Evaluating correlations of ECOTOX and ToxCast data through toxicity benchmark derivation

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Background

- The development of new approach methodologies (NAMs) has allowed for high-throughput *in vitro* chemical toxicity testing on a large scale
  - EPA's Toxicity Forecaster (ToxCast)
    - 10,000 chemicals across nearly 2,000 *in silico* and *in vitro* assays/endpoints screened

- Utility of NAM data has largely focused on potential integration into human hazard assessment, and investigation into application to ecological risk assessment remains limited

- Ecological hazard evaluation continues to rely on apical data from *in vivo* experimentation, which restricts the speed at which chemical toxicity can be evaluated

- **<u>Objective</u>: Examine correlation(s) between points-of-departure (PODs) derived from mammalian-centric, *in vitro* ToxCast data and *in vivo* animal data from ECOTOX**
  - *Positive relationship(s) may support the potential use of NAM data in deriving interim or screening values for ecological risk assessment for data-poor chemicals*

ECOTOXicology Knowledgebase (ECOTOX)

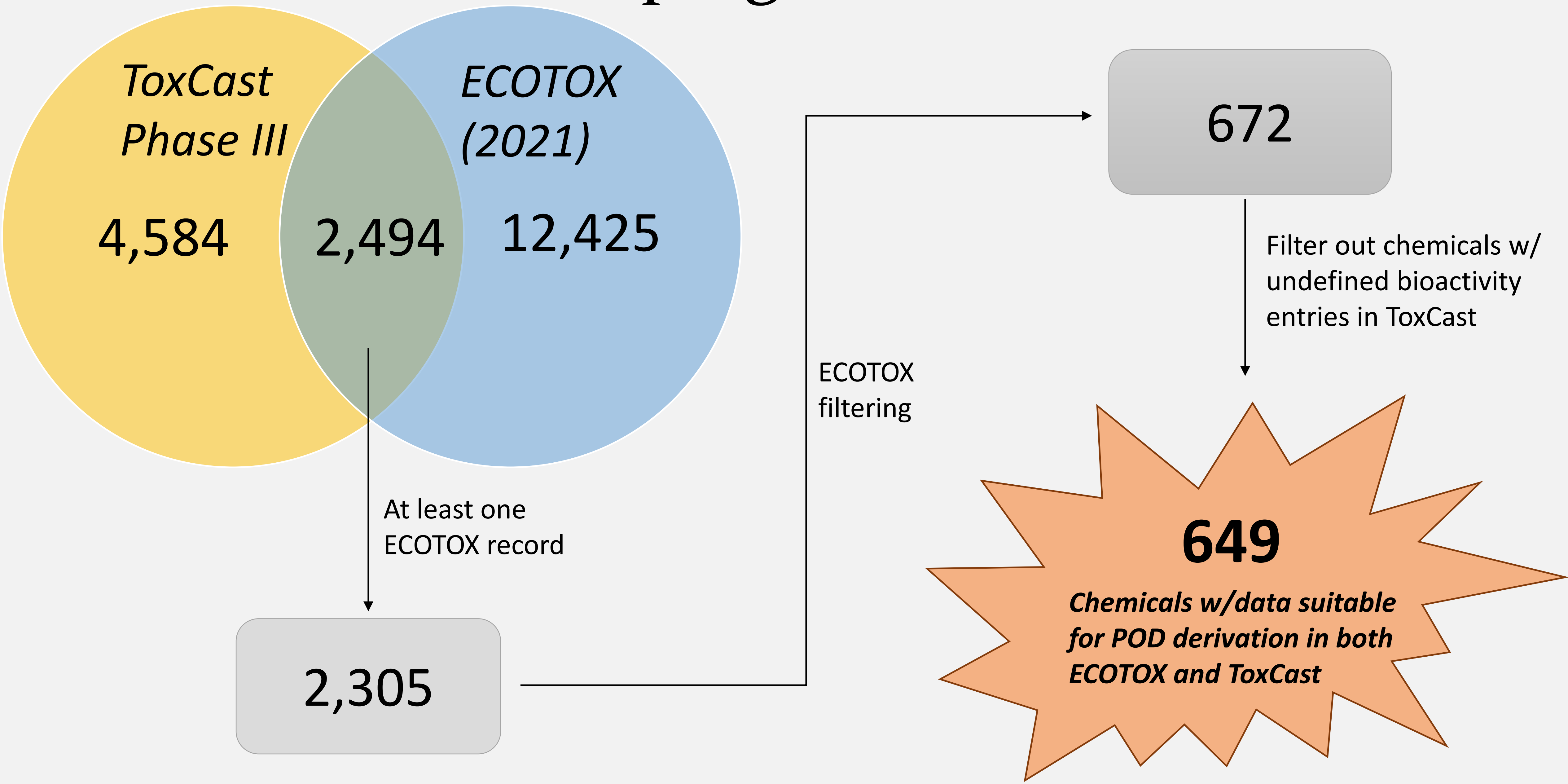
- Curated ecological toxicity data assembled from peer-reviewed literature
- Contains data from many species and study types
- A single paper/study may provide multiple records and endpoints
  - Tiers 1 (apical) and 2 (biochemistry/bioactivity)
  - Acute vs. Chronic

- Single-chemical ecotoxicity data for over 12,000 chemicals and ecological species with over one million test results from over 50,000 references (Olker et al., 2022)

Main Data/Benchmarks for Comparison

- ToxCast (*in vitro*)
  - 5^{th} centile of activity above cutoff concentration (ACC_5)
  - Lower-bound cytotoxic burst (CB)
- ECOTOX (*in vivo*)
  - minimum effect concentration(s)
- QSARs (*in silico*)
  - Minimum QSAR by species

Developing the Dataset



POD Derivation Methods

ToxCast PODs

1. **Lower-bound cytotoxic burst**

2. **ACC$_5$**

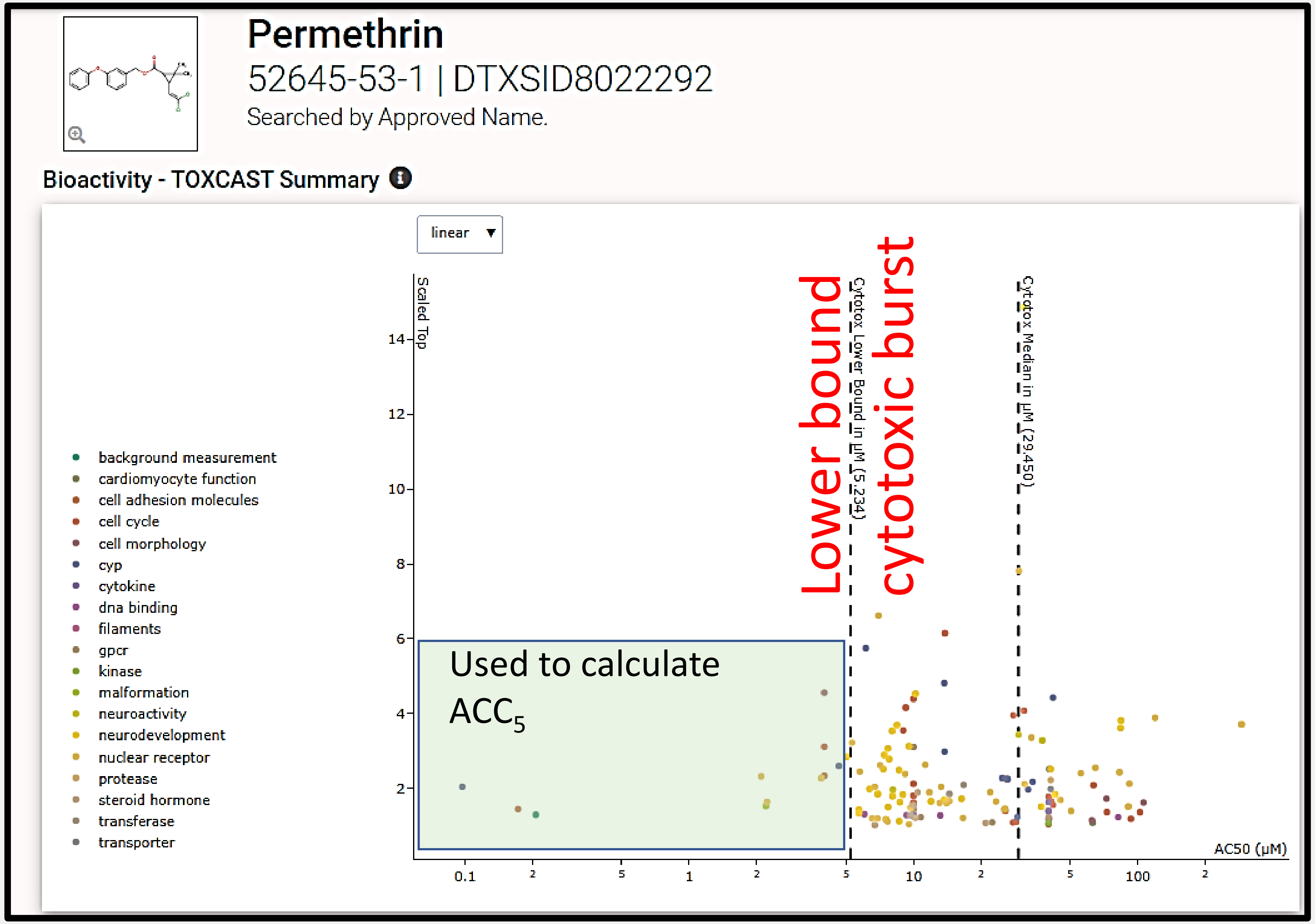
Extract ToxCast data from CompTox Chemicals Dashboard

