoring app

- Pulls appropriate data from data mart
- Applies scoring and filtering rules

View Scores and Flags for ECOTOX records

- High level summary information
- Quickly narrow down to the information of greatest interest

NAMs overview

- Alternative PODs based on ToxCast and/or QSAR
- Flag evidence for specific MoA

Drill down into details as appropriate

- **Transparent presentation of underlying data**
- **Data provenance (sources, record ids, references)**

- High level summary
- Key information

- Chemical property information
- Detailed QSAR results
- Full taxonomy for query species

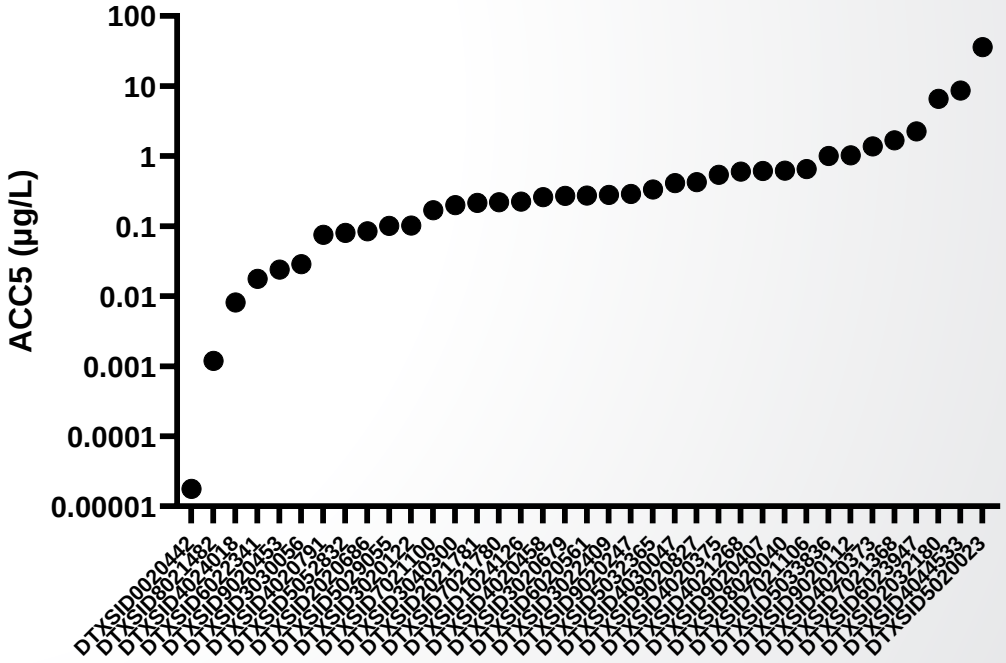
All relevant data fields (upon which scores are based) for each individual ECOTOX record retrieved.

All relevant data fields from Invitro db upon which ToxCast-derived PODs and mechanistic inference calls were based and assay annotations

Objective 2

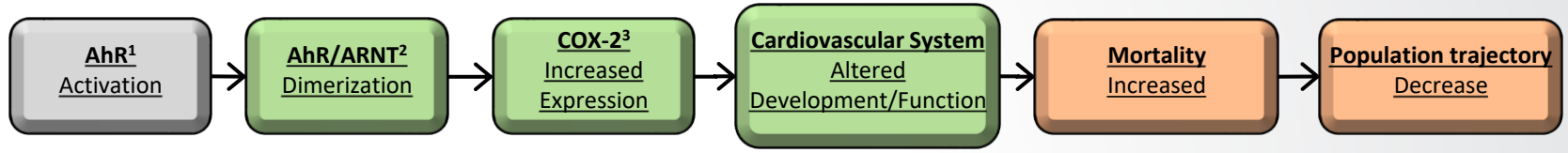
Derive points of departure (POD) from ToxCast data. Compare PODs to traditional toxicity values used in previous Region 10 ESA Biological Evaluations.

