



SETAC Europe 36th Annual Meeting

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Evaluating the Protectiveness of High-Throughput Transcriptomics Data from fish cell lines for Environmental Risk Assessment

SERS

Safety, Environmental
& Regulatory Science



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Glossary:

HTTr – High Throughput Transcriptomic

tPODs – transcriptomic point of departure

QIVIVE – Quantitative In Vitro to In Vivo Extrapolation

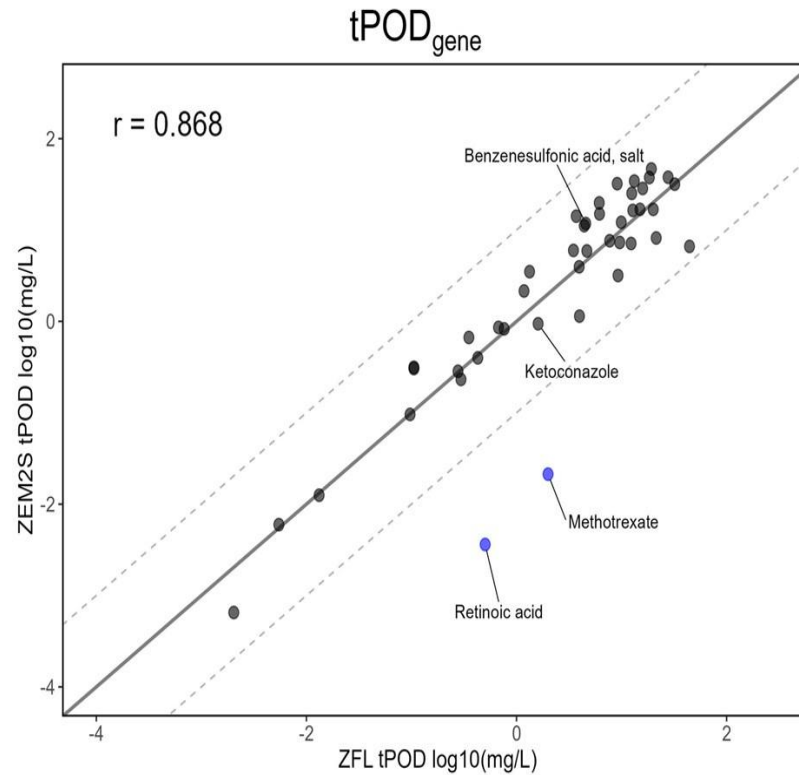
ERA – Environmental Risk Assessment

Can zebrafish cell lines
generate meaningful
HTTr data?

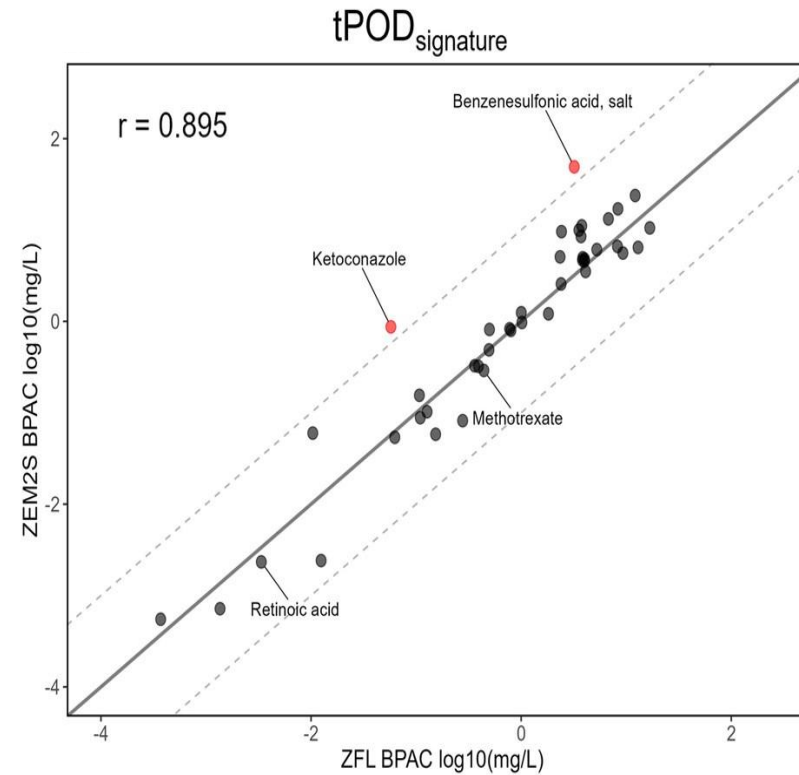
Are tPODs protective of
aquatic toxicity effects?



