Using AOPs TO Quantitatively Predict Chemical Impacts on Fish Reproduction

PPDC Workshop

July 9, 2013

Introduction

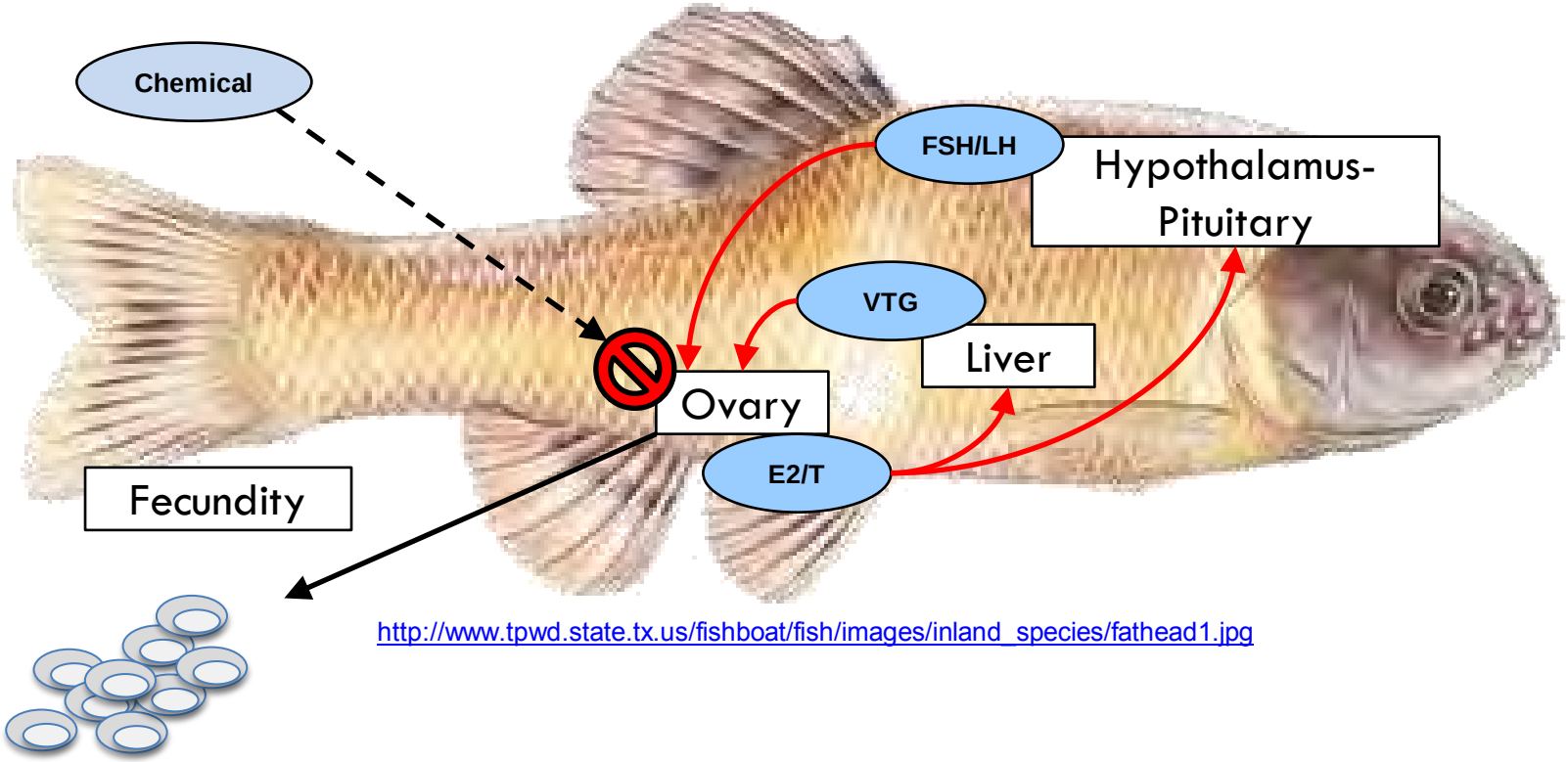
The Problem

- Animals act in a complex manner when exposed to chemicals.
- Effects often determined on lower biological level data (in vivo and in vitro assays) but need to predict effects on populations
- Dose-response often nonlinear.

Solutions

- Extrapolation across biological scales to predict population impacts
- Systems biology models representing a dynamic, quantitative model of the fish reproductive AOP
- Parameterization of a fish reproductive AOP model with in vitro/in vivo data

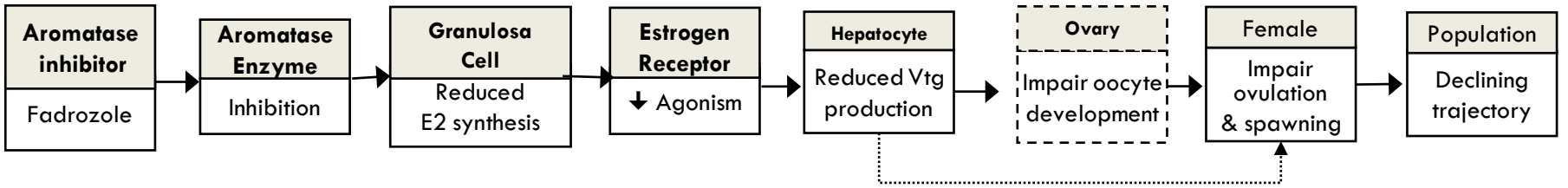
Hypothalamus-Pituitary-Gonadal (HPG) axis controls reproduction