↓ Filtering

ToxCast active hits below lower-bound cytotoxic burst

↓ Analyze ACC distribution

ACC$_5$



ECOTOX PODs

- Full records for all ToxCast chemicals were pulled from ECOTOX
- Certain data types were excluded (not shown here)
- ECOTOX PODs were derived by taking the minimum effect concentration for each chemical within the filtered dataset
- Final PODs represented a diverse suite of benchmarks accounting for differing endpoints and effects:
  - *Overall ECOTOX PODs* – included all available data
  - *Effect-type PODs* – Tier 1 vs. Tier 2 data
  - *Exposure length PODs* – acute vs. chronic
  - *Species-specific PODs* – fish/frogs, invertebrates, or aquatic plants

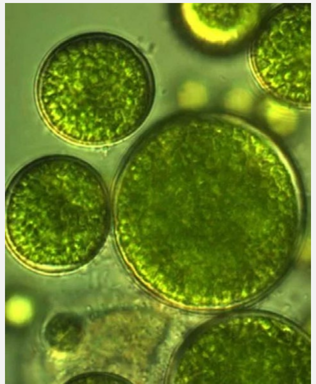
QSAR PODs

- QSARs included TEST estimates derived for fish, invertebrates, and plants (retrieved from RapidTox Qlik App)

- (1) Minimum QSAR estimates across species were used for POD comparisons

- (2) Subsequently, QSAR “PODs” were matched based on CASID and species to compare PODs on a general taxonomic basis (i.e. fish, invertebrates, plants)

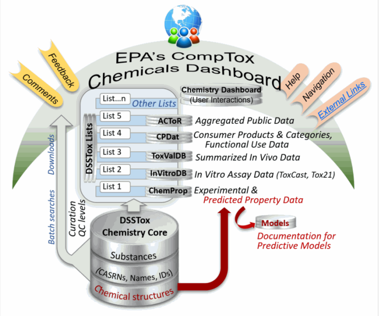




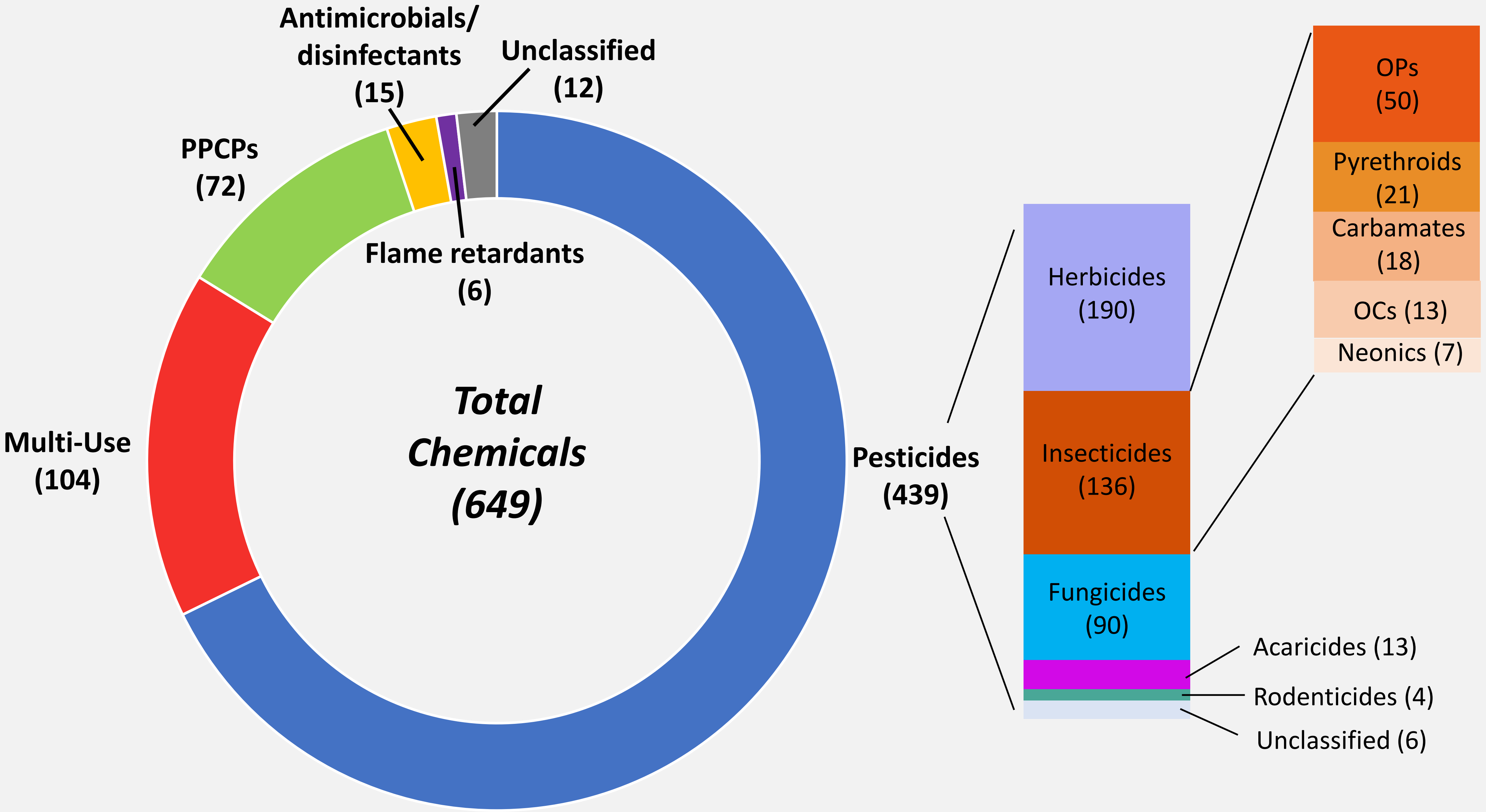
Chemical Classification Methods

- Common CAS were matched across differing PODs to generate datasets for comparative analyses

- Chemical class was assigned progressively using data collated from several databases
  - Chemical classifications were pulled from the GLRI chemical database and CompTox and matched to chemicals in our dataset using common CAS numbers
  - Classifications for the remaining chemicals were obtained through manual searches of various open-access databases (e.g., PubChem, DrugBank, Wikipedia, Pesticide Properties Database)