Two complementary tPOD concepts

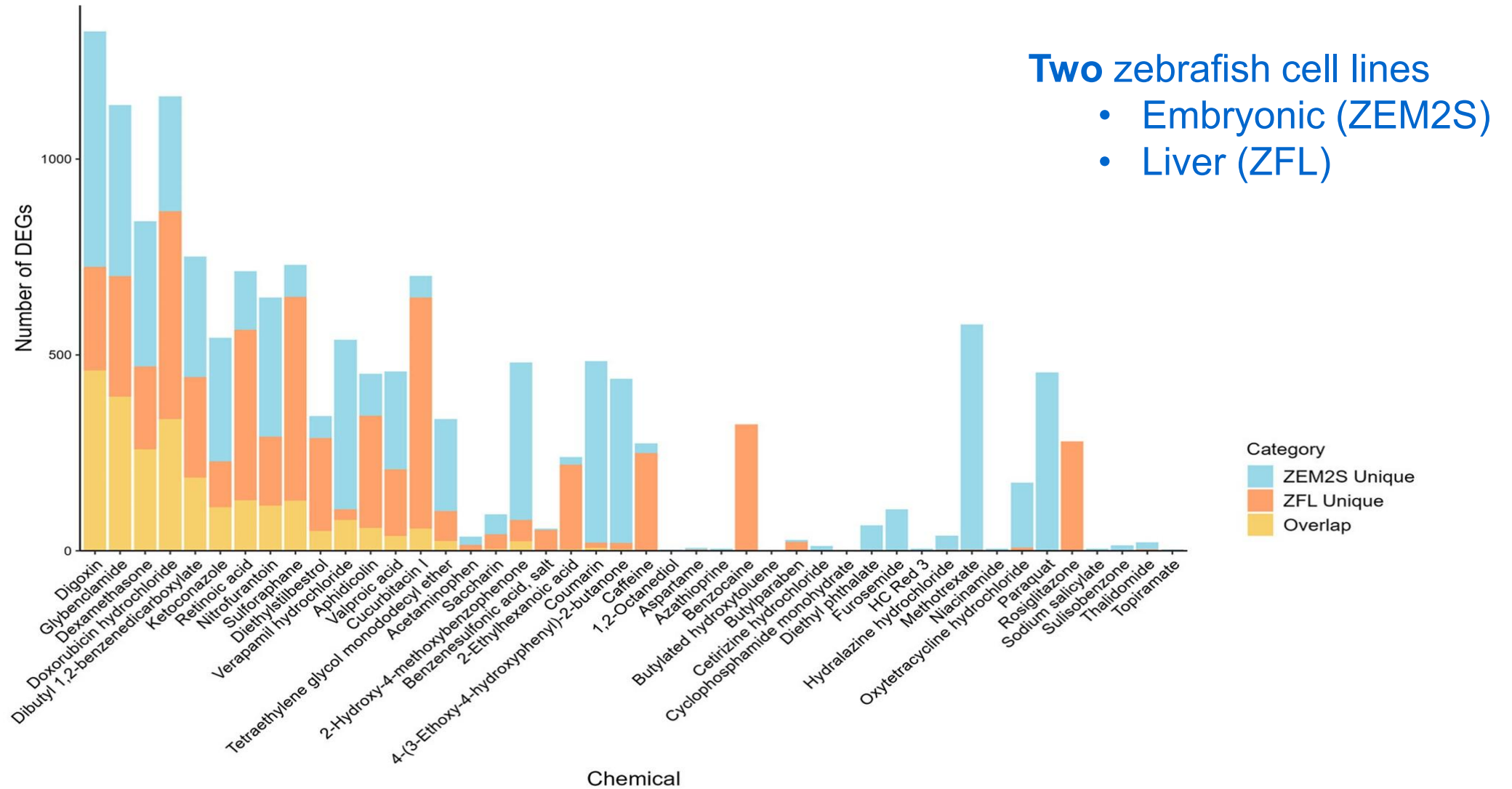


concentration–response
at the gene level using
benchmark dose methods

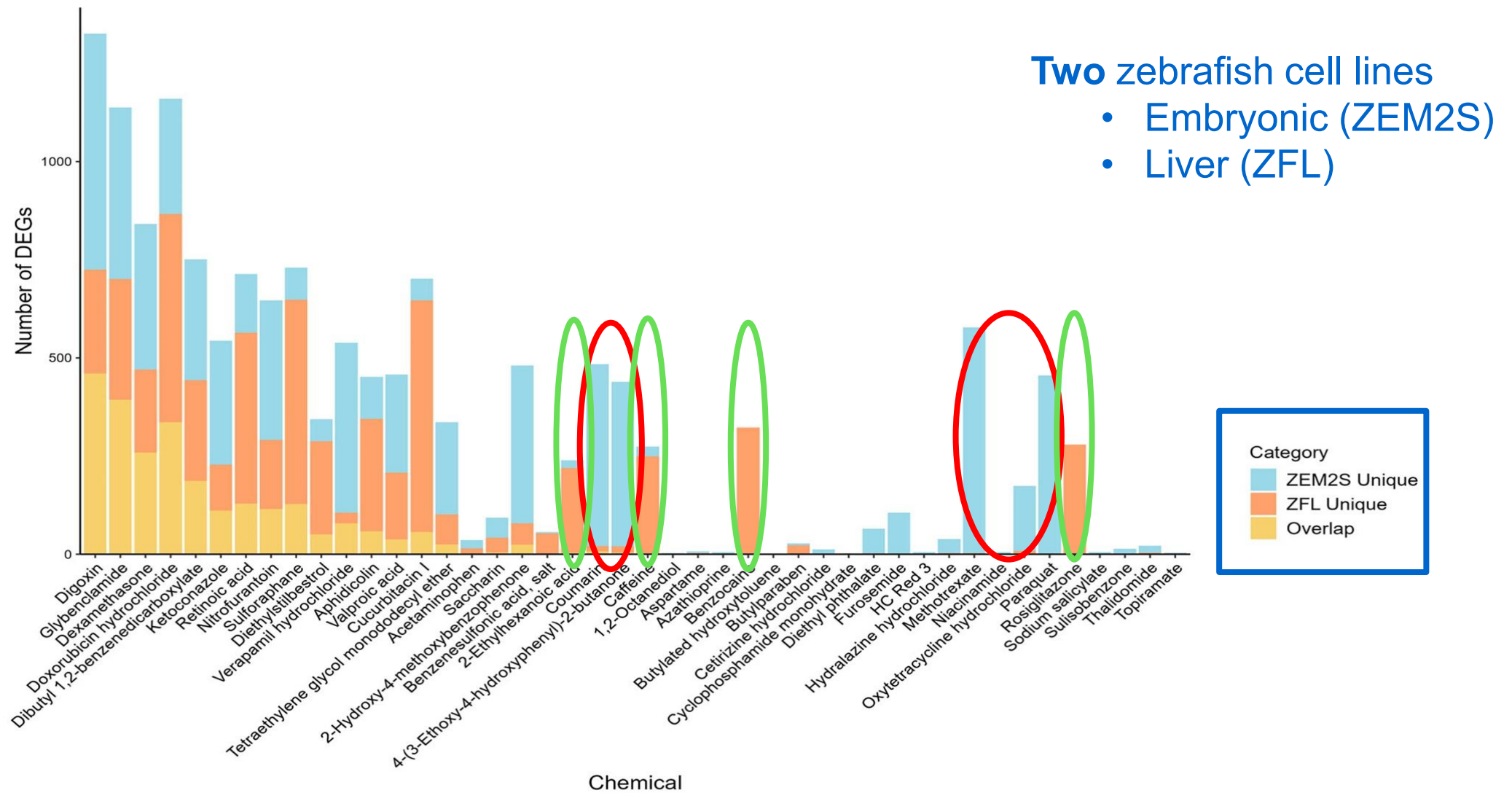


dose–response at the
pathway level using
enrichment scoring

Differential responses across cell lines



Differential responses across cell lines



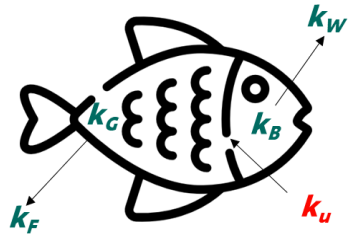
Counts of unique differentially expressed genes

Making in vitro data environmentally relevant

Base of the BIONIC model

$BCF_{ss^*} = \text{concentration in fish } (C_B) / \text{concentration in water } (C_W) = k_U / k_E$

$$\frac{dC_B}{dt} = k_U C_W - k_E C_B$$



$$\frac{\text{uptake}}{\text{elimination}} = \frac{\text{gill uptake } (k_U)}{\text{gill elimination } (k_W) + \text{Biotransformation } (k_B) + \text{faecal elimination } (k_F) + \text{growth dilution } (k_G)}$$

* steady-state, $dC/dt = 0$

Adapted from Armitage, et al (2017) ET&C

The model can be used for

reverse dosimetry which

internal points of departure (PODs)

can be translated into

environmental (external)

