# Translating from Case Studies to Implementation of NAMs for Chemicals Management Modernization in Canada

*APCRA Public Webinar, March 11, 2020*

*Current status of application and integration of NAMs in regulatory decision-making*

Source: Al-Koshi Cleaning Chemicals

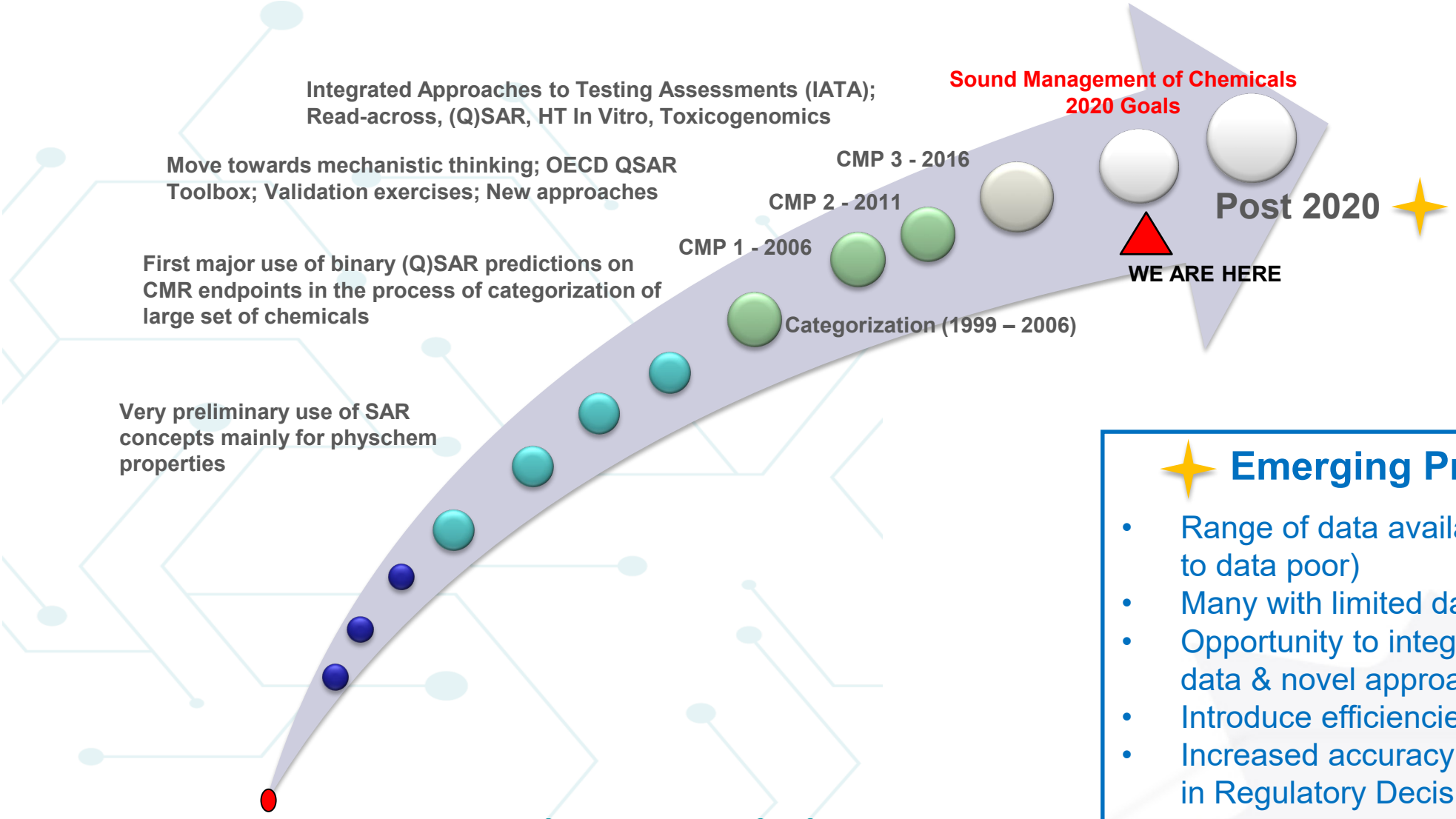
***Tara Barton-Maclaren,*** *PhD, Research Manager, Existing Substances Risk Assessment, HC*

Canada

# Outline

- Evolution of risk assessment under the Chemical Management Plan (CMP)
  - Science Approach Documents
- Translating Case Study Findings into Application
  - Focus on Bioactivity Exposure Ratio (BER) approach
  - Workflow development and implementation under the CMP
- Exploratory work to address data gaps to facilitate broader application for the Canadian Domestic Substances List (DSL)
  - High Throughput Toxicokinetics (HTTK) data
  - Lack of intersection between the DSL and ToxCast database
  - Prioritization of genotoxic chemicals

# Evolution in Risk Assessment Modernization (CMP)




## Emerging Priorities

- Range of data availability (data rich to data poor)
- Many with limited data sets
- Opportunity to integrate emerging data & novel approaches
- Introduce efficiencies
- Increased accuracy and confidence in Regulatory Decision Making

# Science Approach Documents Under the CMP

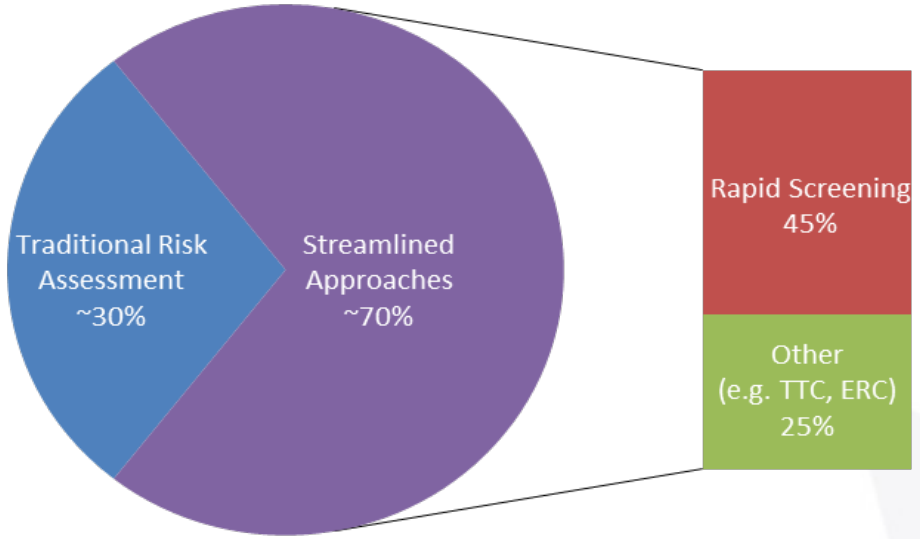
- A Science Approach Document (SciAD) describes a novel approach to evaluate the environmental or human health risk of substances
- A SciAD does not include any regulatory conclusions but rather demonstrates the approach which can be used in future assessments or prioritization exercises
- Published SciADs:
  - Threshold of toxicological concern (TTC)-based approach for certain substances
  - Ecological Risk Classification (ERC) Approach
  - Biomonitoring-based approach 1 for beryllium, vanadium, trichlorooxo and vanadium oxide
  - Biomonitoring-based approach 2 for barium-containing substances, molybdenum-containing substances, silver-containing substances, thallium-containing substances and inorganic tin-containing substances
  - Substances with low human health hazard potential
- In progress SciAD:
  - Bioactivity Exposure Ratio Approach for Prioritization