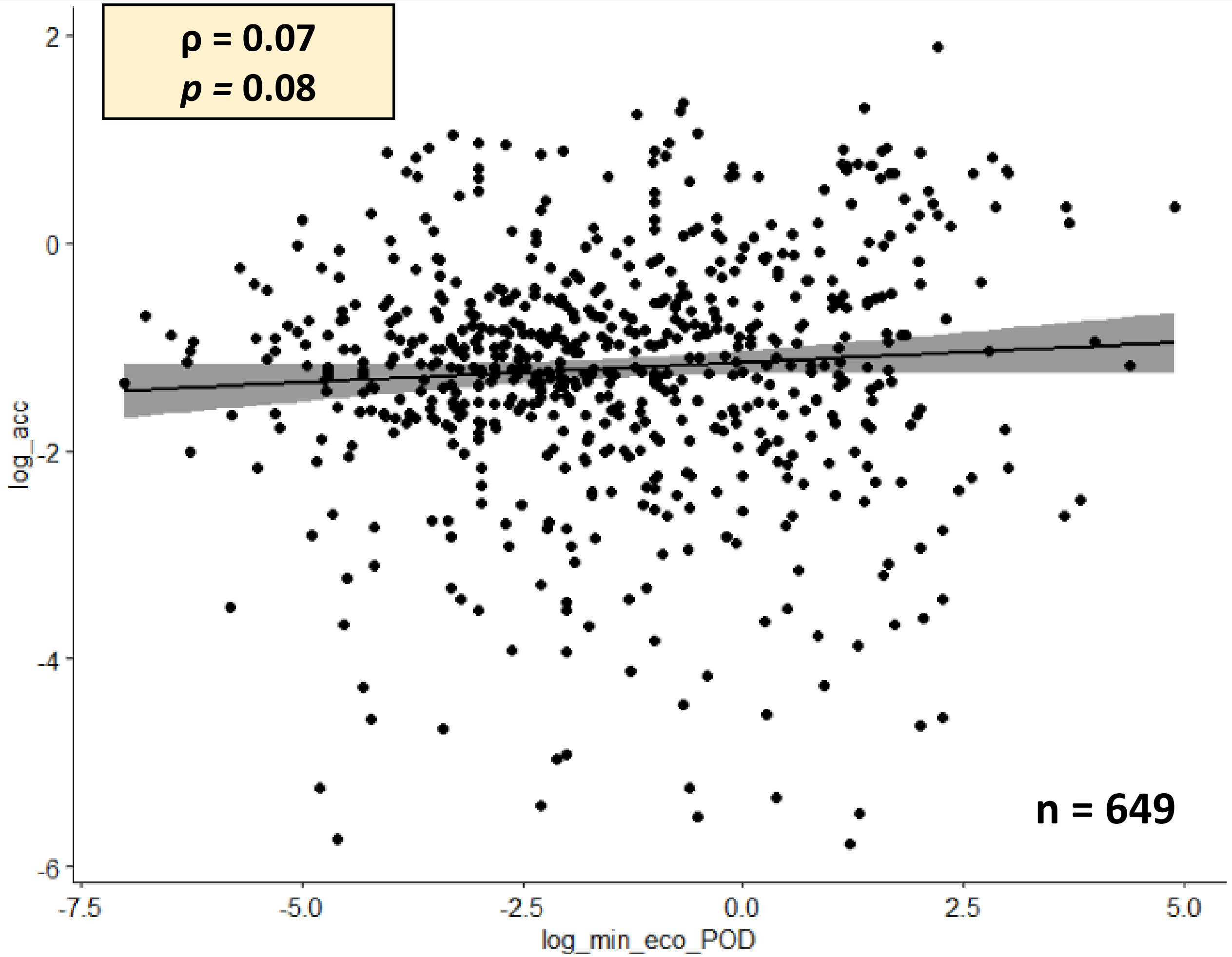
Chemical Space



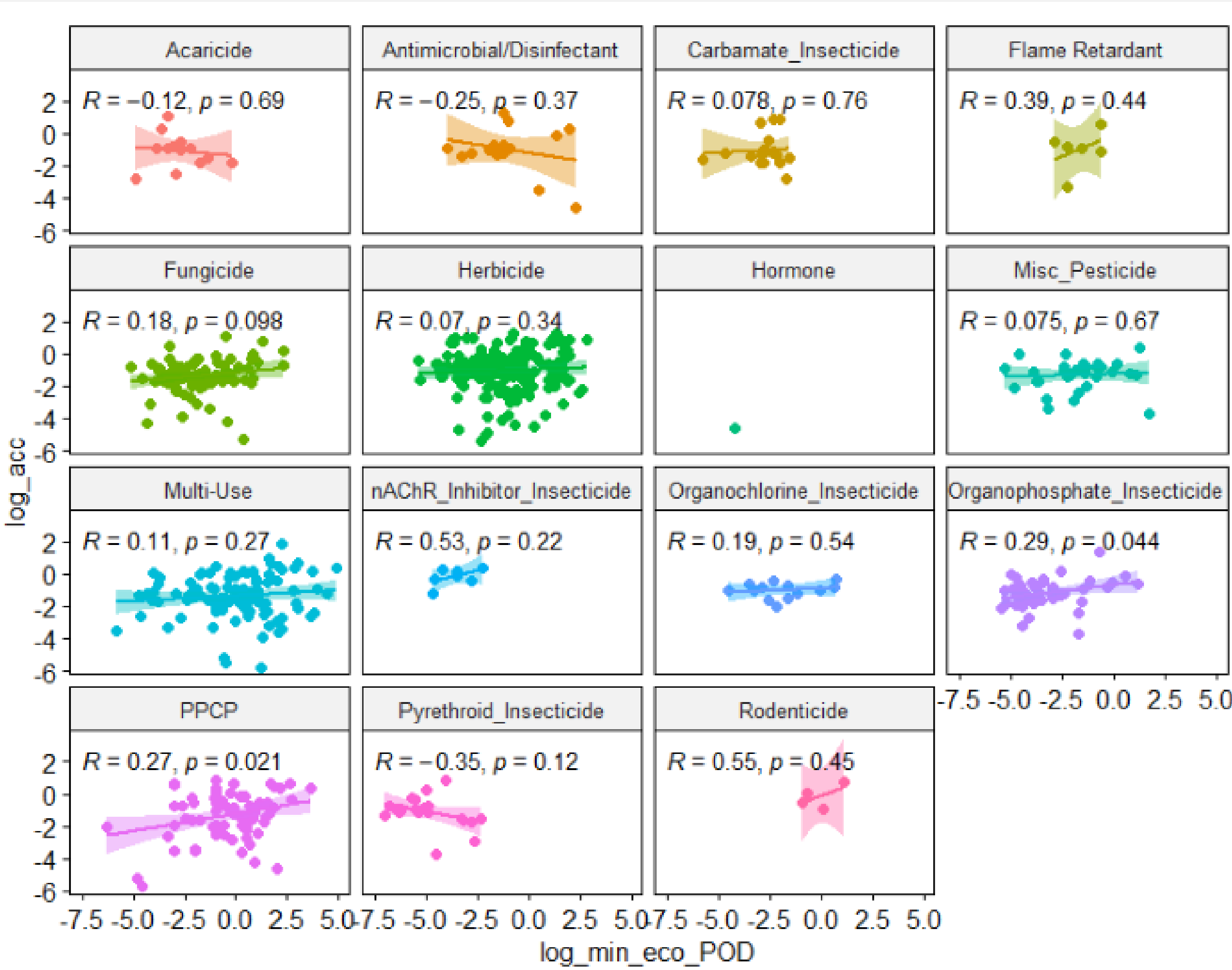
ToxCast vs. ECOTOX

ACC$_5$-ECOTOX Correlations: Overall

Log10 Transformed; Pearson Correlation

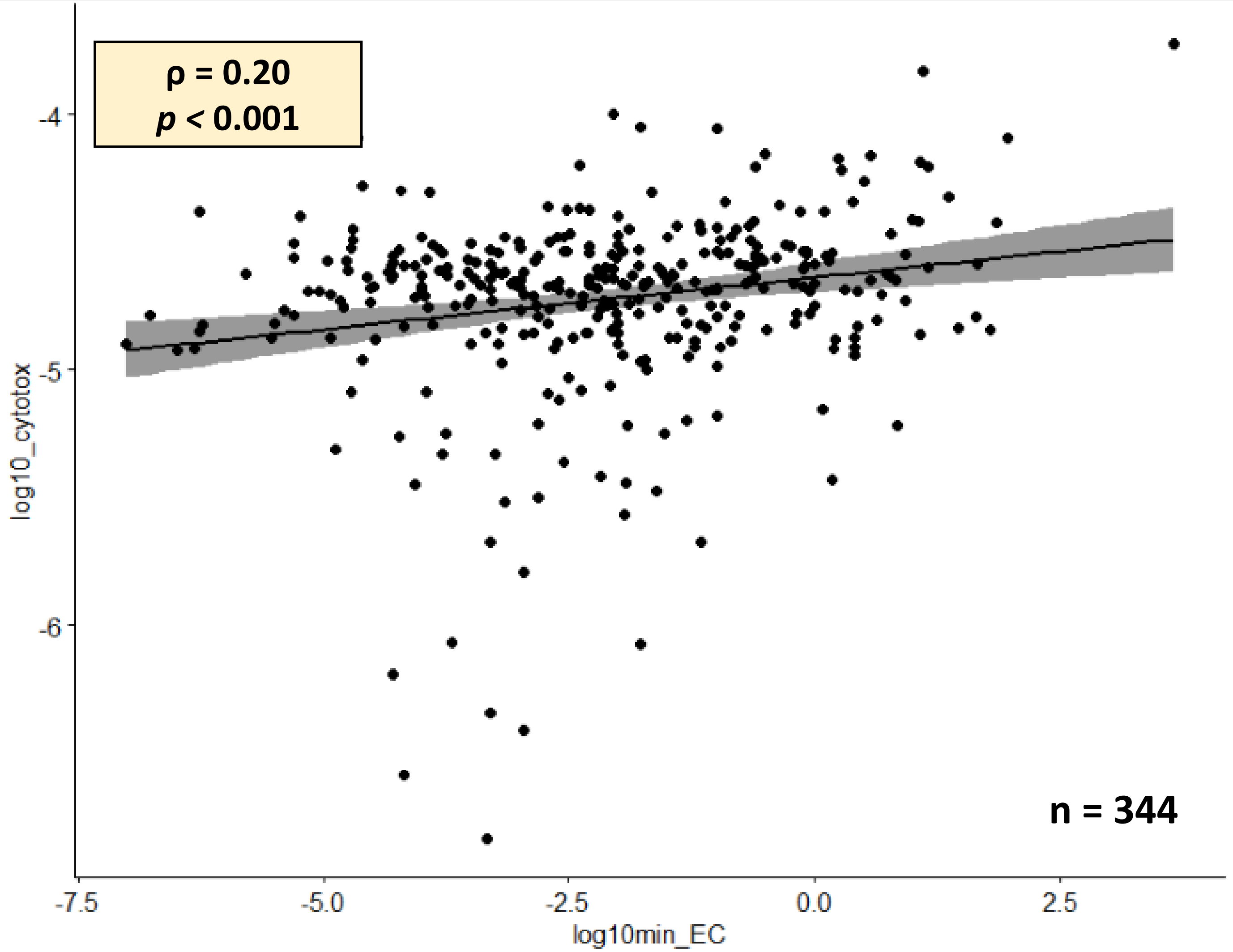


Faceted by Chemical Class