concentrations

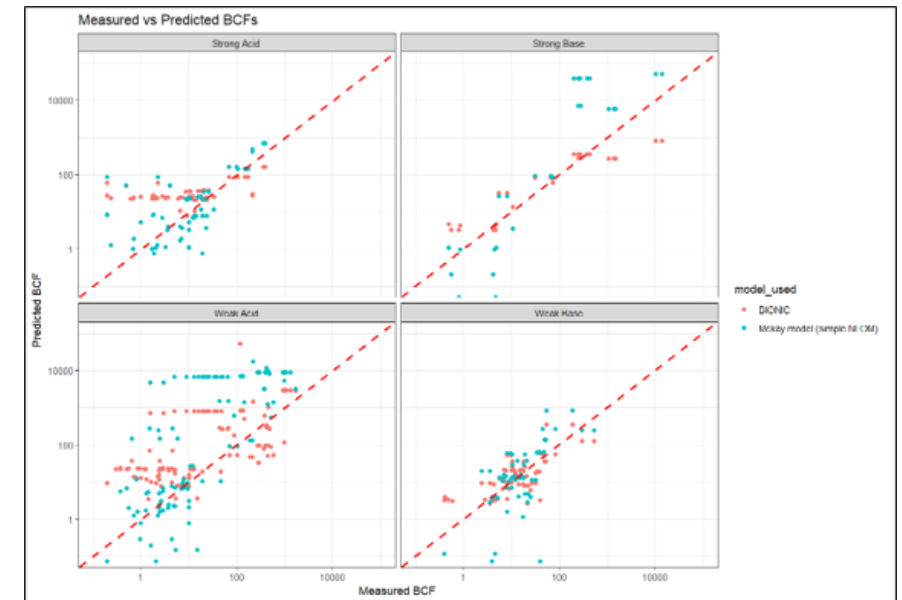


QIVIVE



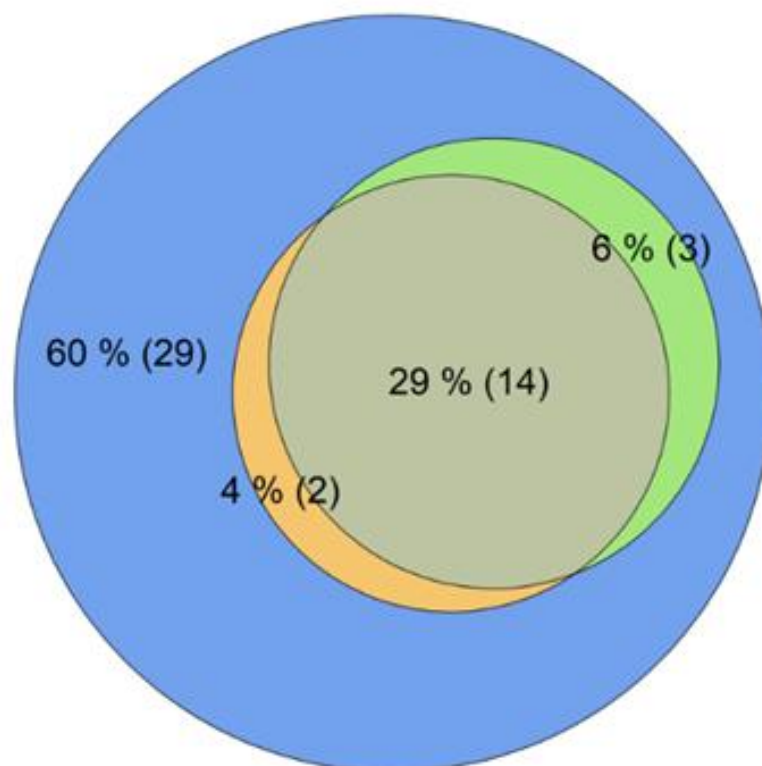
in vitro concentration

environmental concentration (external)



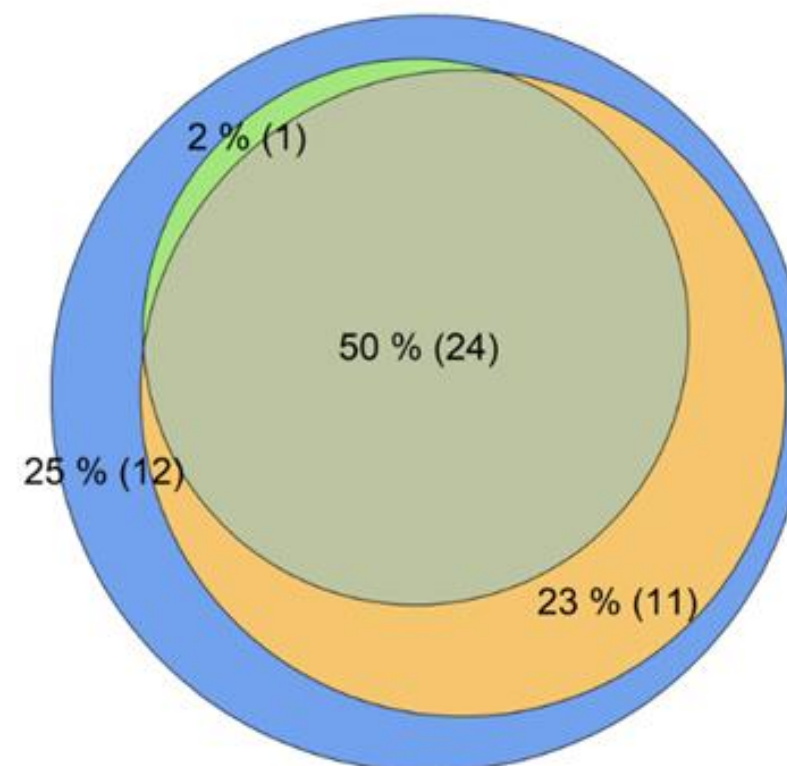
Available in vivo data – filtering criteria

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- Chemicals w/o ECOTOX data
- Chemicals w/ Tier 1 ECOTOX data
- Chemicals w/ Tier 2 ECOTOX data