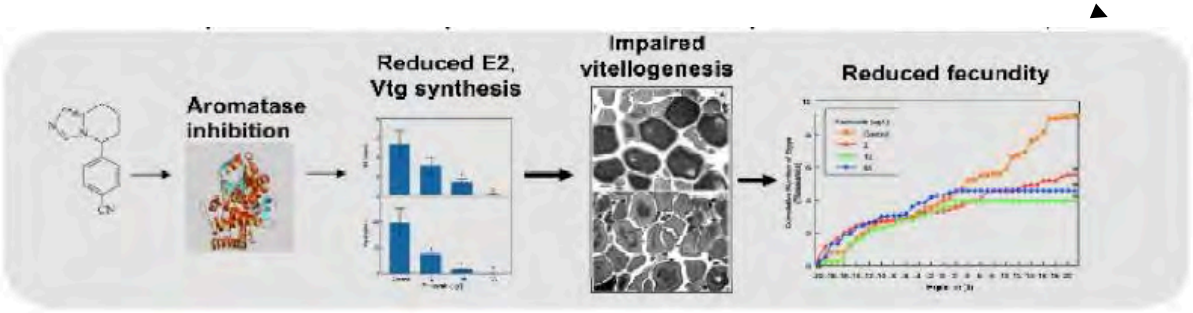


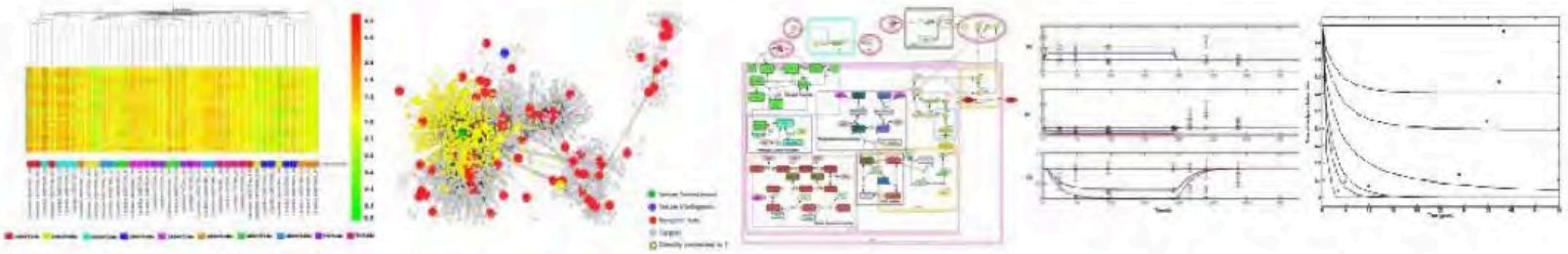
http://www.tpwd.state.tx.us/fishboat/fish/images/inland_species/fathead1.jpg

synthesis and regulation of reproductive hormones 17β-estradiol (E2) and testosterone (T) which controls egg protein production, leading to egg production