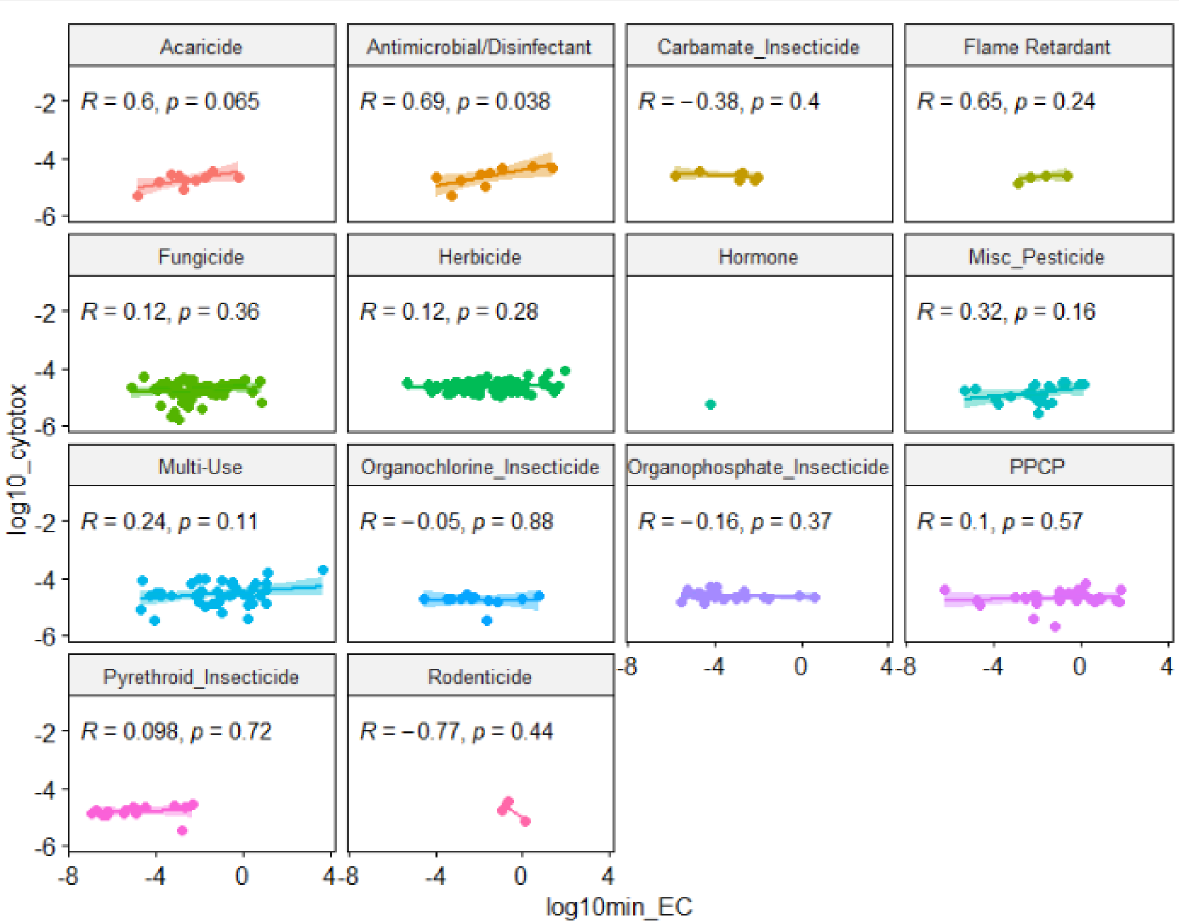


Cytotoxic Burst-ECOTOX Correlations: Overall

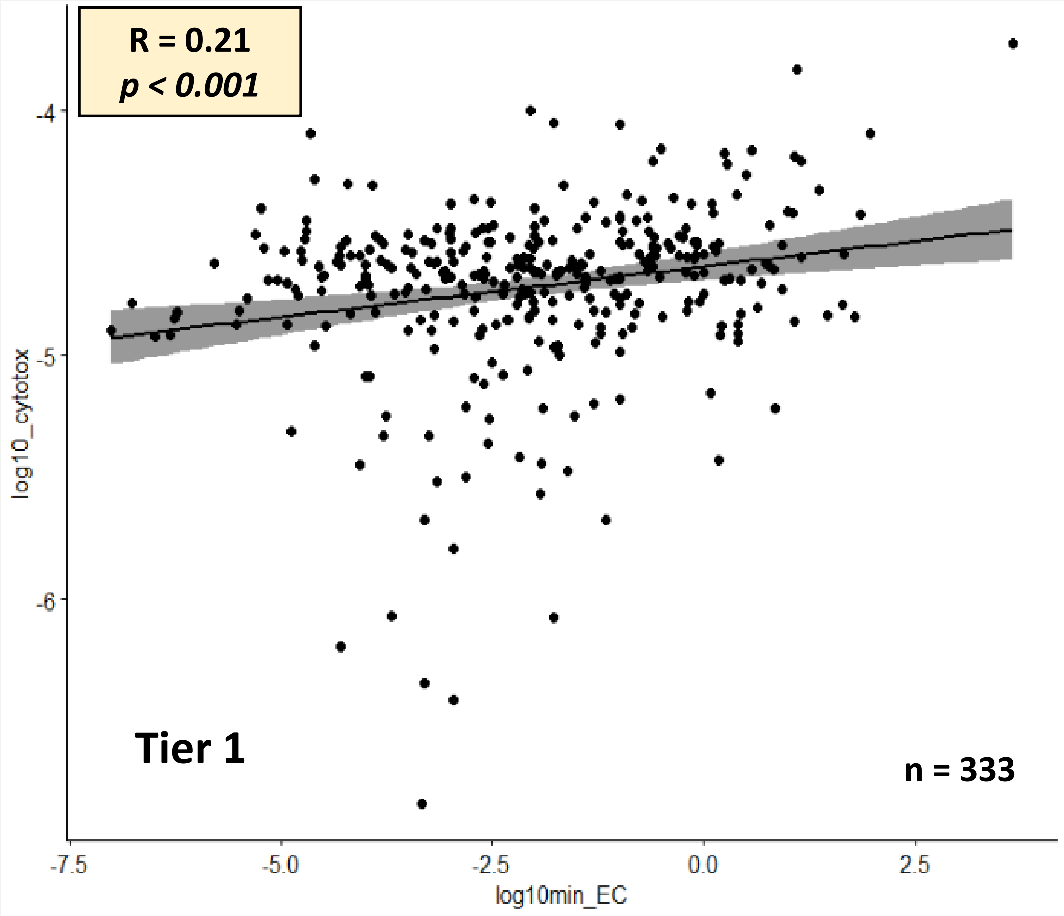
Log10 Transformed; Pearson Correlation

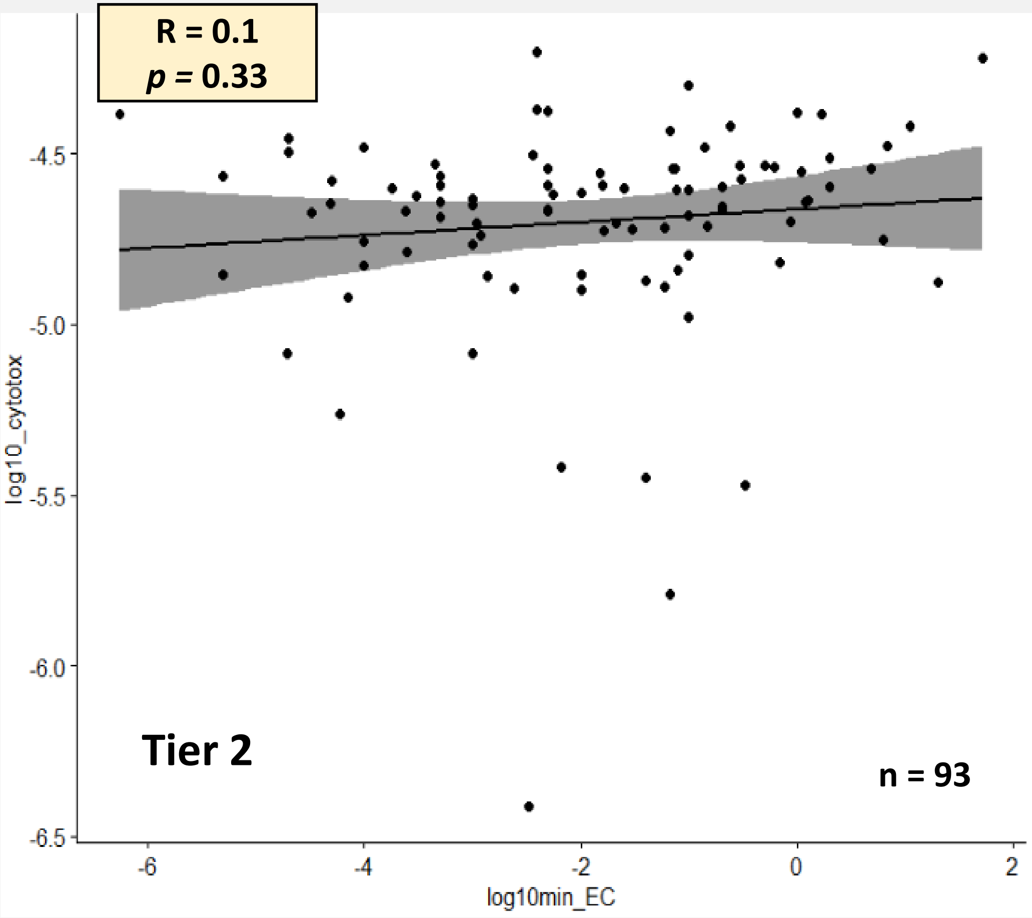


Faceted by Chemical Class



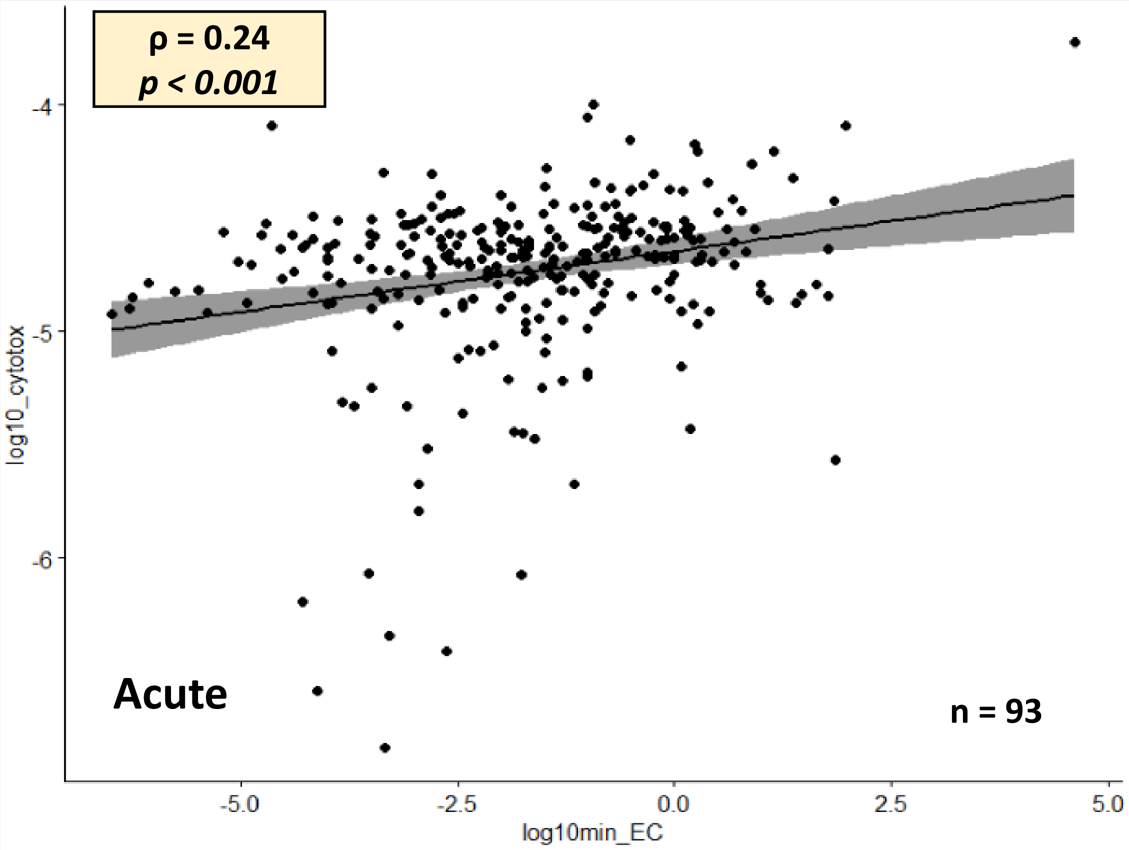