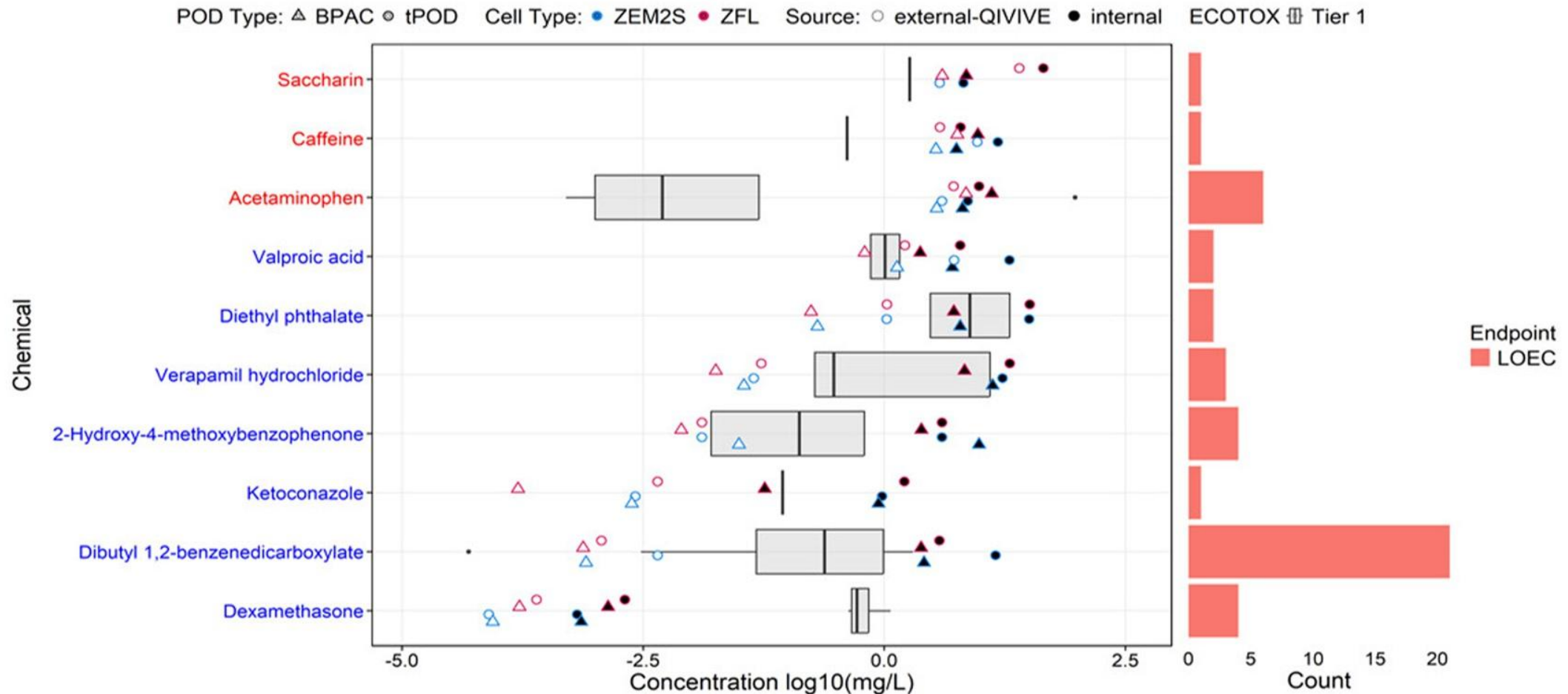
**"quality-filtered"
dataset**
(Schaupp et al. 2023)



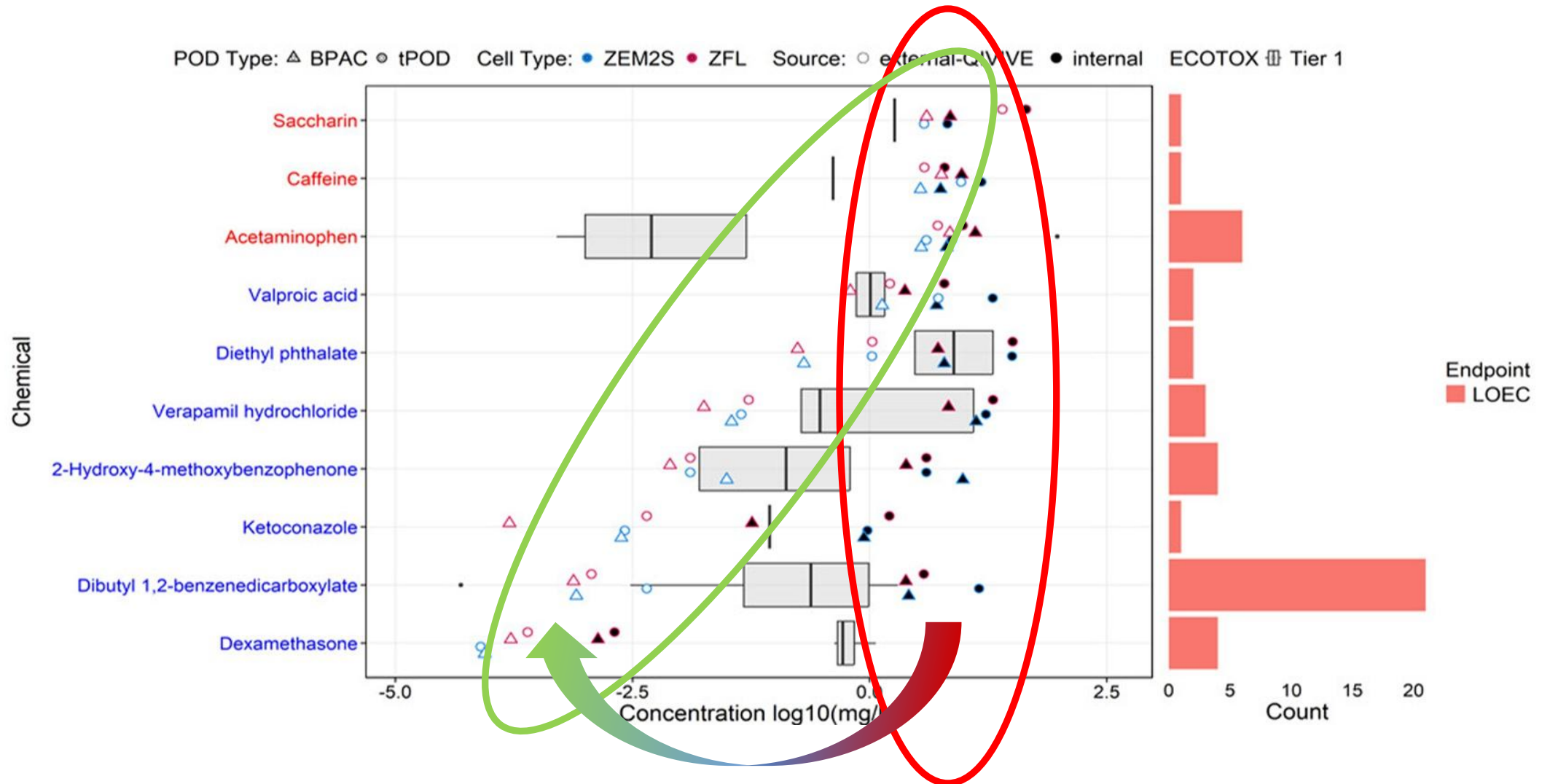
- Chemicals w/o ECOTOX data
- Chemicals w/ Tier 1 ECOTOX data
- Chemicals w/ Tier 2 ECOTOX data