Published SciADs: https://www.canada.ca/en/health-canada/services/chemical-substances/science-approach-documents.html

https://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=A96E2E98-1

# Science Approach Documents Under the CMP

- Streamlined assessment approaches and science approach documents were critical for meeting commitment to assess all priorities within the CMP timelines
- Supports the development and application of novel risk assessment approaches and the use of emerging science
- All approaches are externally peer reviewed and also open for public comment
- Allow for early feedback, enhanced engagement and stakeholder support
- Assist in identifying substances of higher priority for further action and/or addressing substances that may be of low concern to either human health or the environment in a more effective manner




* Accounts for, at minimum, one department utilizing a streamlined approach
** For both departments utilizing a streamlined approach on the same set of substances, proportion is ~ 50 % streamlined approaches vs. ~ 50 % traditional risk assessments

# Translating Case Study Findings into Applications

Case Study

Approach

*IN PROGRESS*

Practice

- Hazard ID
- Risk-Based Priority Setting
- Problem Formulation
- Risk Assessment

Toxicological Sciences

**Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization**

Katie Paul Friedman, Matthew Gagne, Lit-Hsin Loo, Panagiotis Karamertzanis, Tatiana Netzeva, Tomasz Sobanski, Jill Franzosa, Ann Richard, Ryan Lougee, Andrea Gissi, Jia-Ying Joey Lee, Michelle Angrish, Jean-Lou Dorne, Stiven Foster, Kathleen Raffaele, Tina Bahadori, Maureen Gwinn, Jason Lambert, Maurice Whelan, Mike Rasenberg, Tara Barton-Maclaren, Russell S Thomas ✉

*Toxicological Sciences*, kfz201, https://doi.org/10.1093/toxsci/kfz201

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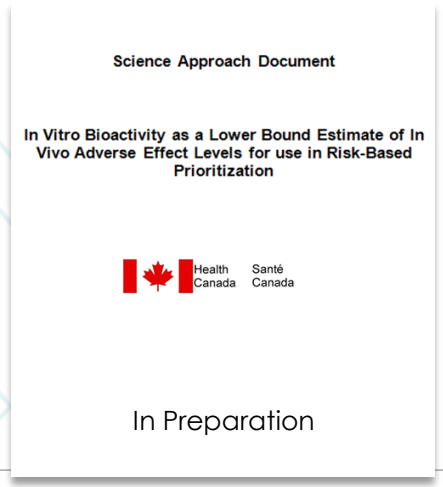
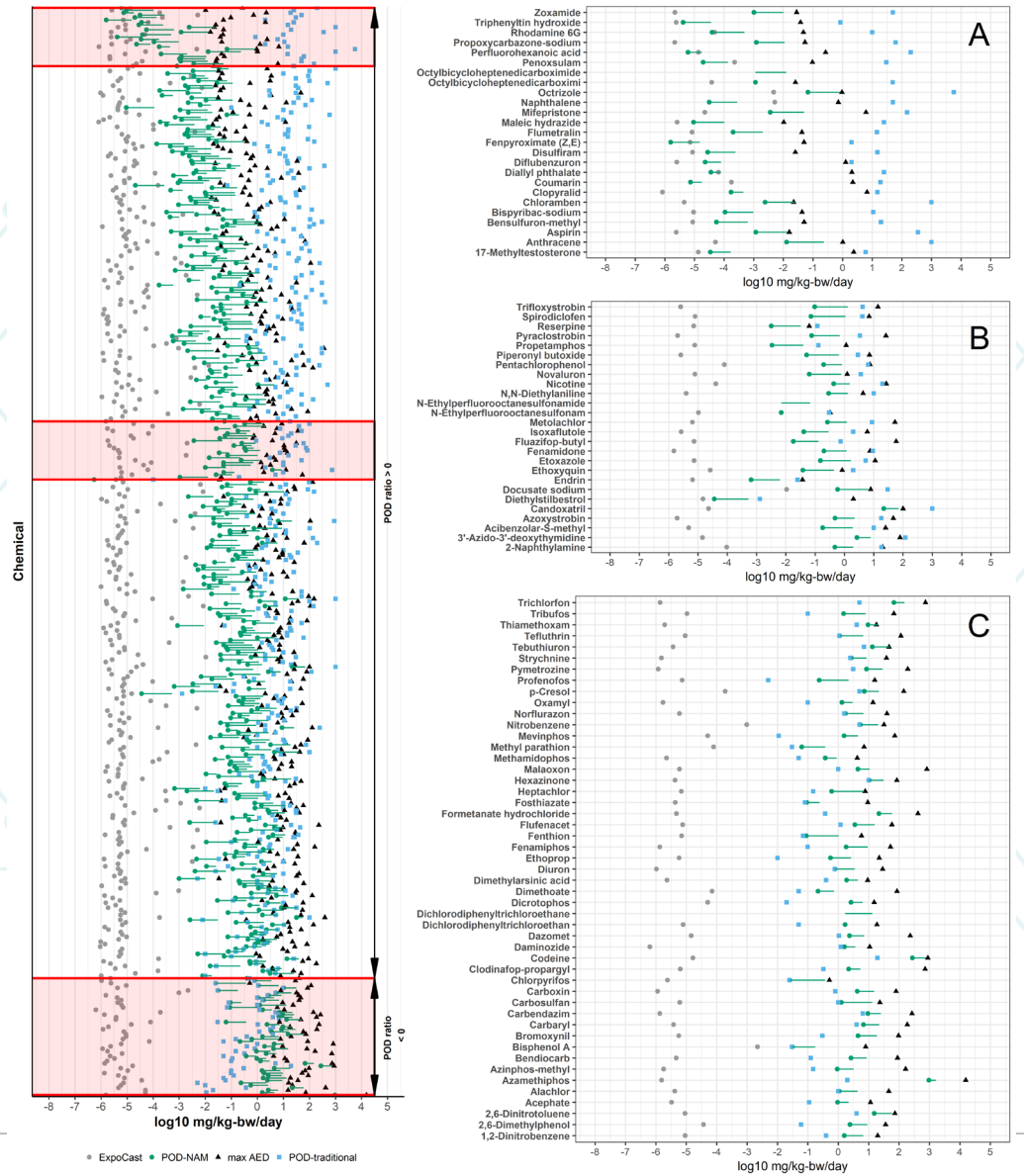