Cytotoxic Burst-ECOTOX: Tiers 1 and 2

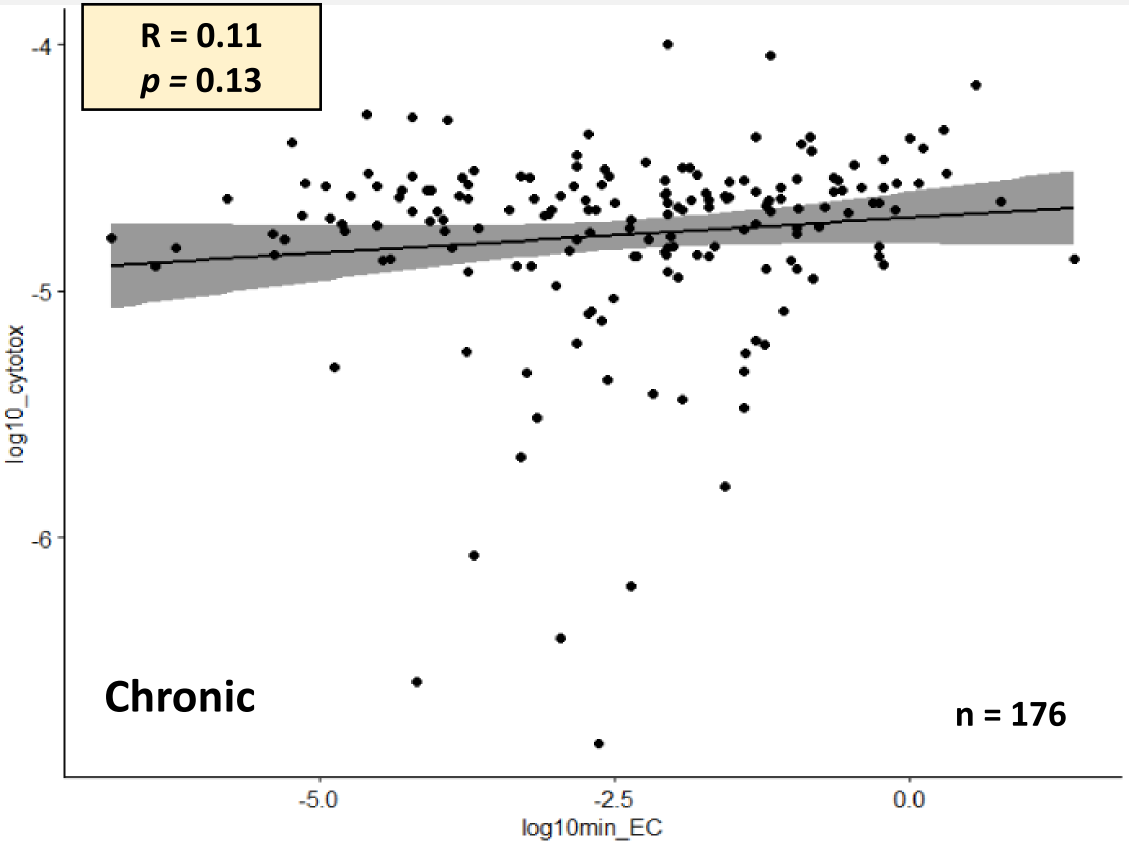




-Significant correlation between **Tier 1** ECOTOX PODs and cytotoxic burst

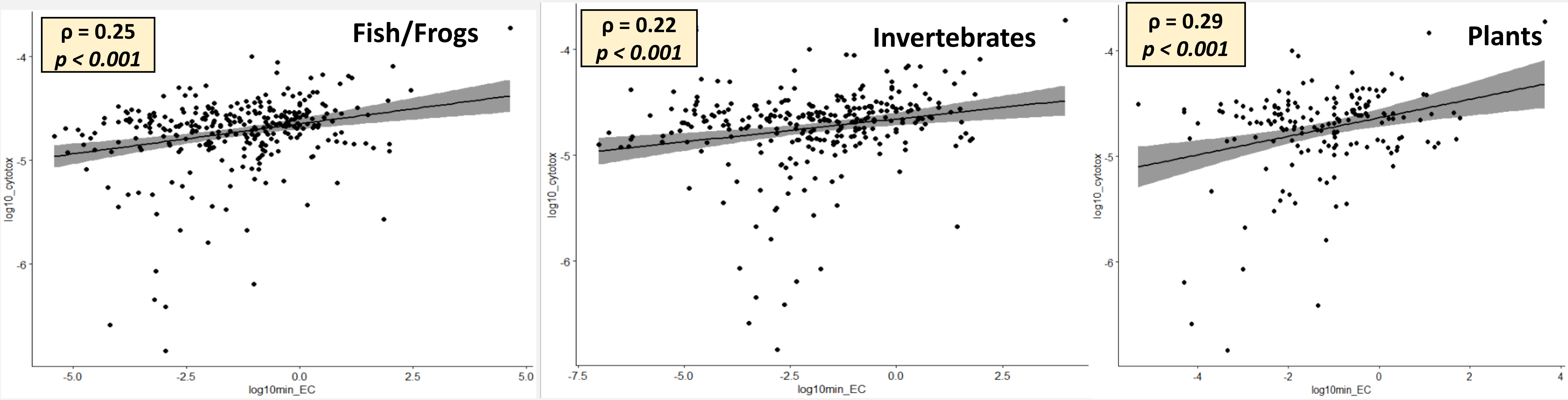
Cytotoxic Burst-ECOTOX: Acute vs. Chronic