**"expanded-criteria"
dataset**

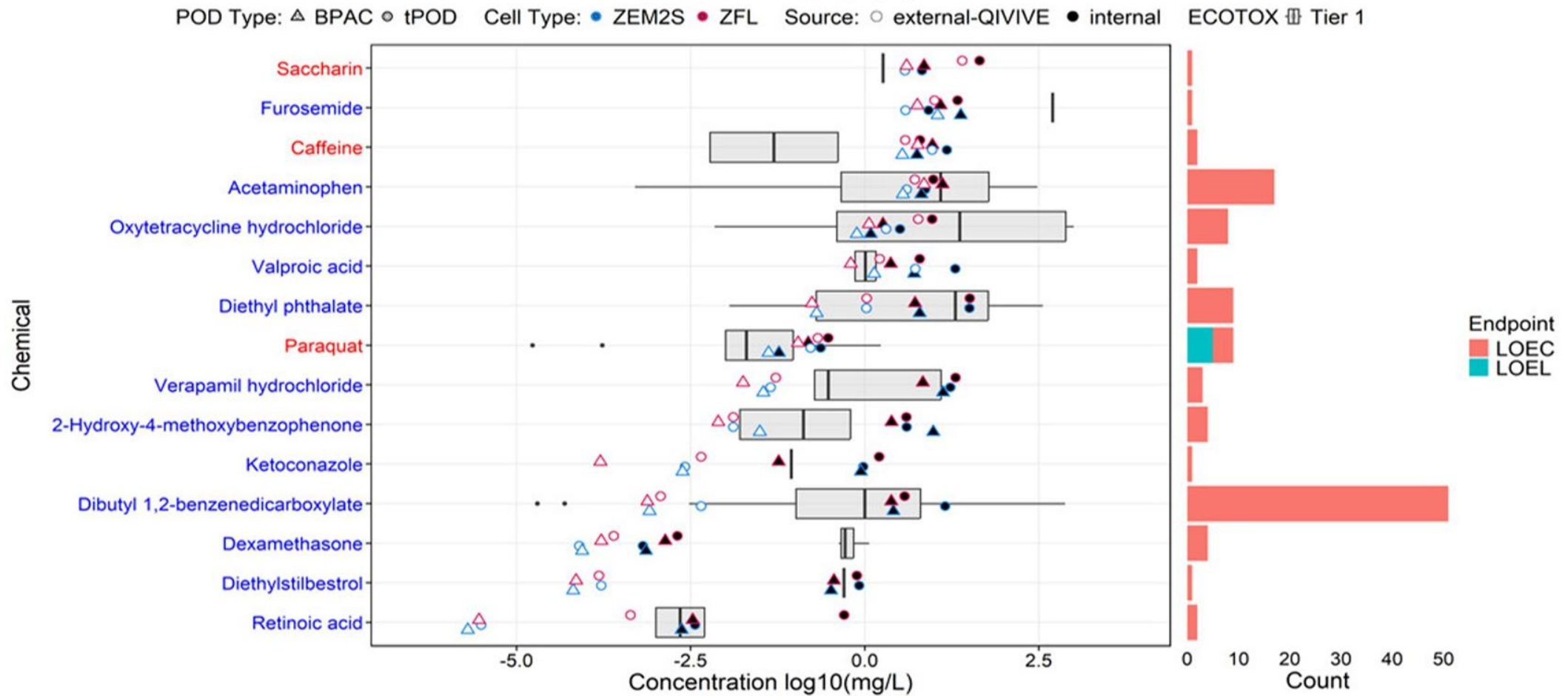
Are tPODs protective of apical effects?



Are tPODs protective of apical effects?