# APCRA BER Retrospective Case Study




- Of the 448 substances, 90% had a $POD_{Bioactivity}$ that was less than the $POD_{Traditional}$ value with a median $log_{10}POD$ ratio of 2 (100-fold).
- The range of $log_{10}POD$ ratios found was -2.7 to 7.5.
- The bioactivity POD served as a protective metric relative to traditional toxicological endpoints

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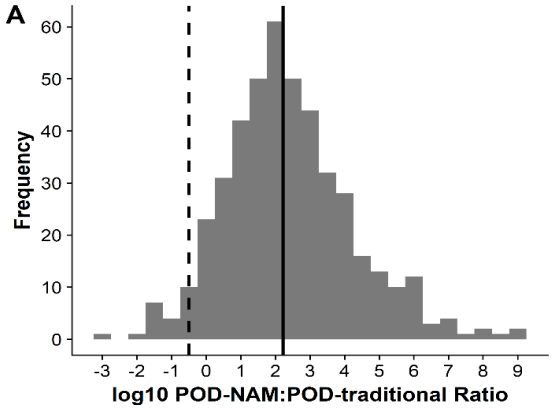



**This collaborative effort significantly informs the methods and provides the foundation for the approach presented in the Health Canada SciAD**

# Overview of key elements in Health Canada SciAD

**APCRA Workflow**

Step 1: Extract ToxCast $AC_{50}$ distribution from active assays (µM)

Step 2: Apply assay filtering criteria

Step 3: Calculate 5th percentile of $AC_{50}$ distribution "bioactivity threshold"

Step 4: Apply high-throughput toxicokinetic (HTTK) modelling to get administered equivalent dose (AED) (mg/kg-bw/day)

$POD_{Bioactivity}$

Compare

**Health Canada Published Risk Assessments**

CMP Assessments (N=46)

Extract NO(A)ELs and LO(A)ELs

Label PODs:
- Minimum
- Risk characterization
- Effect Type
  - systemic
  - developmental
  - reproductive