-Significant correlation between **acute** ECOTOX PODs and cytotoxic burst

Cytotoxic Burst-ECOTOX: By Taxa

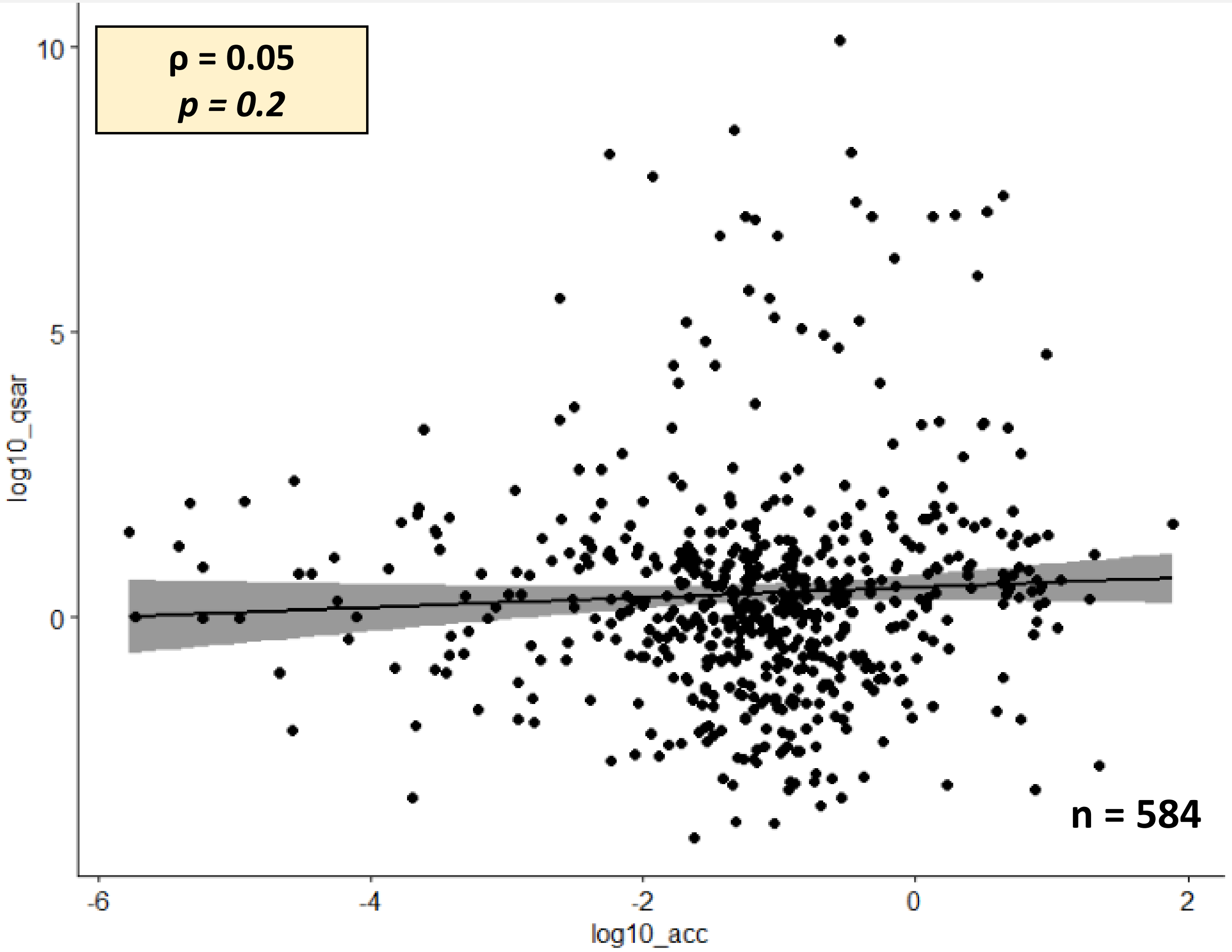


-Similar (significant) correlations across three major taxon groups

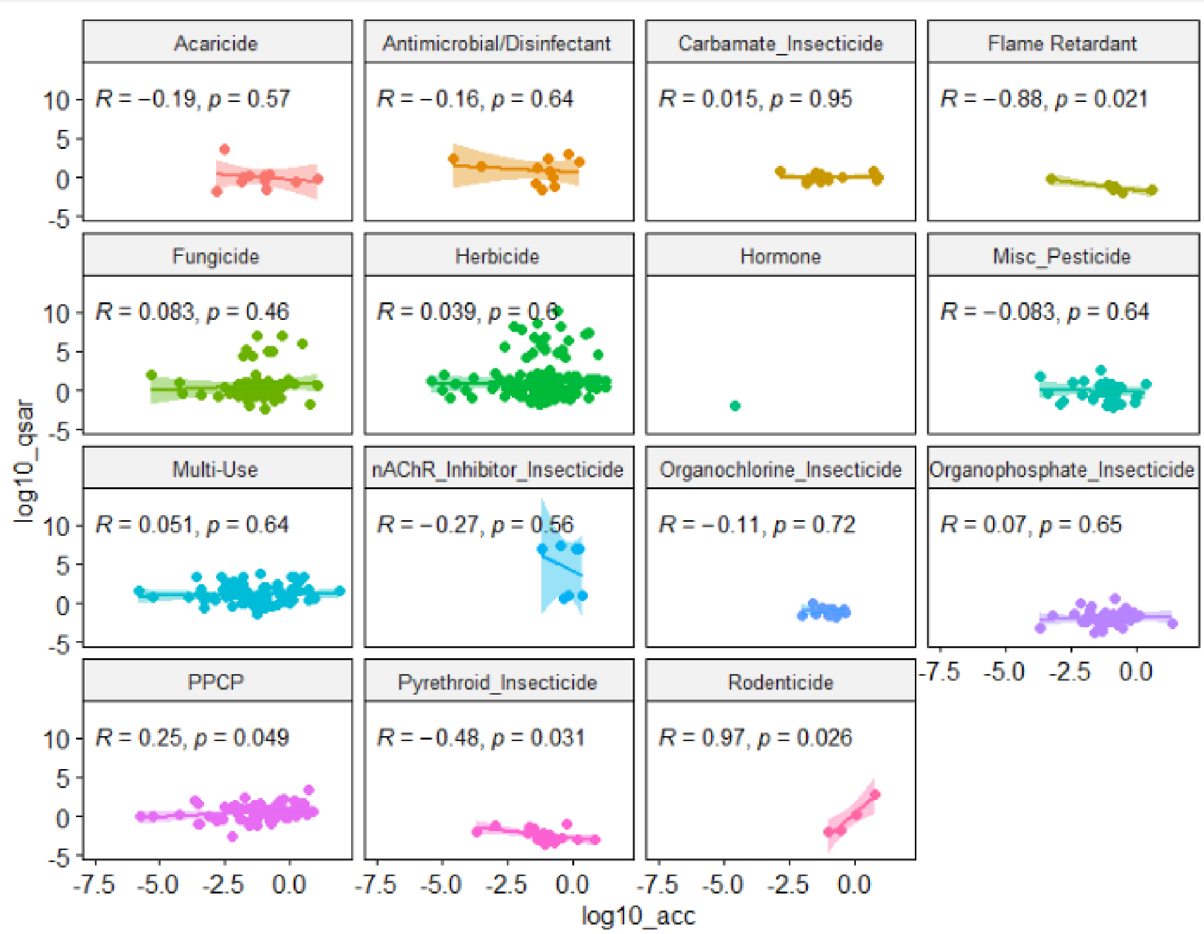
QSAR vs. ToxCast

ACC_5-QSAR Correlations: Overall

Log10 Transformed; Pearson Correlation

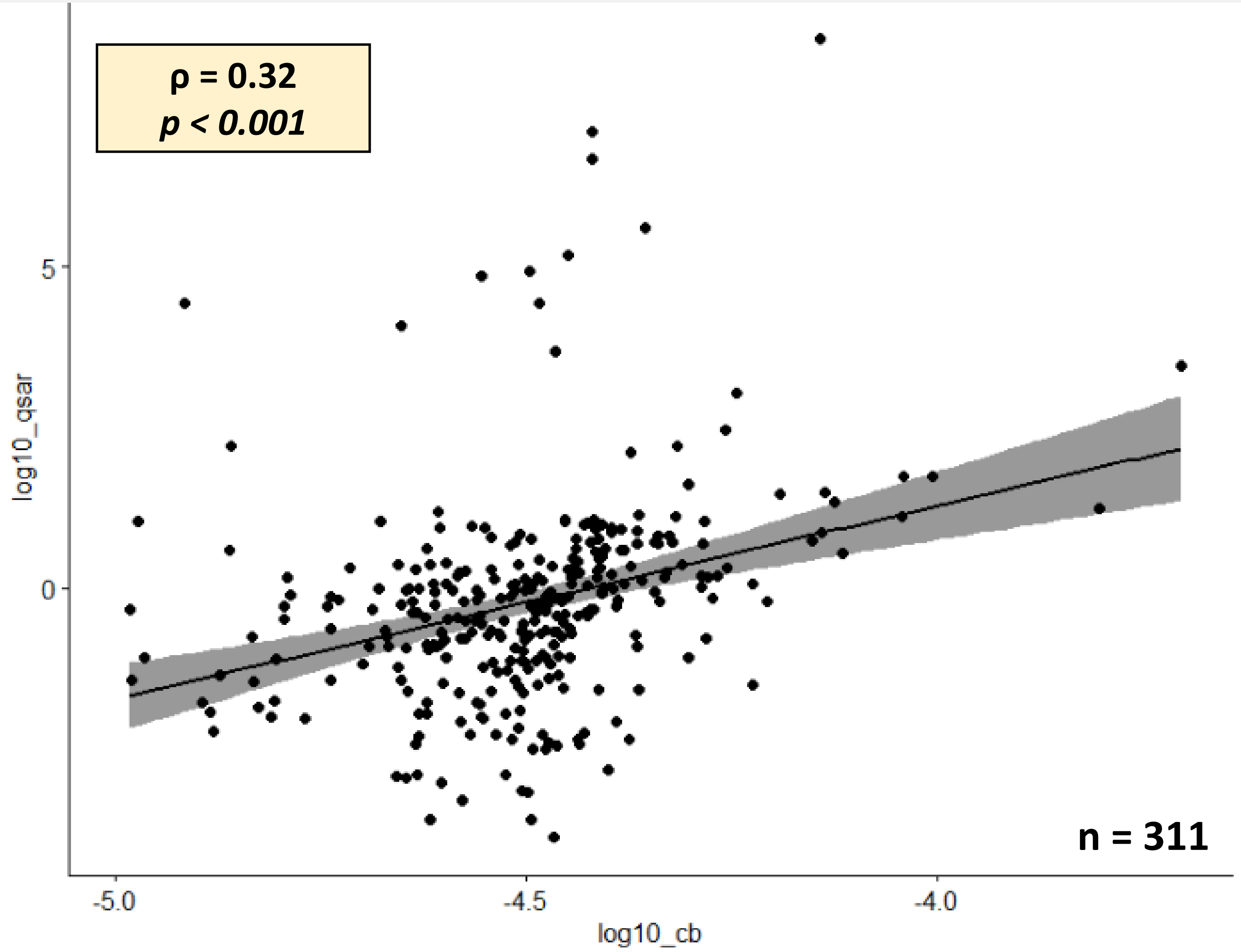


Faceted by Chemical Class

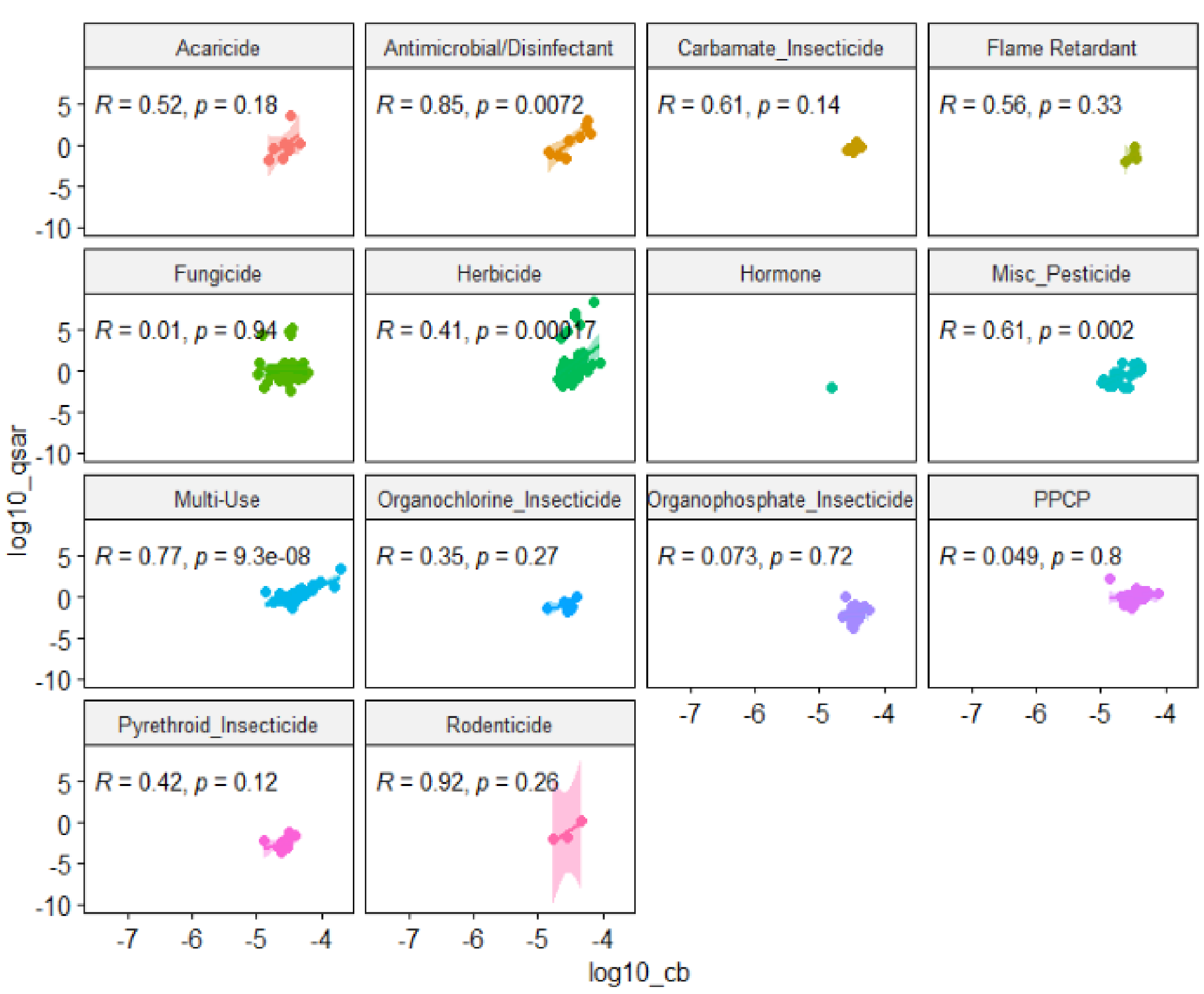


Cytotoxic Burst-QSAR Correlations: Overall

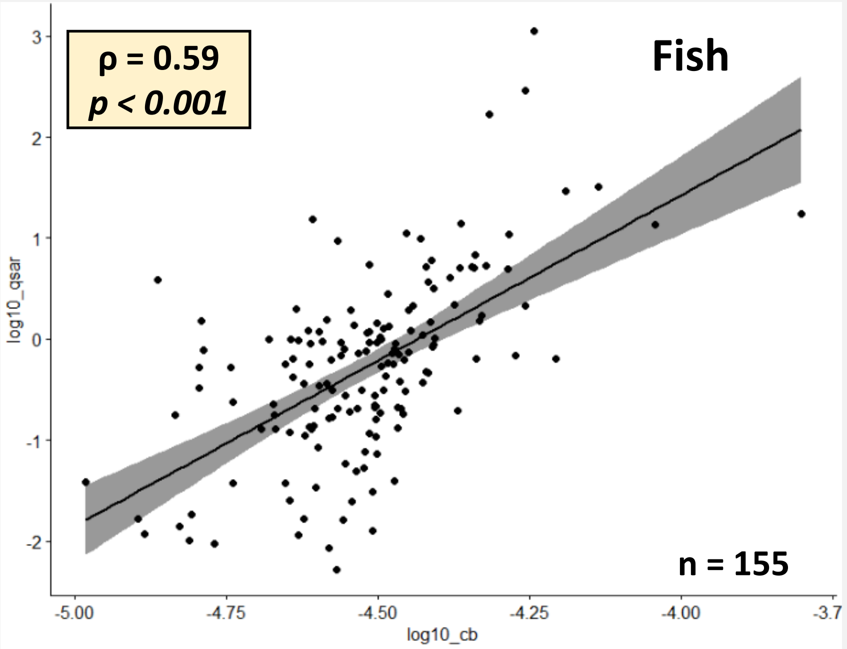
Log10 Transformed; Pearson Correlation

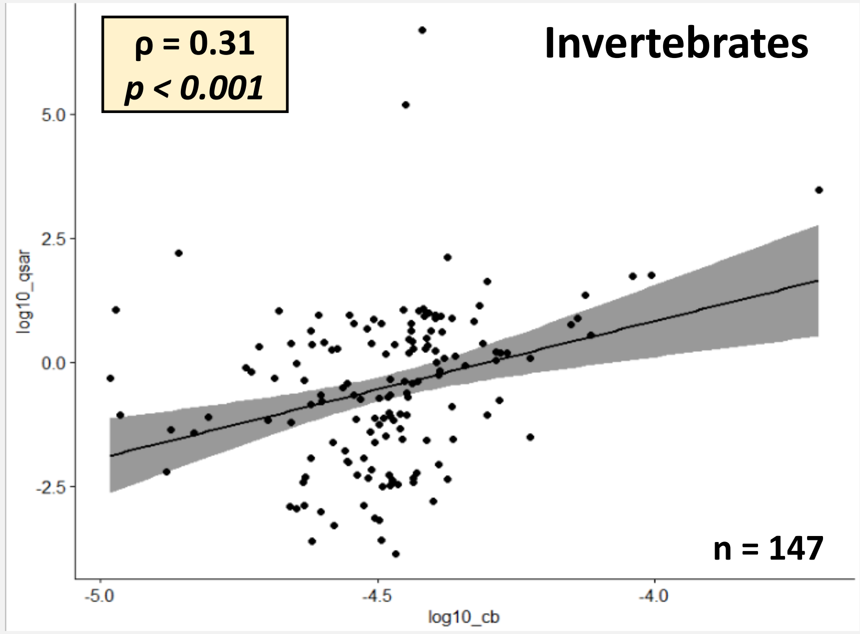


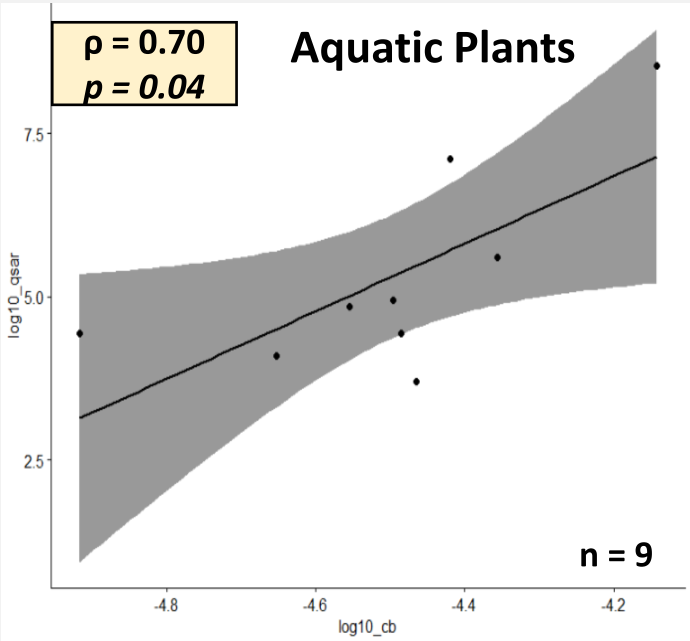
Faceted by Chemical Class



Cytotoxic Burst-QSAR Correlations: Taxa

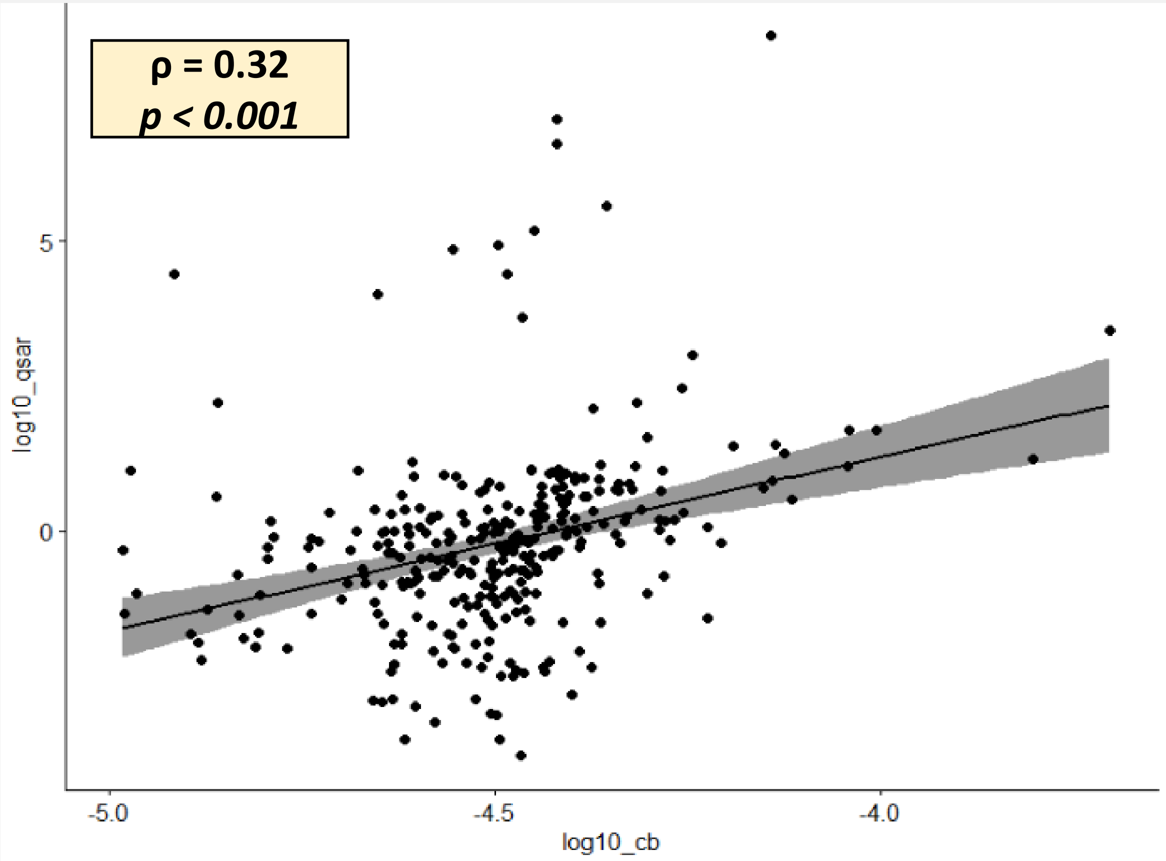