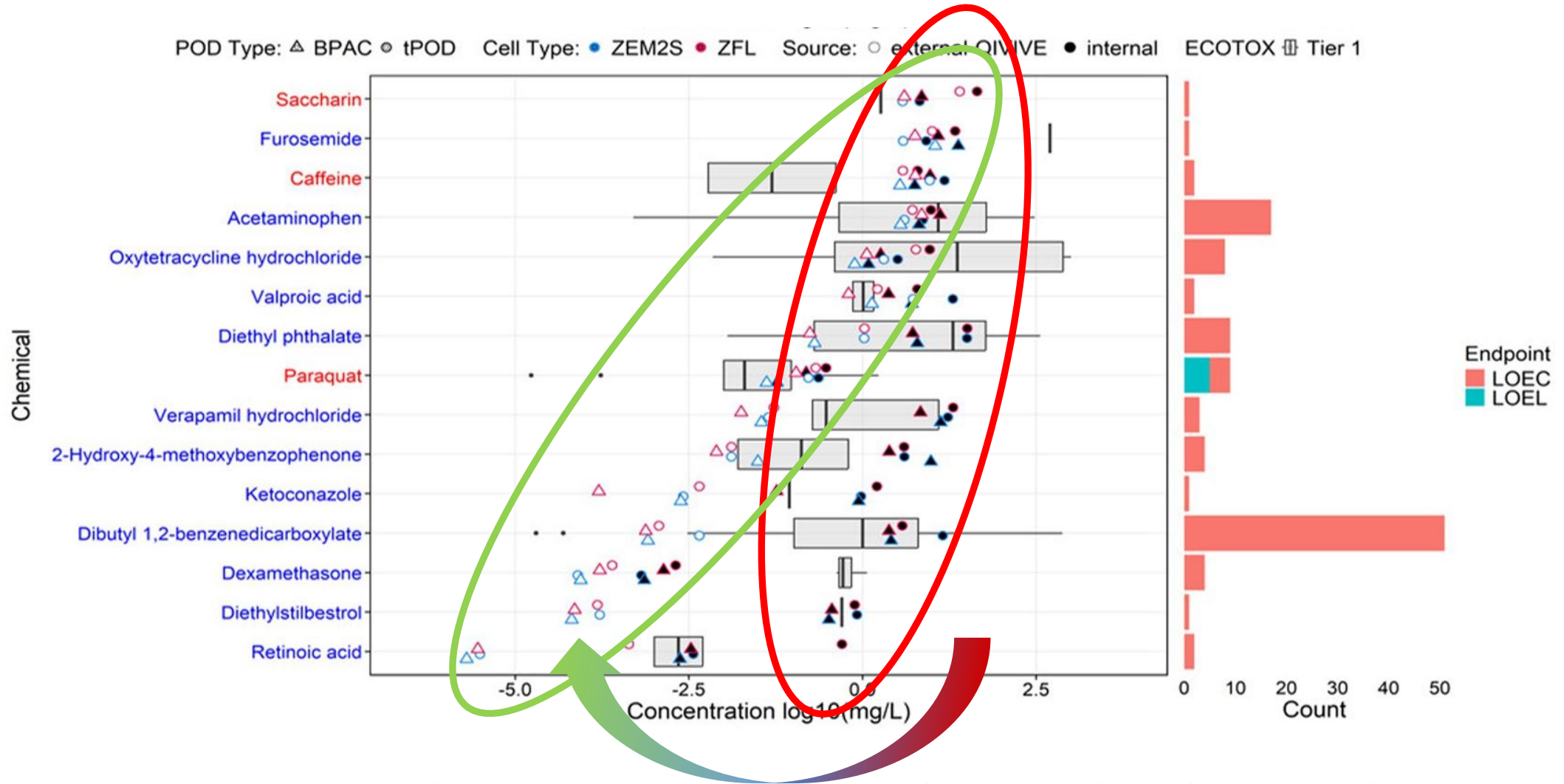


Are tPODs protective of apical effects?