Reproduction-related Adverse Outcome Pathway (AOP): aromatase inhibition







Screening for toxicological effects and chemicals

Pathway and network impacts

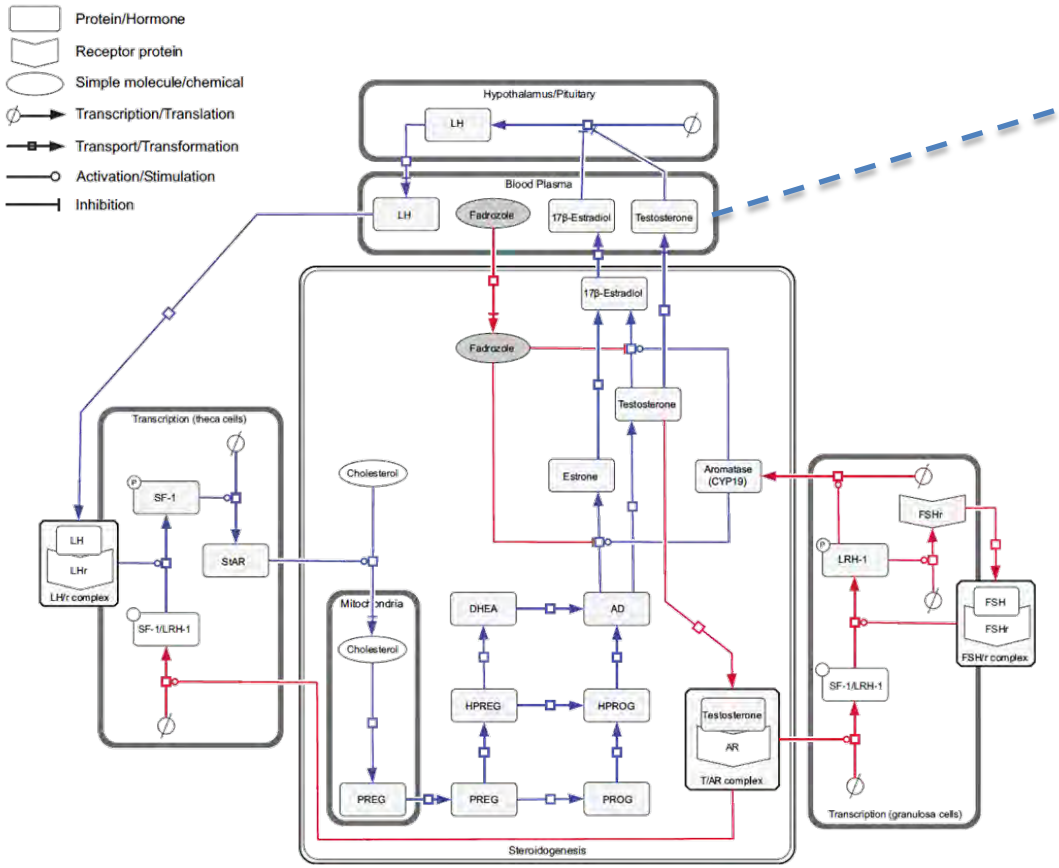
Mechanistic modeling

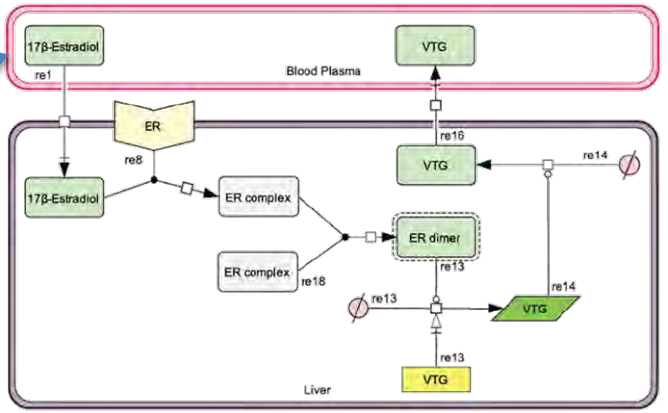
Predicted effect

Population impact

Conceptual mathematical model

M. Mayo et al., (in preparation)

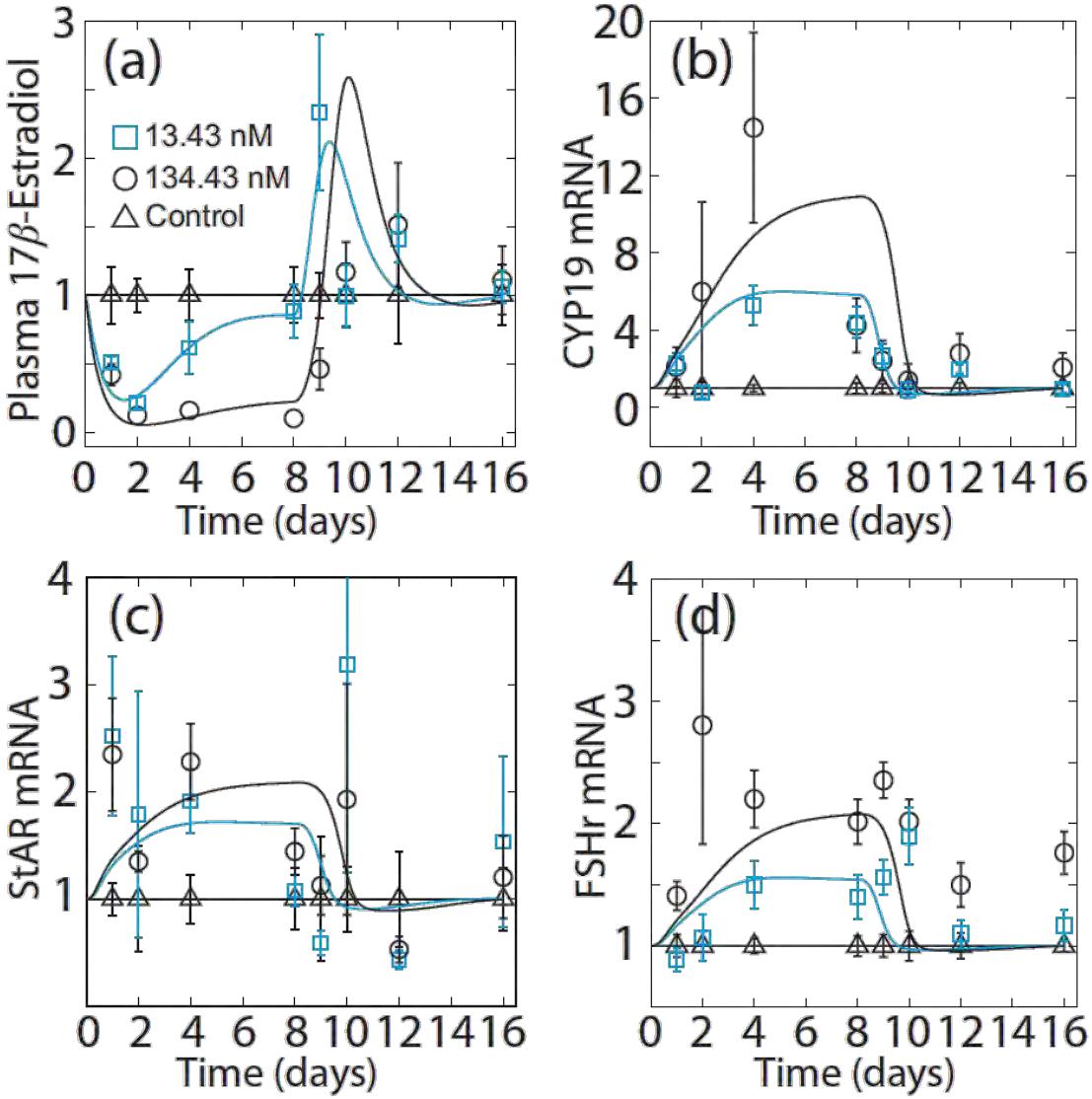


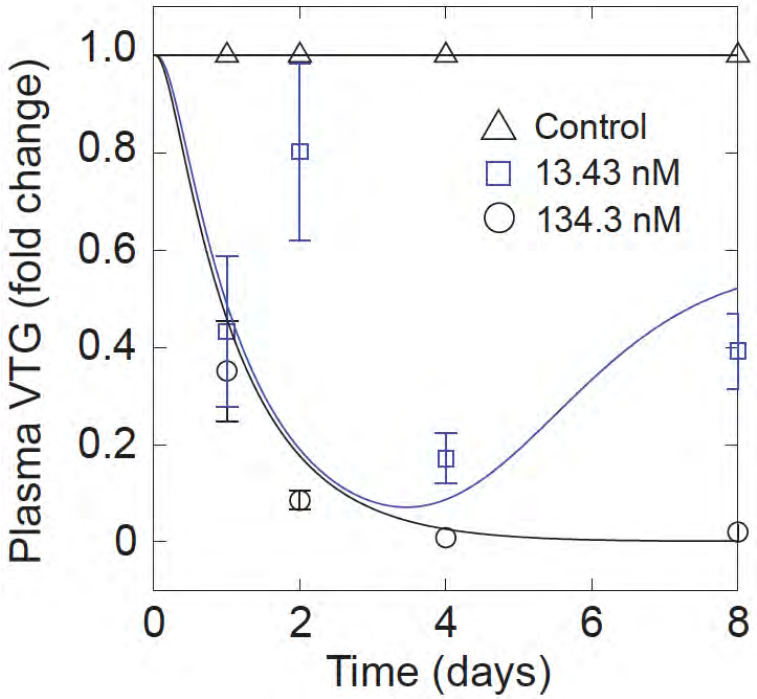


- Androgen receptor signaling initiates transcription, translation, and phosphorylation events
- Varying Fadrozole exposures cause varying plasma E2 response