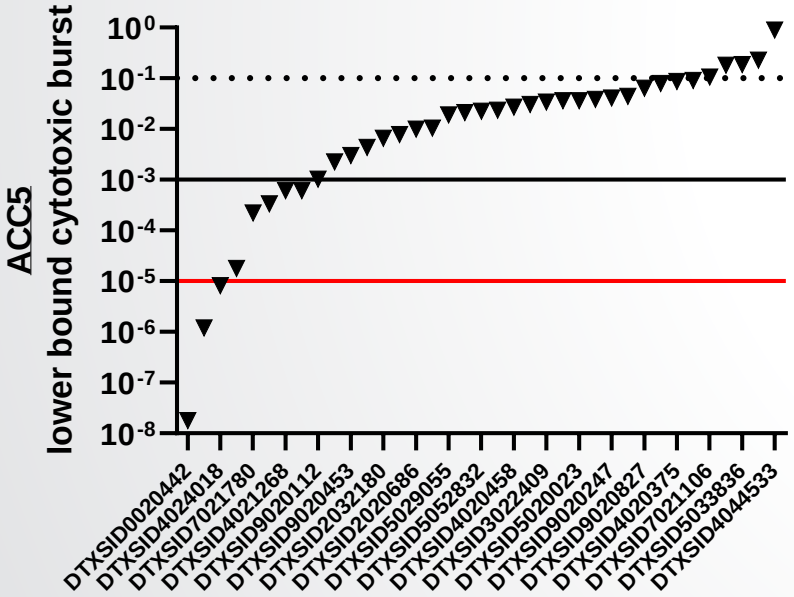
- **R10** provided list of 80 compounds for which BEs have been completed or are anticipated (ToxCast data available for 37)
- **ORD** – using stand-alone version of the R10 RAPID ToxCast Qlik App to rapidly generate ToxCast PODs (ACC_5) for all
- Will compare ACC_5 to PODs used in previous BEs, based on in vivo data
- Extend to all chemicals tested in ToxCast for which data have been collected in ECOTOX

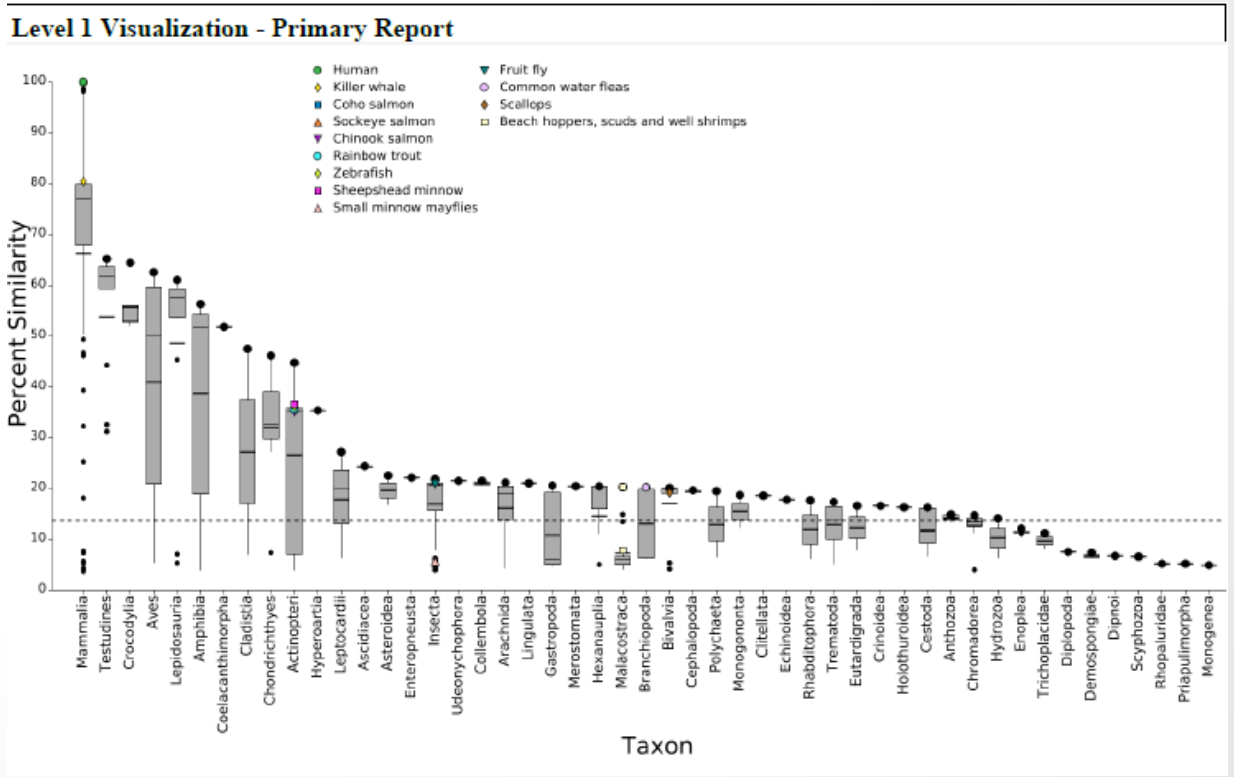


Objective 3

Use ToxCast data to identify specific mode(s) of action and associated protein target(s); evaluate relevance to listed species (e.g., Orca, salmon) using SeqAPASS and AOPs.