$POD_{Traditional}$

Extract Exposure Estimates

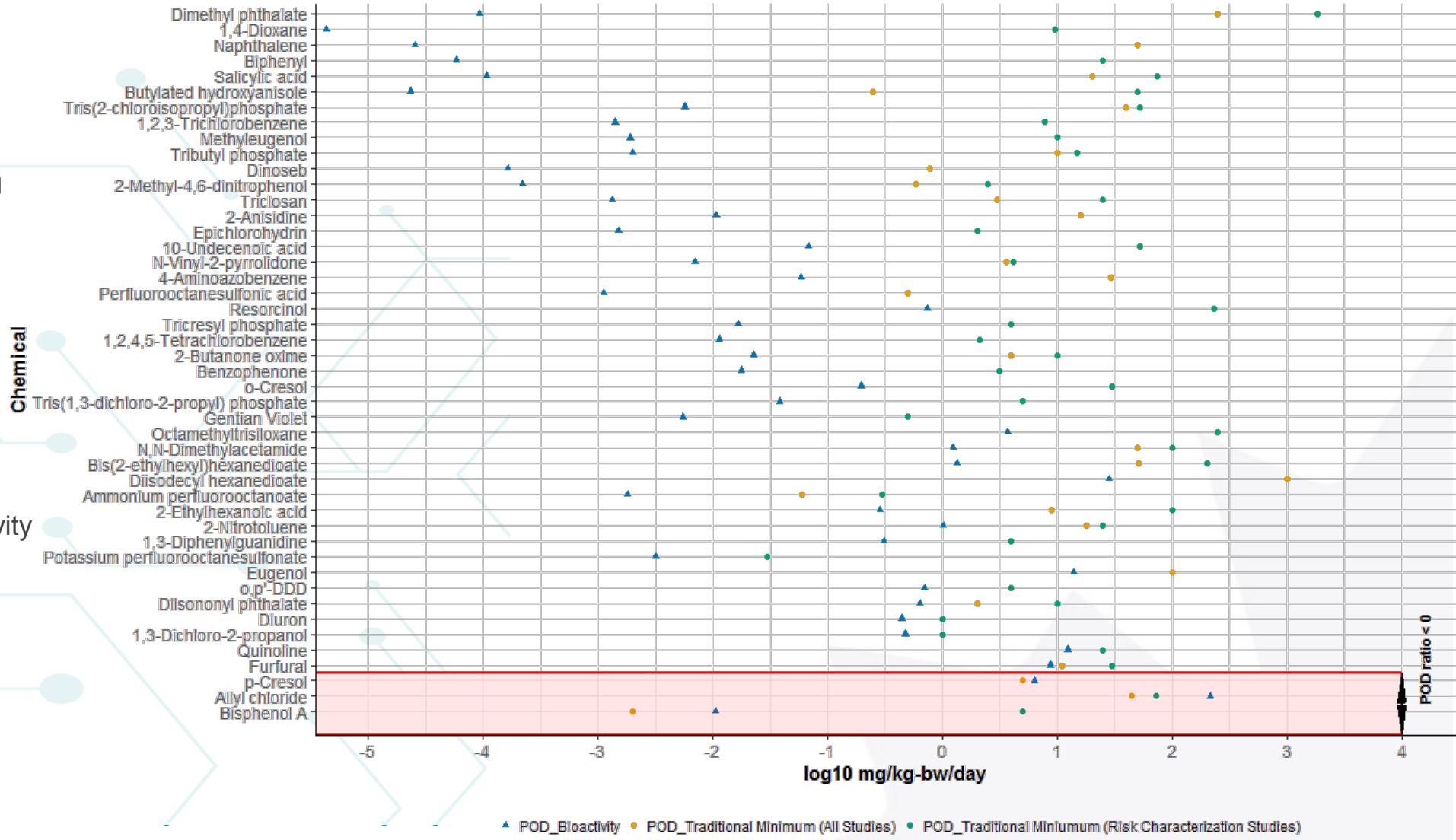
Calculate BER

Propose Default Uncertainties Factors

Triggers for Prioritization

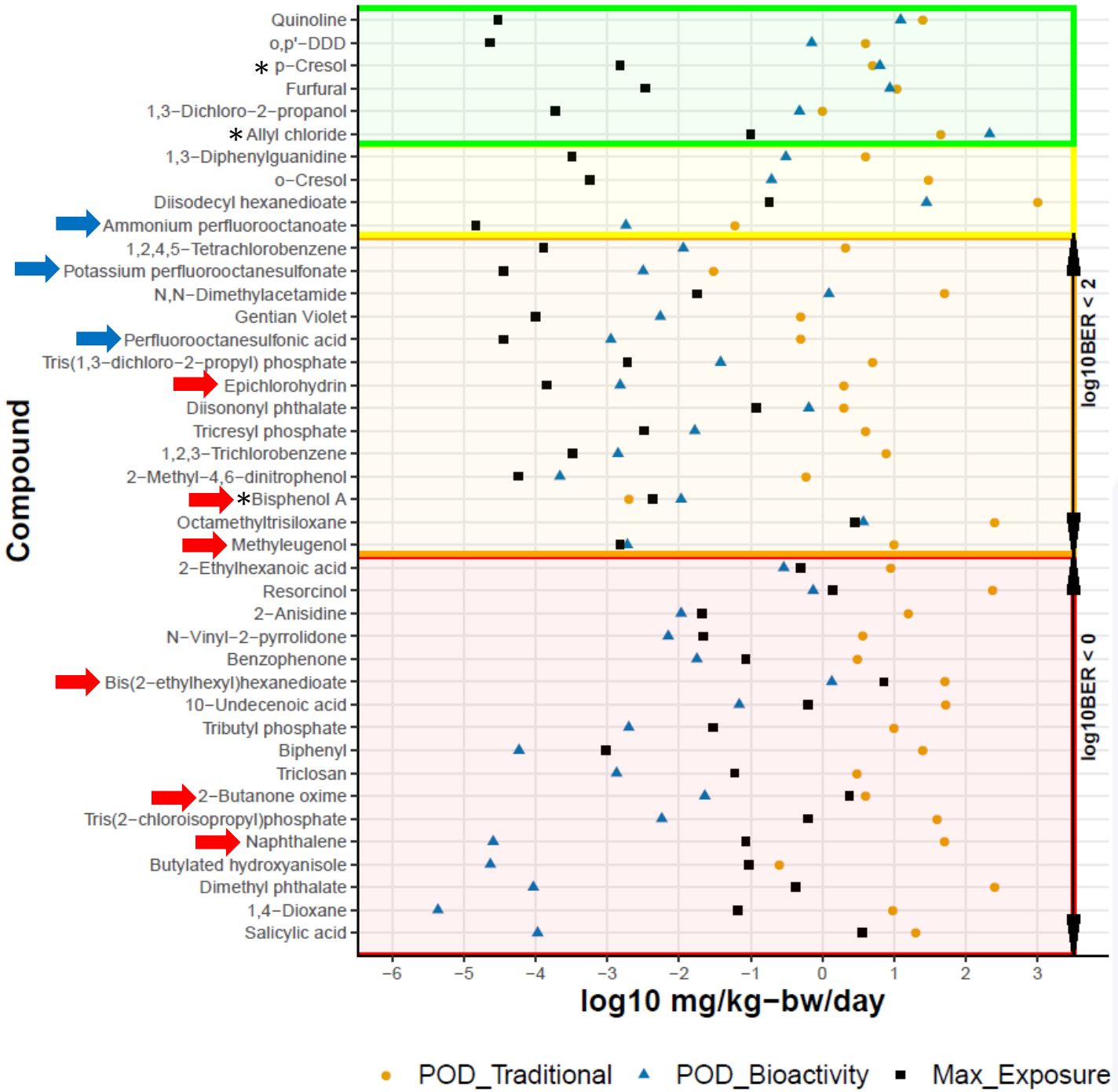
# $POD_{Bioactivity}$ is Protective of $POD_{Traditional}$ (minimum and risk characterization)

- $POD_{Bioactivity}$ < $POD_{Traditional}$ for 43/46 chemicals (45/46 when compared to risk characterization POD)
- On average, $POD_{Bioactivity}$ is 100-fold lower than $POD_{Traditional}$ on arithmetic scale



# BERs Based on CMP Estimates of Exposure

- $POD_{Bioactivity}$ was compared against maximum exposure value based on consumer products, environmental media, and biomonitoring data
- log10BER < 2 (equivalent to MOE of 100) were considered as priorities
- All six non-genotoxic compounds considered toxic to human health under CEPA section 64(c) were identified as compounds of concern using this approach (red arrows)
- Substances considered ecotoxic under CEPA section 64(a) (blue arrows)

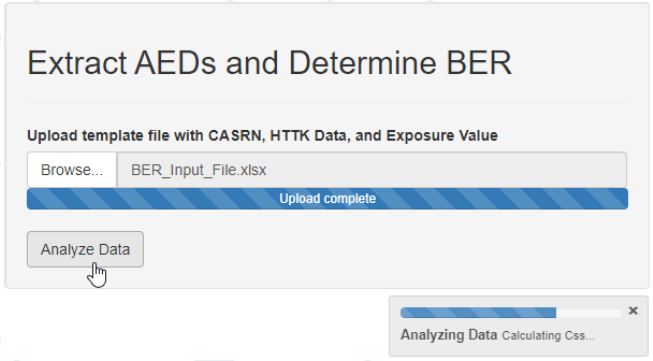


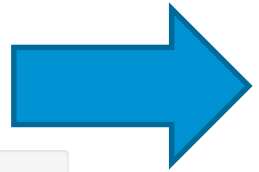
# Implementation of Workflow at Health Canada