- Liver compartment (vitellogenesis)
- Takes plasma E2 input and models:
  - ER binding E2
  - ER complex homodimerization
  - ER complex transactivation of vitellogenin

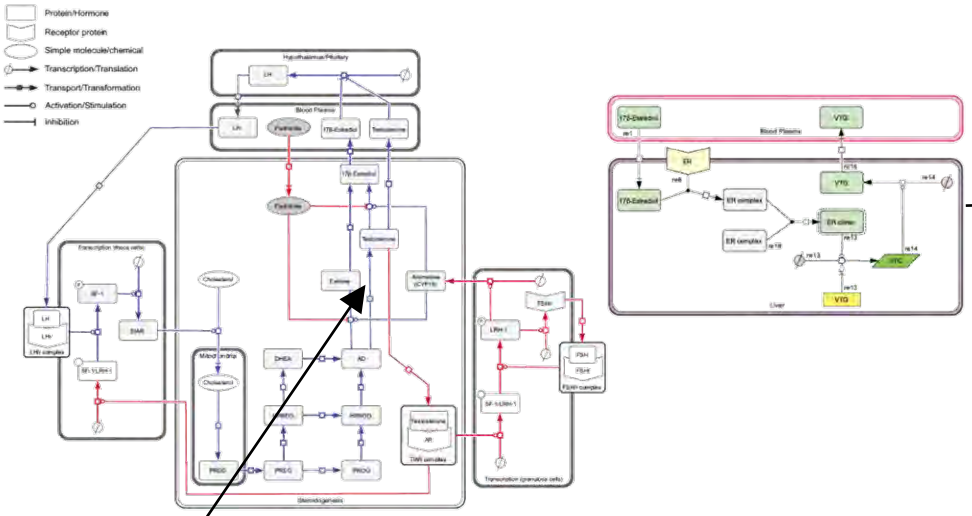
Predicting hormone and egg protein concentration profiles



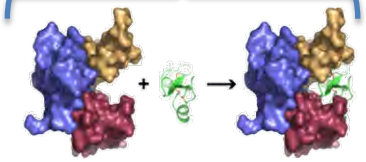


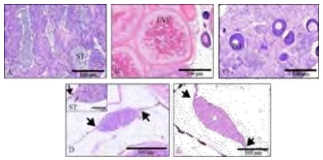
Quantitative AOP

Aromatase inhibitor	Aromatase Enzyme	Granulosa Cell	Estrogen Receptor	Hepatocyte	Ovary	Female	Population
Fadrozole	Inhibition	Reduced E2 synthesis	↓ Agonism	Reduced Vtg production	Impair oocyte development	Impair ovulation & spawning	Declining trajectory