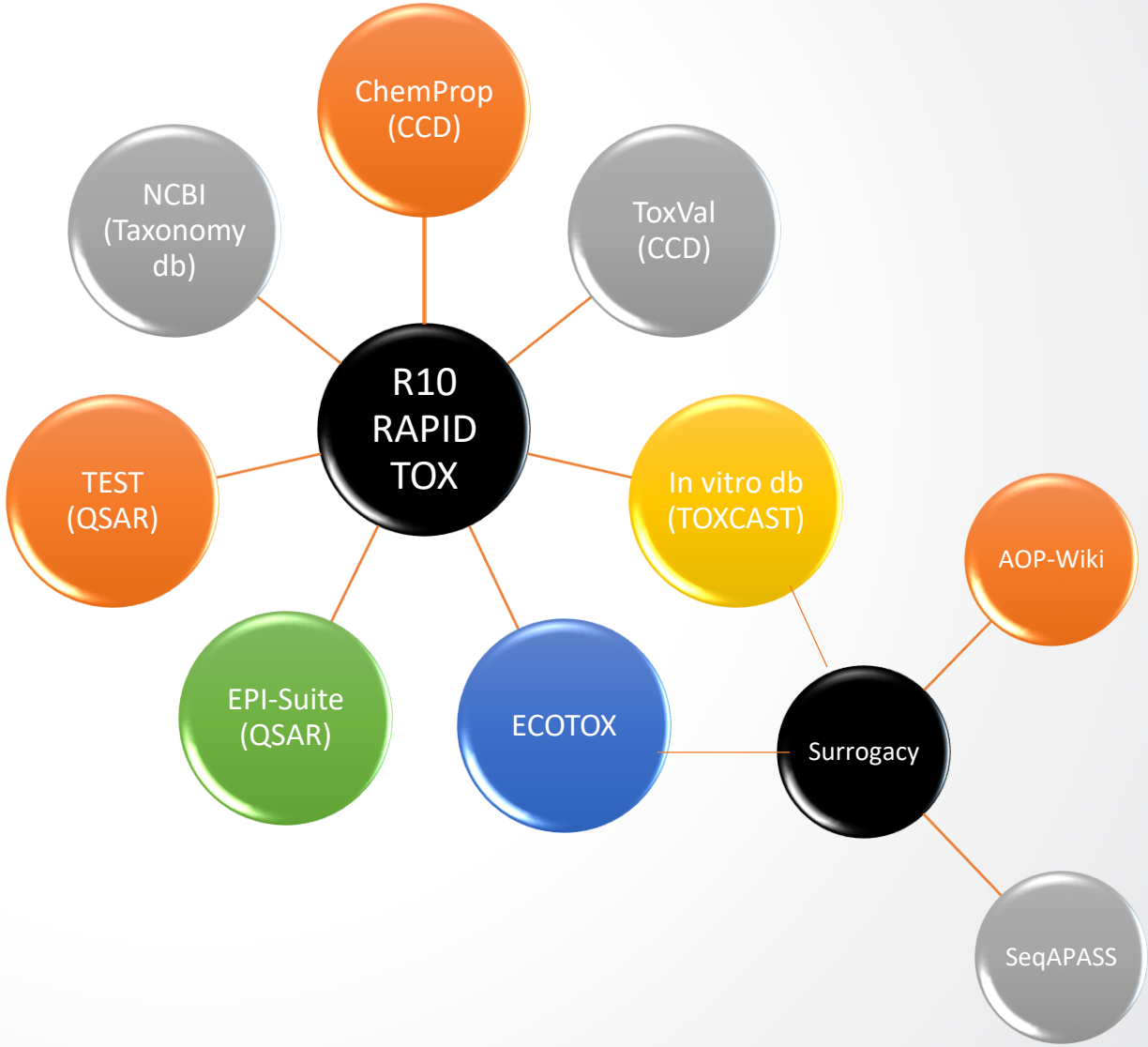






Bringing together CSS data and tools

Integration of CSS data and tools into R10 ESA assessment processes



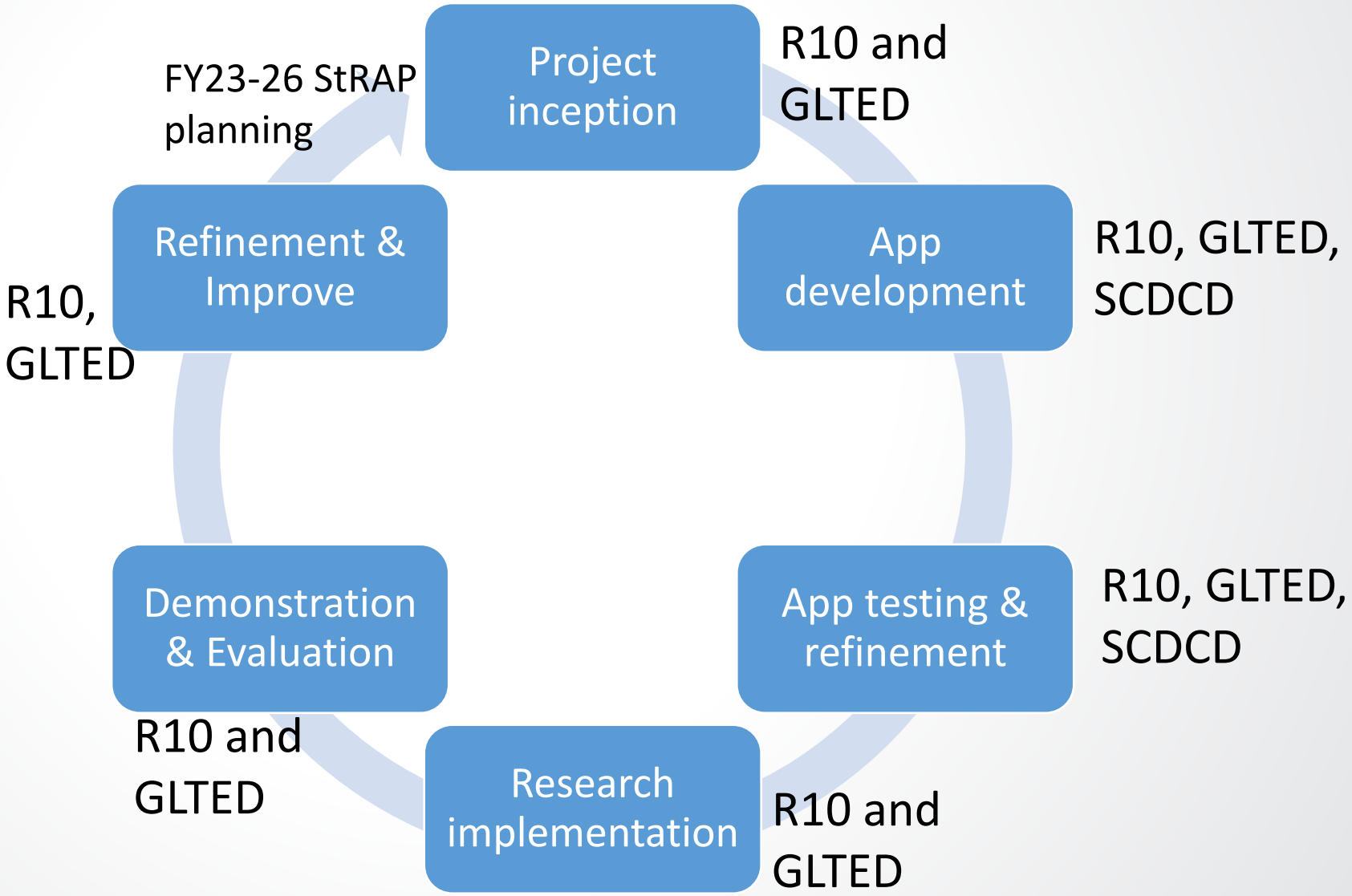
Collaborative Development

Project Management

Bi-weekly meetings
- R10
- GLTED
- SCDCD

Quarterly meeting
- R10 advisors
- GLTED

Ad hoc meetings



Benefits to R10

- Use of the App is anticipated to:
  - **Improve standardization** in screening chemicals for evaluation which **increases consistency** and confidence in the final suite to be evaluated in a BE.
  - Greatly **expedite** gathering available and filtering through available toxicity data to prioritize and select PODs for BE development.
  - Allow for the repeated use of PODs for subsequent hazard assessments thereby **increasing the frequency of meeting regulatory deadlines** and keeping up with requests for assistance.
  - Create the foundation to achieve other **research** objectives of the RARE.

Acknowledgements

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Angela Adams (R10)

Rob Elleman (R10)

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