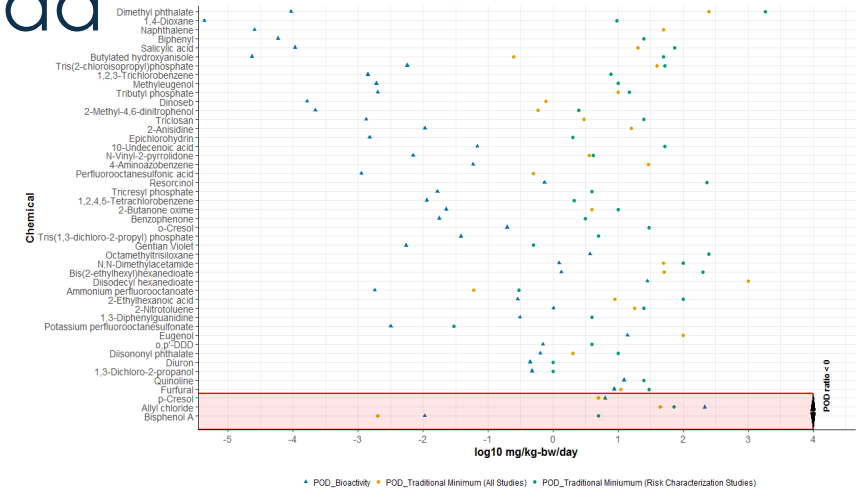
1)CASRN
2)HTTK Data
3)Exposure Estimate

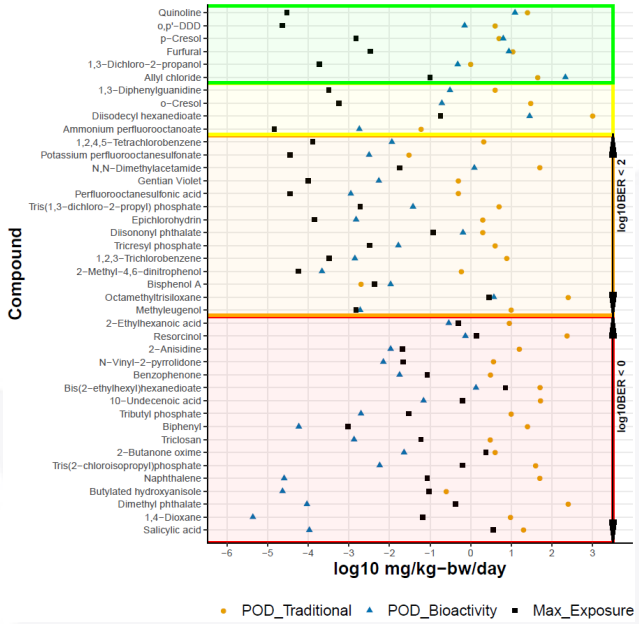
OR

Shiny
by RStudio



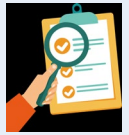






Both make use of ToxCast invitro_db (MySQL), tcpl (R package) and httk (R package)

# Uncertainties and Variabilities Characterized

| Type | Factor | Rationale |
|---|---|---|
| Deriving $POD_{Bioactivity}$ ($UF_{Bioactivity}$) |  | Incomplete biological space covered by assays in ToxCast. Uncertainties associated with the three compartment model to estimate $C_{ss}$ using in vitro toxicokinetic parameters. |
| Immortalized Monocultures and Culture Conditions ($UF_{Cells}$) |  | Considers effects of using monocultures and immortalized cell lines, as well as culture conditions, on endpoint measurements. Limitations of single cell type as a surrogate for systemic effects as well as limited metabolic competence. |
| Inter-individual (human) variability ($UF_{Human}$) |  | Inter-individual variability related to toxicodynamics and toxicokinetics. Note this is already partially accounted for in the HTTK model. |
| TOTAL | | |

## Key Findings

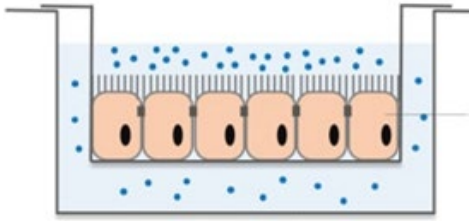
- CMP specific analysis provides further evidence that using a $POD_{Bioactivity}$ would be equal to or more protective than using a $POD_{Traditional}$ when used for prioritization decisions in the majority of cases
- Steps can be taken to account for substances where the $POD_{Bioactivity}$ may not be protective
  - exclusion of certain chemical classes (i.e. organophosphates or carbamates)
  - application of certain uncertainty factors when using the approach

## Implementation

- Science Approach Document on utility in CEPA specific context in preparation
- Proposing that the BER approach be applied to “bin” substances for consideration in priority setting as the program continues to evolve beyond 2020
- Anticipate that the approach will be conducted using an “evergreen” philosophy
  - As further *in vitro* and high content assays advance, these technologies and the data generated will be considered as available for the ongoing evolution of the approach and screening of substances

# Ongoing Work to Address Needs for NAM Application in the Program

# HTTK Research supporting Health Canada Workflow



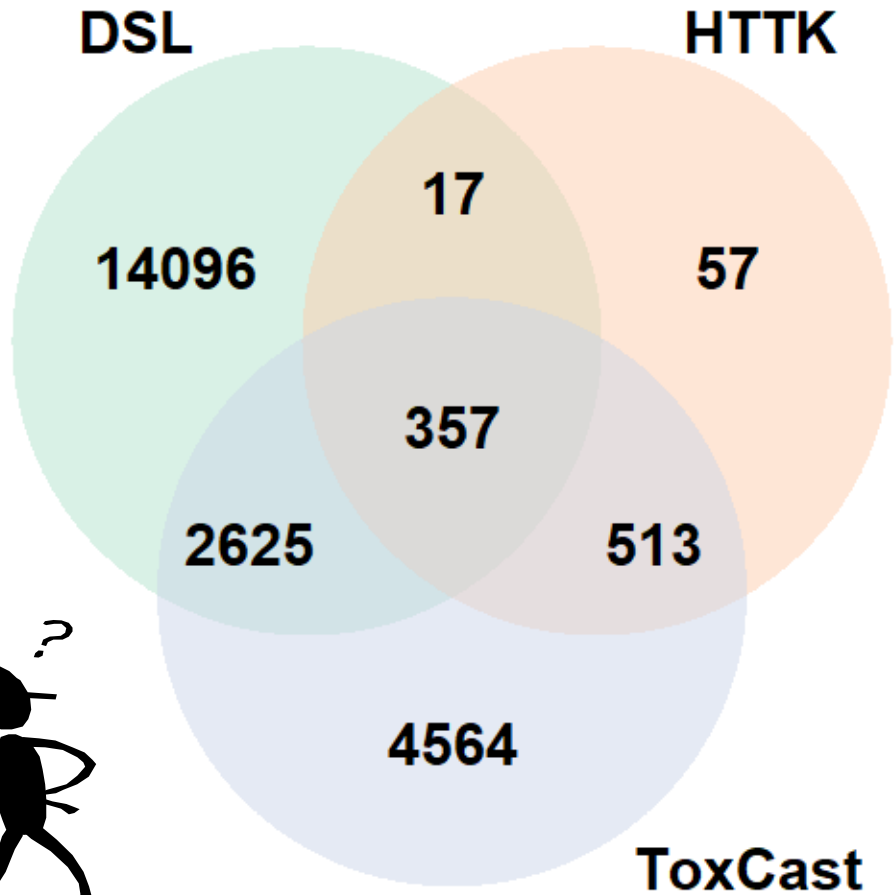
1. Generating new *in vitro* TK data for extrapolation of chemicals and supplement current HTTK
   - 5 Cycles & 250 chemicals total
2. Explore unique TK properties not found in HTTK with 2D/3D cells
   - Transporters with PFAS and hepatic Phase 2 metabolism
3. Develop complex TK models and compare *in vitro* vs *in silico* modeling results
   - PFAS & Bisphenols analogues