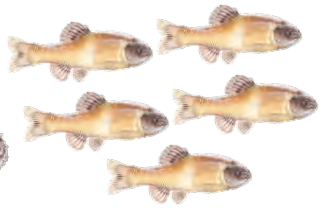
Egg production → Population effects





Organ/tissue level**

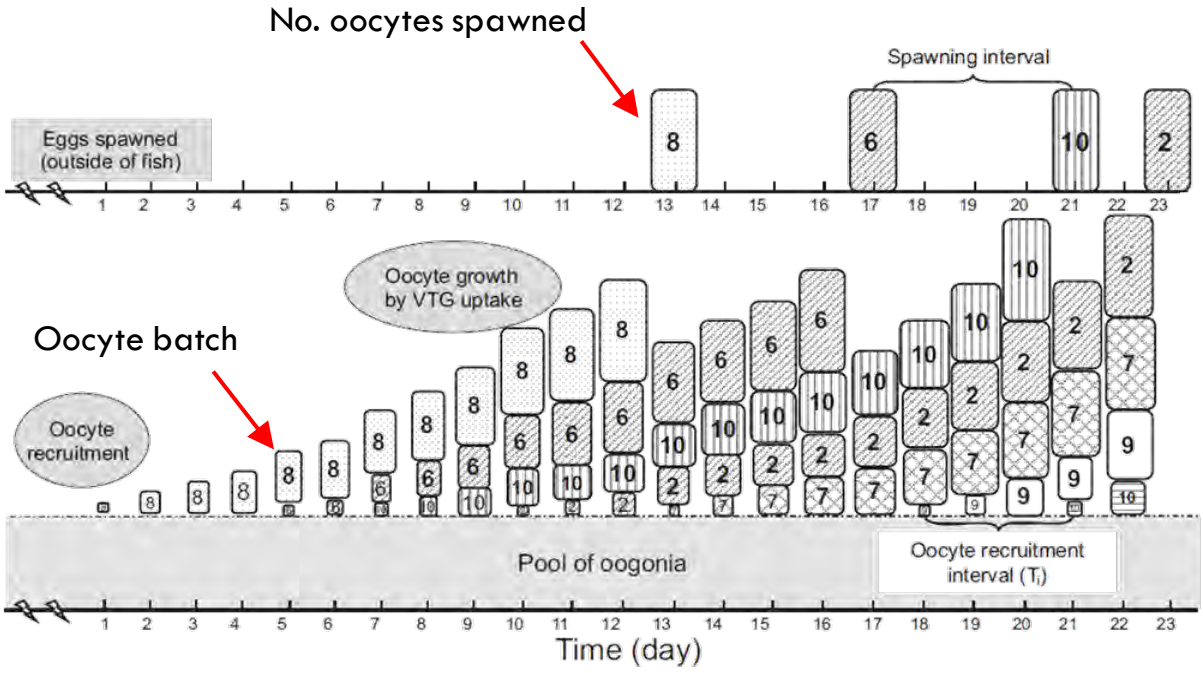
Animal level



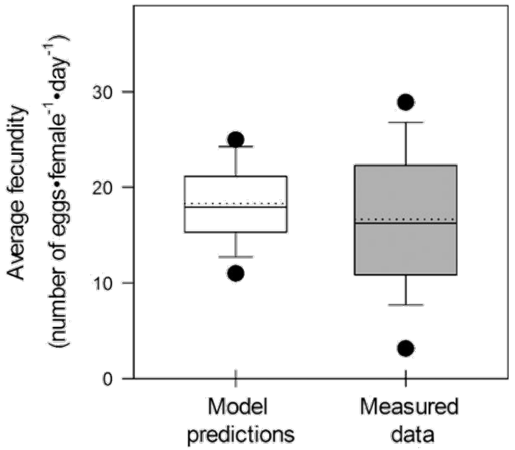
Population level

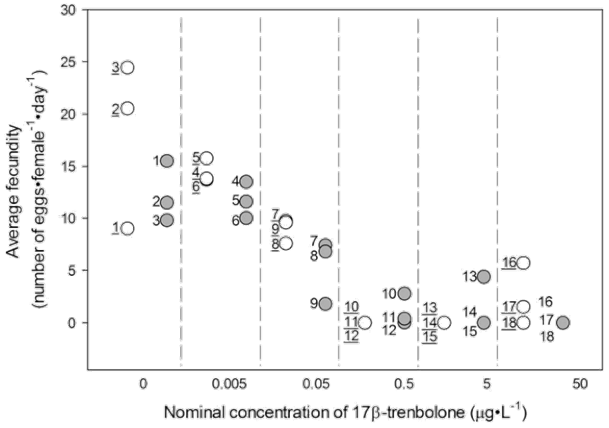
Linking VTG to fish fecundity

- Leverage an existing mathematical model of FHM oogenesis
- Takes (dynamic) VTG concentration as input



Z. Li et al., Can. J. Fish Aquat. Sci. **68**, 1528 (2011).





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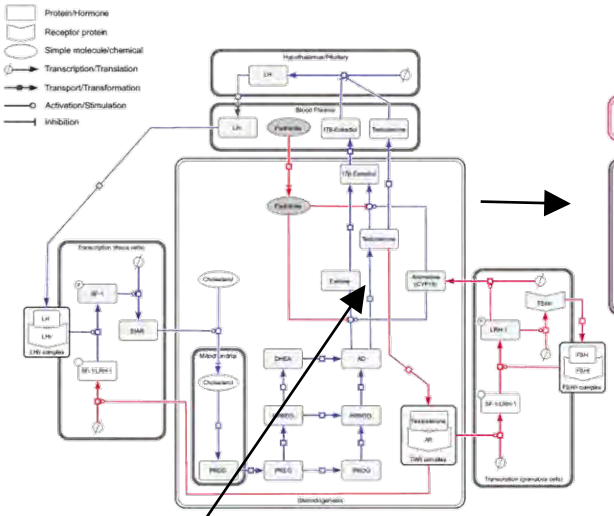
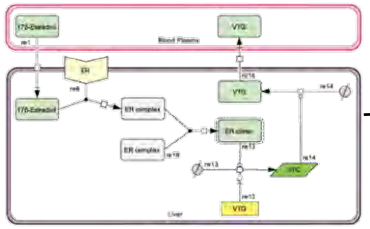
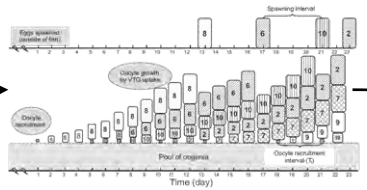
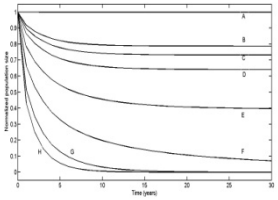




