**APCRA New Case Study Proposal**

1. **Title of Case Study:** Investigating the applicability of bioactivity data to inform quantitative hazard assessments for ecological species using bioactivity-to-exposure ratios (eco-BER)

2. **Lead organization:** Ecological Assessment Division, Environment and Climate Change Canada

3. **Point of Contact:** Cristina Inglis, Unit Head ([ HYPERLINK "mailto:cristina.inglis@canada.ca" ])

4. **Potential Collaborator(s):** Exposure and Biomonitoring Division, Health Canada

5. **Collaborator(s) Point of Contact:** Dr. Andy Nong, Computational Toxicologist ([ HYPERLINK "mailto:andy.nong@canada.ca" ])

6. **Problem to be addressed by case study:**
   Quantitative consideration of *in vitro* bioactivity data in ecological risk assessments is often limited. This is due, in part, to uncertainty with conducting and interpreting *in vitro*-to-*in vivo* extrapolations (IVIVE) for species of ecological interest, such as fish.

   Recently there has been progress toward understanding how *in vitro* bioactivity can inform human health point-of-departure (POD) evaluations (see APCRA case study titled: Examining the utility of *in vitro* bioactivity as a conservative POD). The present ecological case-study proposal will compliment that knowledge by providing baseline information to support application of IVIVE for consideration in ecological risk assessment or prioritization initiatives.

7. **Aim/Purpose of case study:**
   The purpose of this case study is to inform how *in vitro* bioactivity data could be leveraged as a quantitative line of evidence to estimate maximum acceptable toxicant concentrations (MATCs)[1] and to evaluate how those compare to MATCs derived from traditional aquatic toxicity studies.

   Environment and Climate Change Canada (ECCC) has started a preliminary investigation to support development of the case study, which focuses on five chemicals, and select RTK models (see details below). The results (currently in development) are targeted for communication at the APCRA meeting to support discussions with interested collaborators, including whether/how to expand the chemical space and/or modeling options for this case study.

8. **Main Steps/General Timeframe:**

   - Identify a set of chemicals with both *in vitro* bioactivity data and chronic fish ecotoxicity data
     - For each chemical, extract relevant data: chronic fish endpoints (NOEC/LOEC), bioactivity $AC_{50}$ values, and phys-chem data (MW, MP, Kow, WS, Km)

[1] The **maximum acceptable toxicant concentration** (MATC) is the geometric mean between the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC) results of a chronic aquatic toxicity test

- ECCC has identified and extracted data for a preliminary set of 5 substances: 4-nonylphenol, atrazine, lindane, dibutyl phthalate and 1,3 dichlorobenzene

- Select *in vitro* partitioning models to estimate true cellular exposures
  - For each *in vitro* assay of interest, gather assay meta data necessary to run the models (plate and well sizes, media volume and protein content, etc.)
  - ECCC is currently examining the Armitage *et al.* (2014) partitioning model to obtain estimated cellular exposures
    - Preliminary results show that cellular concentrations can be enriched by 22 to 570 times the nominal bioactivity concentration ($AC_{50}$ values). Two variables appear to influence the distribution of a chemical within an *in vitro* test system: a) assay design parameters, such as number of cells per well, medium volume, and percent fetal bovine serum; and b) chemical properties, such as lipophilicity.

- Select fish RTK models to estimate *in situ* exposure equivalents from bioactivity data
  - ECCC is currently examining the zebrafish and fathead minnow RTK models described in Rowland *et al.* (2017)
    - Health Canada collaborator, Dr. Andy Nong, currently reviewing RTK model inputs and outputs

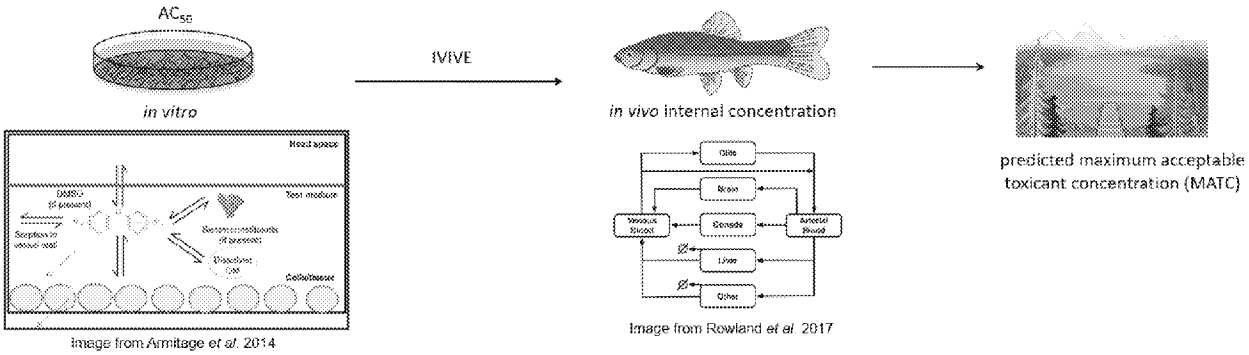
- Compare the *in situ* exposure concentrations predicted from RTK models with traditional effect values to determine if bioactivity data can provide a conservative estimate of hazard potential

- Consider use of bioactivity data in an ecological bioactivity-to-exposure ratio (eco-BER) approach for chemical prioritization and/or as a line of evidence in ecological screening assessments of chemicals

- Develop a tool, based on pragmatic input parameters, for regulators to use where bioactivity data exists for chemical(s) of interest

9. **Expected Impact of Case Study:** This case study will advance the consideration of *in vitro* bioactivity data as a quantitative line of evidence for ecological prioritization and risk assessment of chemicals. The case study may establish a method to conservatively translate *in vitro* bioactivity data into predicted MATCs for species of ecological interest in screening level ecological risk assessments. In addition, it may be useful to consider in a bioactivity-to-exposure ratio approach for chemical prioritization, where the magnitude of the ratio may provide an indication of the level of concern with a particular chemical or set of chemicals, which may be valuable for chemical prioritization.

# Summary




References:


Armitage *et al.* 2014. Application of mass balance models and the chemical activity concept to facilitate the use of *in vitro* toxicity data for risk assessment. *Environ Sci Technol* 48(16):9770-9779.

Rowland *et al.* 2017. Physiological fidelity or model parsimony? The relative performance of reverse-toxicokinetic modeling approaches. *BMC Syst Biol* 11:35.