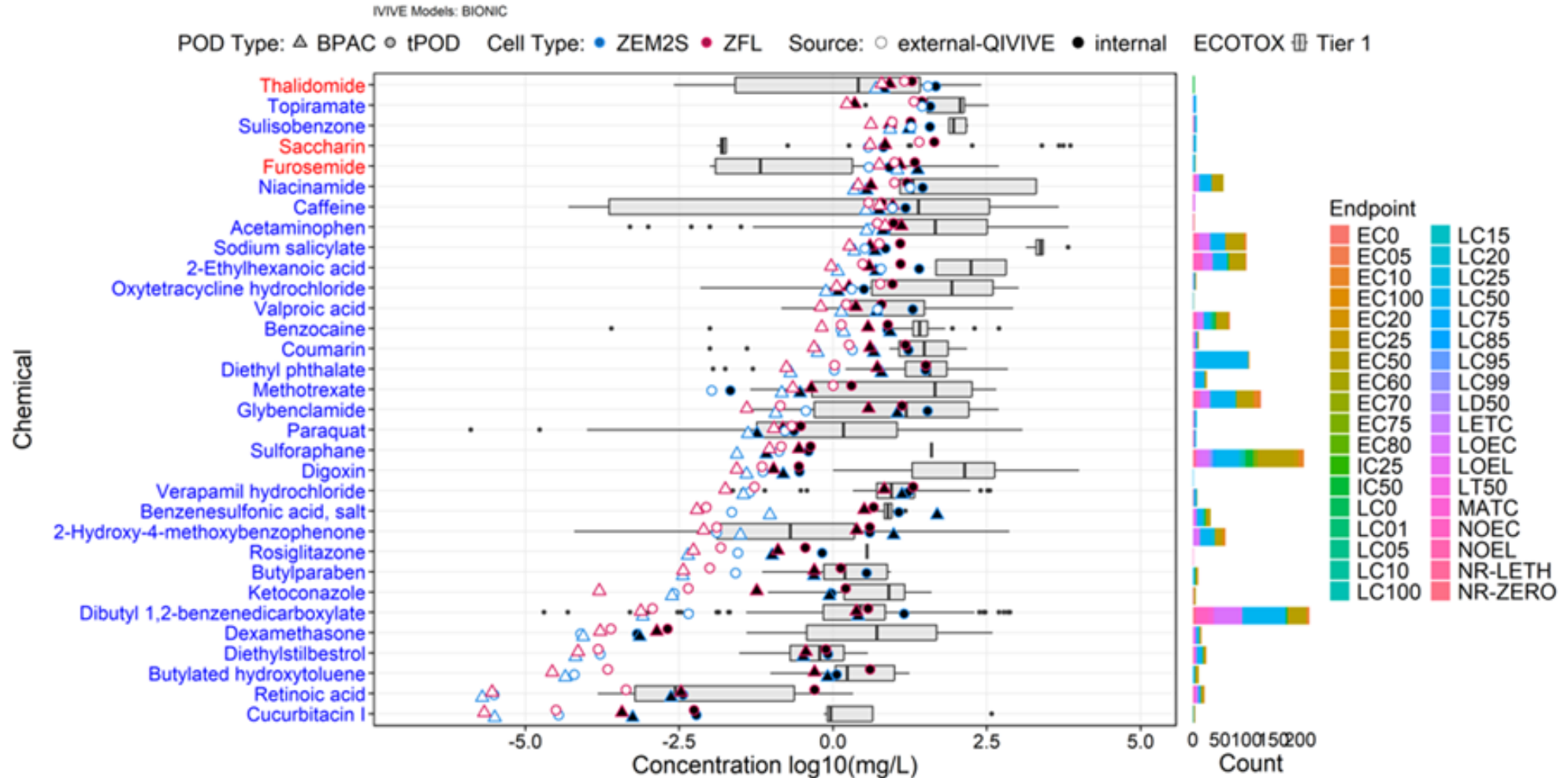
Comparison of tPOD values with quality-filtered tier 1 in vivo all species data from the ECOTOX knowledgebase

Are tPODs protective of apical effects?



Comparison of tPOD values with quality-filtered tier 1 in vivo all species data from the ECOTOX knowledgebase

Comparison with "expanded-criteria" dataset









3 things to remember

- ✓ Zebrafish cell line HTTr provide biologically meaningful, scalable data
- ✓ tPODs converted to predicted external water concentrations using QIVIVE models were generally protective of aquatic in vivo
- ✓ QIVIVE is essential to achieve protectiveness





Zebrafish cell lines and high-throughput transcriptomics: advancing in vitro and bioinformatics methods for supporting environmental risk assessment

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Abstract

Historic animal-based toxicity testing methods cannot keep pace with the need for prioritizing new and existing chemicals for comprehensive risk assessment. New approach methodologies such as high-throughput in vitro transcriptomics screening have emerged to address this challenge. However, most in vitro methods were developed using mammalian cell lines, including human, and may not adequately represent environmental species, potentially limiting the utility of this methodology for supporting environmental risk assessment. The objective of this study was to evaluate whether zebrafish cell lines can generate biologically meaningful chemical effects data in a high-throughput transcriptomics pipeline that is protective of toxicologically relevant aquatic apical endpoints. Forty-two test chemicals were screened in 2 commercially available zebrafish cell lines (ZFL liver and ZEM2S embryonic fibroblast) using the TempO-Seq zS1500+ platform. Transcriptomic points-of-departure (tPODs) were derived using 2 methods: Gene-level analysis (tPOD_{genes}) with BMDExpress software and biological pathway-altering concentrations (BPACs/tPOD_{signatures}) from signature-based dose-response analysis. When converted to predicted external water concentrations using quantitative in vitro–in vivo extrapolation models, tPODs were generally protective of aquatic in vivo endpoints from the ECOTOX Knowledgebase. Differential gene expression and biological pathway analysis revealed potential cell-type-specific effects for several chemicals, highlighting the value of using multiple cell types for capturing tissue-specific responses. Lastly, the biological pathway information was used to extrapolate the chemical effects data across species through an integration of protein–protein interaction network analysis and the Sequence Alignment to Predict Across Species Susceptibility tool, which has significant implications for improving the ecological relevance of these methods.

Keywords: toxicogenomics; computational toxicology; in vitro models; bioinformatics; risk assessment

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Thank you!

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Felix Harris
David Ryoo
Carlie A. LaLone



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