Courtesy of Dr. Andy Nong, EHSRB, Health Canada

# Data Gaps Need to be Addressed for Broader Application

- Only 357 DSL compounds have HTTK and ToxCast data available

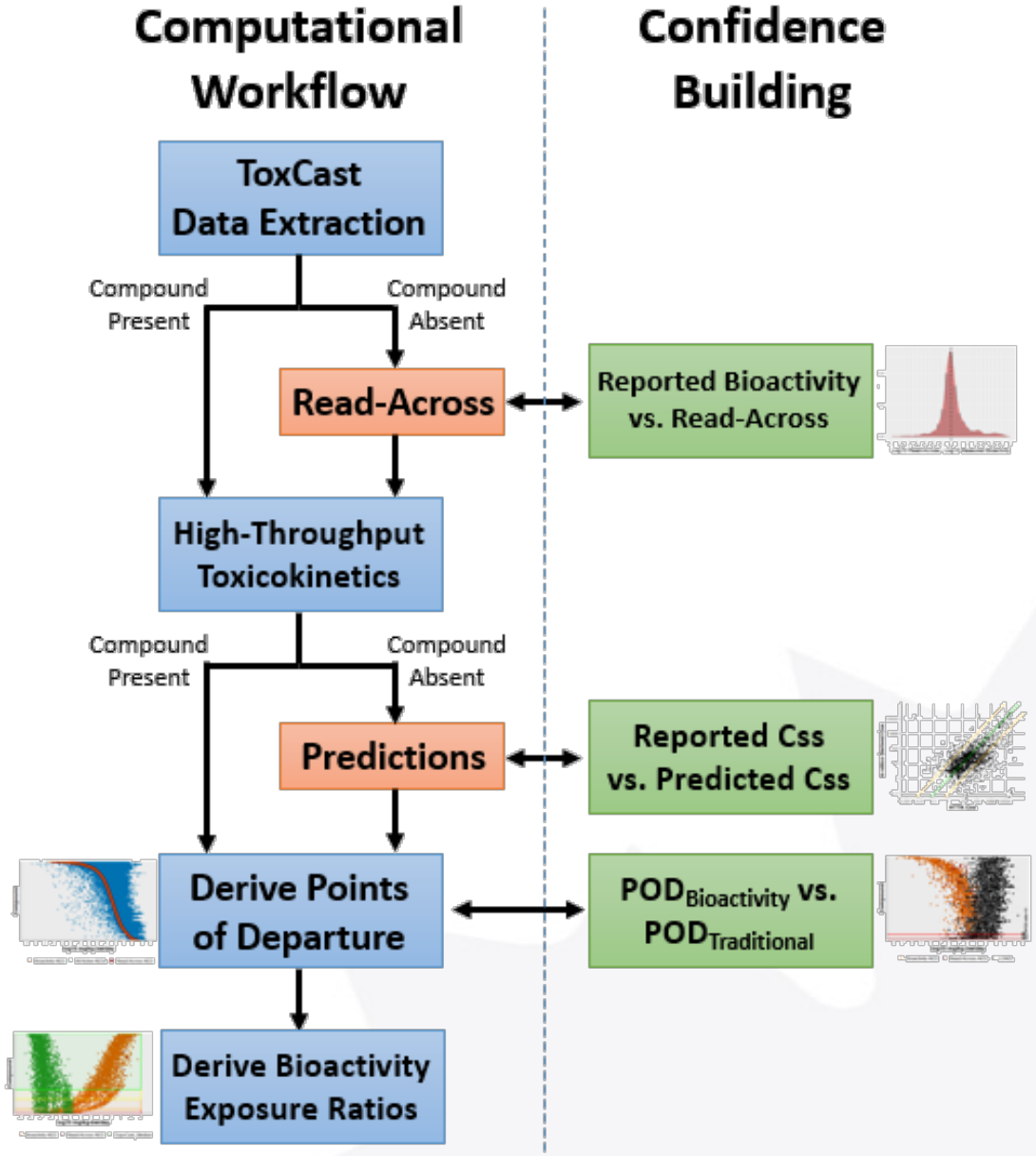
- Two Key Data Gaps to address in order to apply the BER to the DSL:
  1) Lack of intersection between DSL compounds and the current ToxCast database
  2) Lack of HTTK data



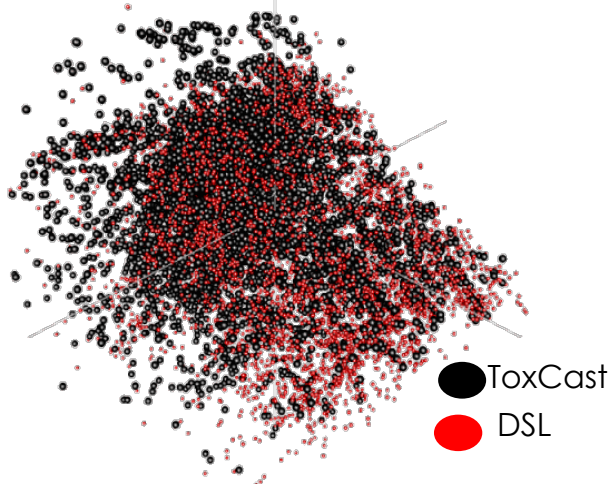

# Data Gaps May be Addressed for Thousands of Compounds Using Computational Workflow

1) The lack of DSL and ToxCast intersection (>6000)
   - Exploring read-across to address bioactivity data gaps as early tier screening tool
   - Developing Machine Learning algorithm to predict bioactivity for compounds based on their chemical structural features