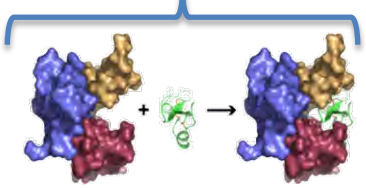
Reduced Vtg production

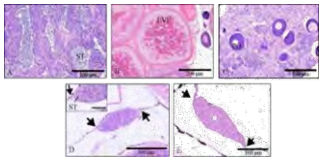


Egg production



Population trajectory





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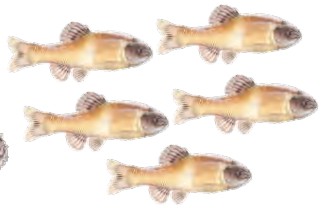
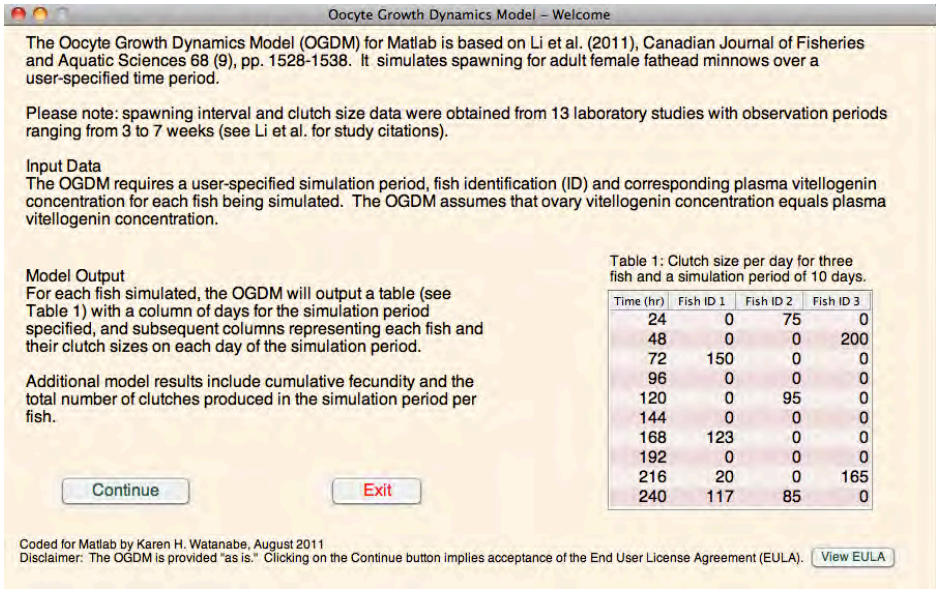


Population level

Continuing work/applications

- Include the effects of other endocrine disrupting compounds
- Design front-end toolkit to carry out "virtual assays" through scenario playing with dynamic exposure conditions
- Use VTG measurements to parameterize model
- Use steroidogenesis/Aromatase inhibition factor to translate in vitro effects to population effects

- Include time dependent exposure
- Permit scenario playing with different effluent exposures to assess impact



- GUI-based software tool in development
  - Directed toward risk & hazard assessors