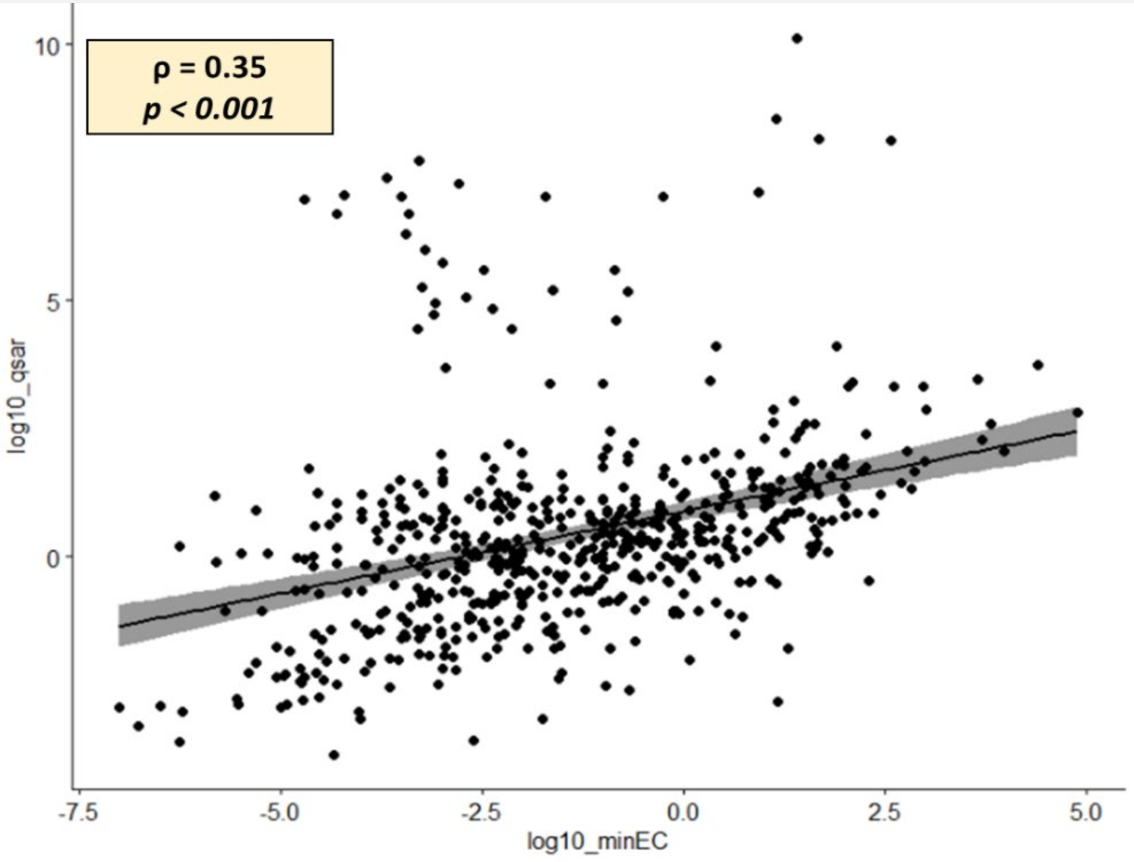


-Positive cytotoxic burst-QSAR correlations, particularly in fish, suggest that CB may reasonably approximate narcosis (non-specific toxicity) *in vitro*

Cytotoxic burst-QSAR

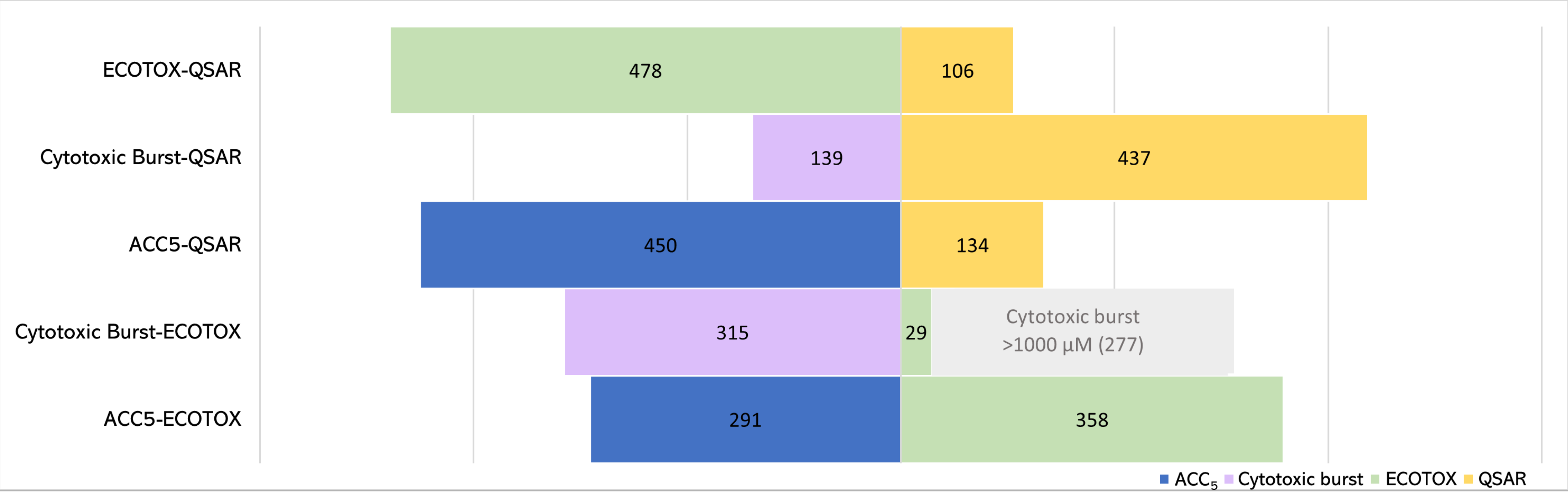


QSAR-ECOTOX



-By correlation, ToxCast cytotoxic burst is as effective as QSAR for predicting *in vivo* ecotoxicity

Relative 'protectiveness' of benchmarks



- Unadjusted ACC_5 or cytotoxic burst is only protective around 50% of the time – not consistently
- ToxCast results may provide indication of pathway-specific or cytotoxic relative potency
- Probably should not be used directly as a point of departure for risk-based screening

Conclusions

- ACC_5 values do not correlate well with ECOTOX-derived PODs nor QSARs
  - ECOTOX PODs are based on mixture of data from different species and study types
  - Most sensitive hits in ToxCast often represent adaptive responses (e.g., xenobiotic metabolism), not necessarily toxic effect(s)

- Lower-bound cytotoxic burst concentrations generally align well with corresponding ECOTOX PODs, as well as QSARs

- *These data suggest a potentially important role for the ToxCast ACC_5, not in terms of providing a lower bound toxicity estimate, but rather in* ***determining whether a more specific mode of action may be relevant***.
  - Potential utility in chemical risk prioritization strategies

- Future work will continue to examine how NAM data might be integrated in ecological risk assessment

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