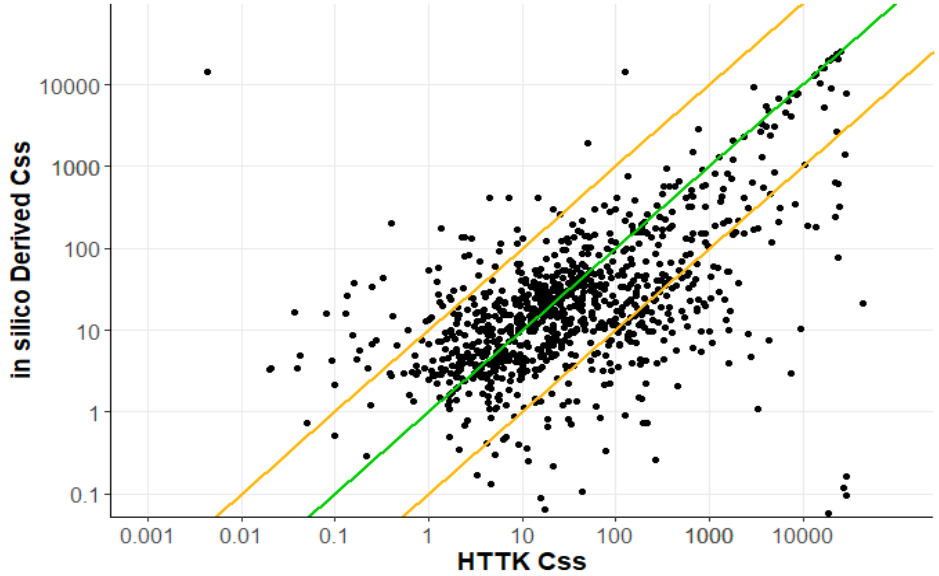
2) Lack of HTTK data (>2000)
   - HTTK data (intrinsic clearance, fraction unbound in plasma protein) not available for many compounds
   - May be addressed by *in silico* predictions (e.g. ADMET Predictor in GastroPlus) of parameters for use in httk R package



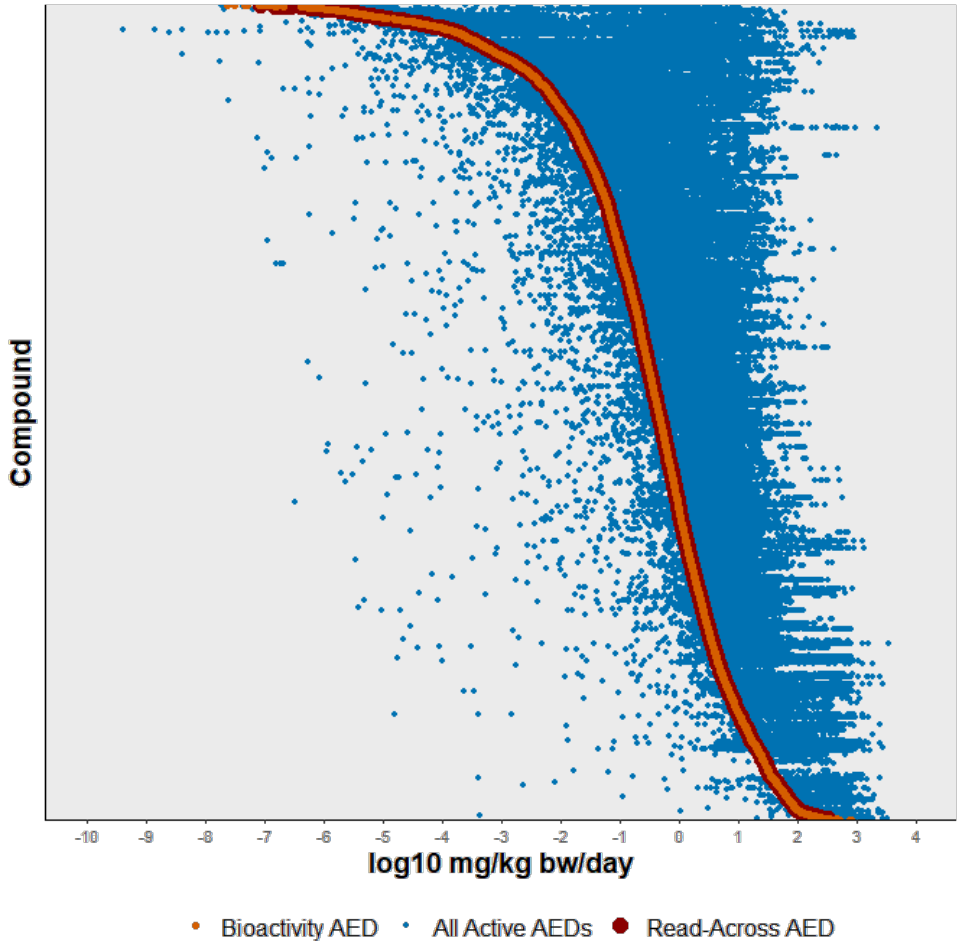
# Addressing Gaps Allows Quantitative Screening for Thousands of DSL Chemicals




Strong chemical space overlap indicating read-across of bioactivity may be a possibility




96% *in silico* derived $C_{ss}$ are within 100-fold of *in vitro* derived $C_{ss}$




- Hazard predictions can be compared to exposure estimates to explore broader application to support rapid risk-based prioritization decisions

# Addressing Genotoxicity

- The BER SciAD does not determine the genotoxic potential of a chemical which is also an important consideration during prioritization

- A complementary approach to screen for potential genotoxic carcinogens is under development and incorporates additional high(er) throughput *in vitro* genotoxicity assays

- Combining computational *in vitro* to *in vivo* extrapolation (IVIVE) approaches with high(er)-throughput, high content data may yield a powerful tool for quantitative genotoxicity assessment

- A New APCRA Case Study Proposal at APCRA4 (October 2019) - A NAM-Based Integrated Approach for Screening Potential Genotoxic Chemicals – Health Canada