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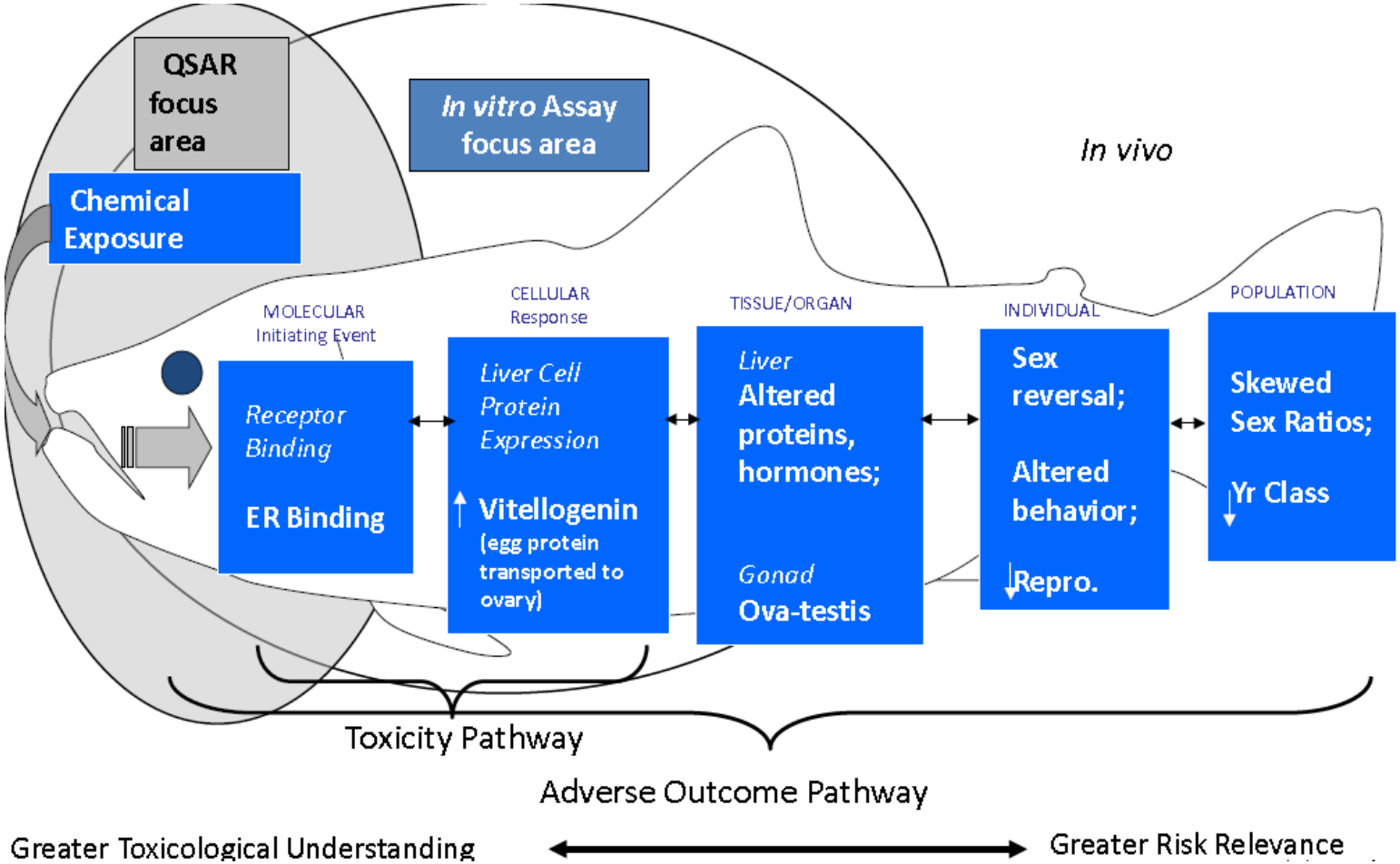
Small Fish Comp-Tox Group

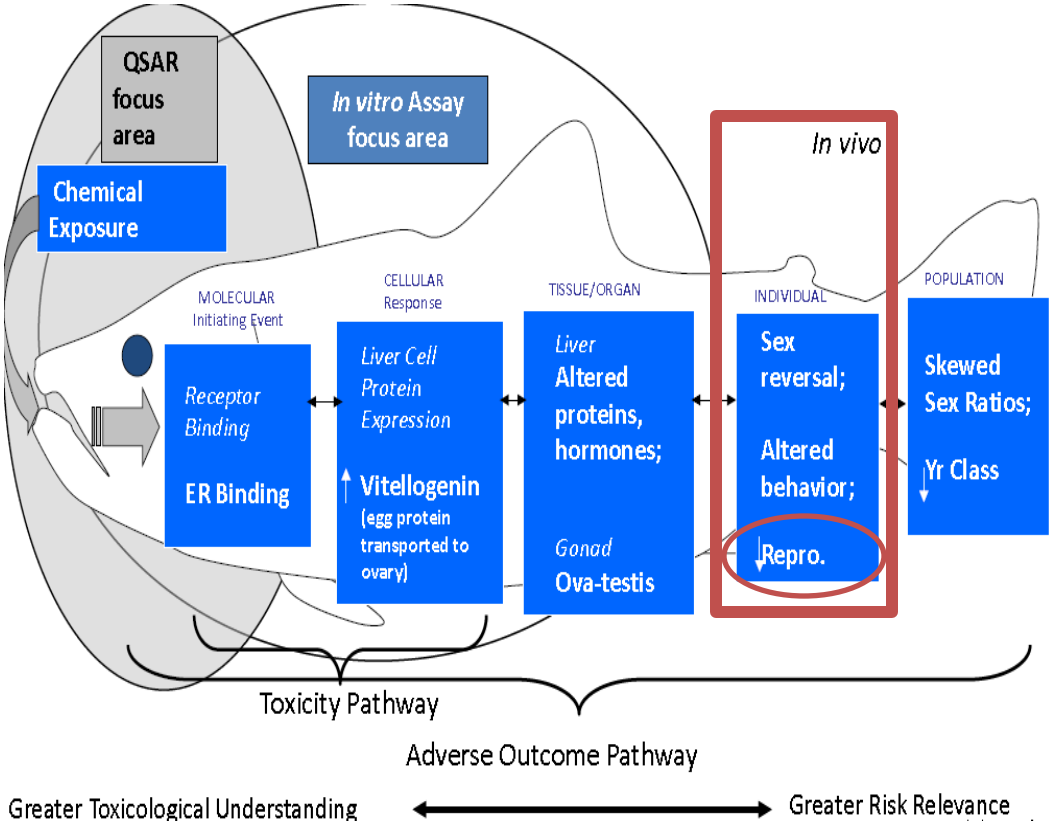
OPP Ecological Risk Assessment Perspective – Fish Reproduction AOP



Source: USEPA 2013 SAP

OPP Ecological Risk Assessment Perspective – Fish Reproduction AOP

- Currently, screening level (apical) endpoints: survival, growth, and **reproduction**
- Small number of fish *in vivo* studies surrogates for all fish species
- Compare most sensitive apical endpoint effect to relevant exposure (quantitative) to evaluate potential risk concerns



OPP Ecological Risk Assessment Perspective – Fish Reproduction AOP

- **Current Utility of AOPs**
  - (Q)SAR and *in vitro* data used to determine whether additional *in vivo* fish toxicity data is needed to support risk assessment
    - Typically for degradates of concern
  - (Q)SAR and *in vitro* data used to determine if bridging fish data across chemicals is appropriate
    - Provides information where a data-gap may exist
  - Provide mechanistic information for weight-of-evidence decisions (*e.g.*, Tier I EDSP battery)
    - *In vitro* assays (*e.g.*, estrogen and androgen receptor binding assays) can provide mechanistic information when evaluating *in vivo* assays including the fish assay
  - Sublethal effects (*e.g.*, clinical toxicity signs including biochemical alterations) can be used to qualitatively characterize risk to fish

OPP Ecological Risk Assessment Perspective – Fish Reproduction AOP

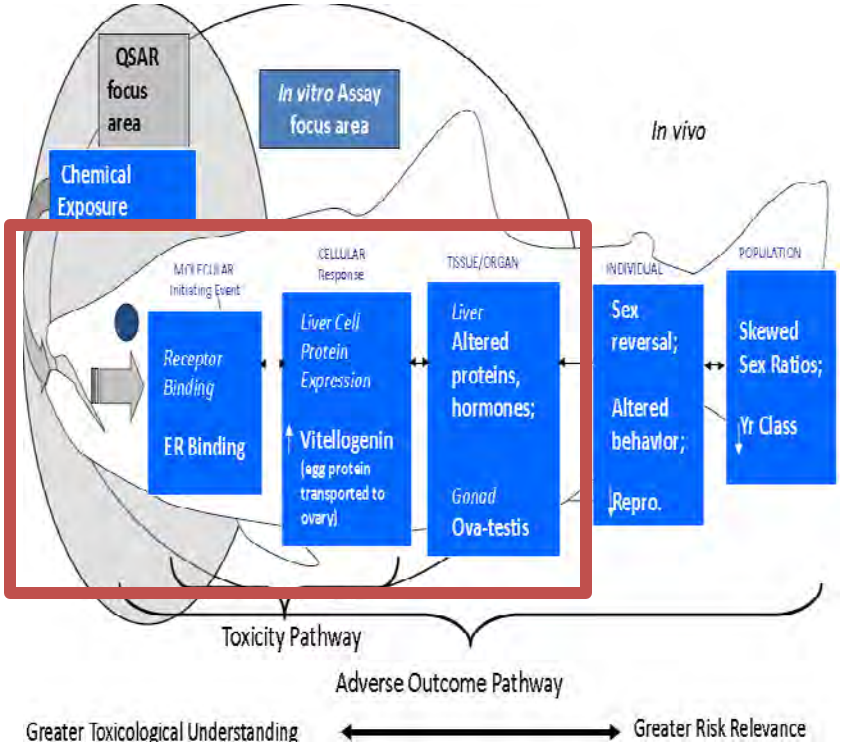
❑Challenges with using AOPs:

❑Quantitative linkages to apical endpoint
- ? Change in Vtg → ↓ Reproduction

❑Accounting for competitive AOPs and/or compensatory mechanisms in whole animals

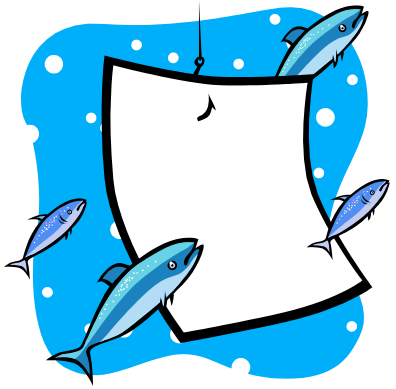
❑Capturing potential adverse effects from a non-defined AOPs
- Reproduction can be affected by many different factors

❑ Uncertainty in if quantitative linkages are reflective for broad range of fish species



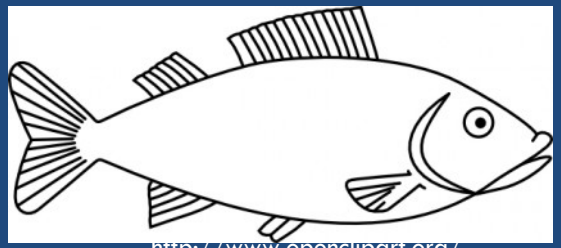
OPP Ecological Risk Assessment Perspective – Fish Reproduction AOP

- **Things to Consider for Risk Assessment**
  - Was the model used to generate data appropriate?
  - Do effects occur at environmentally-relevant concentrations/conditions?
  - Do reproductive effects occur in the presence of potential overt toxicity (e.g., death, erratic swimming, hemorrhaging)?
  - Where are the effects in relationship to other existing toxicity data (dose-response curve and time course)?



OPP Ecological Risk Assessment Perspective – Fish Reproduction AOP

- **Future Development of AOPs that will inform potential effects on fish reproduction**
  - Continue to develop linkages with current AOPs
    - Provide quantifiable measures (linkages) from low to high biological levels of organization (including fecundity)
  - Develop new AOPs
  - Develop network of cumulative impacts from potentially perturbations from multiple AOPs



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Thank You!
Questions?