# Under development – The GeneTox21 platform

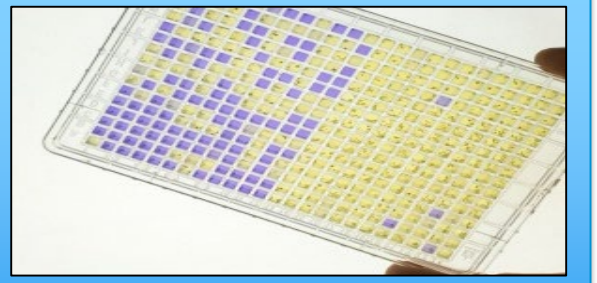

Mutagenicity

Chromosomal damage

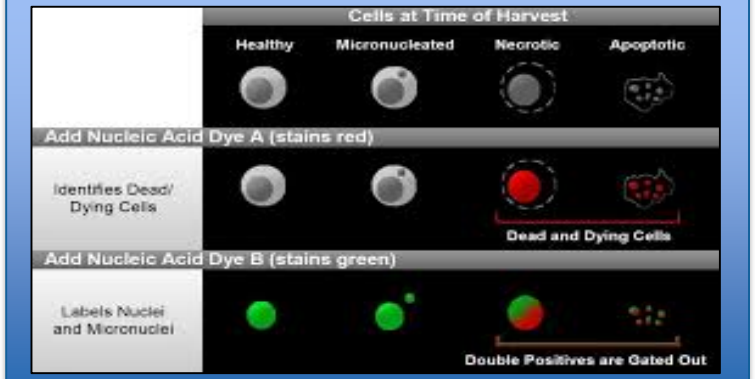
DNA strand breaks

Novel DNA damage assay

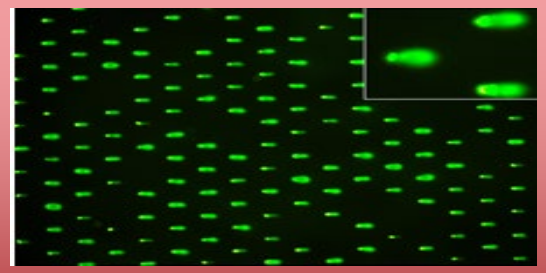
*In vitro* TGR (transgenic rodent)



Ames II




MicroFlow®



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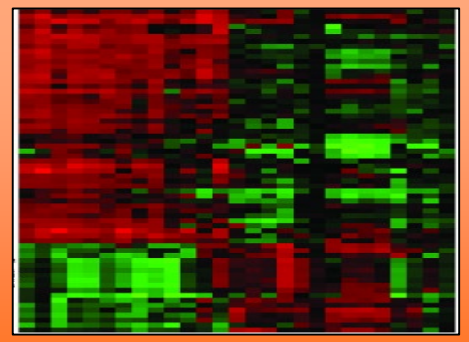

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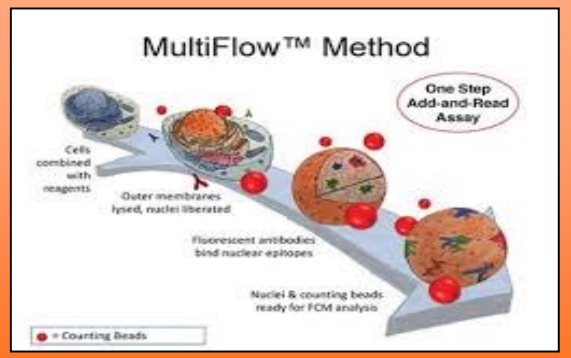
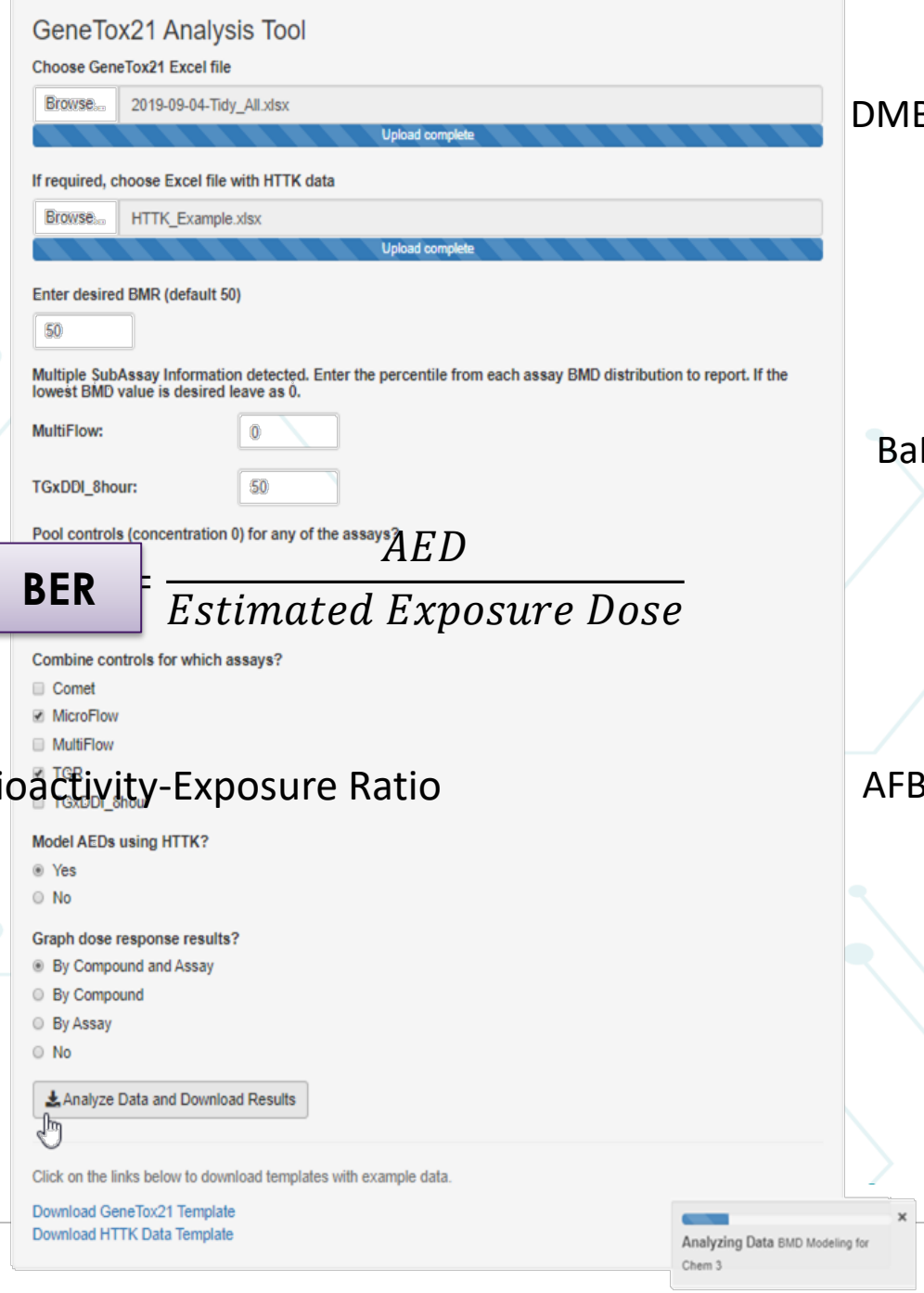



MultiFlow™

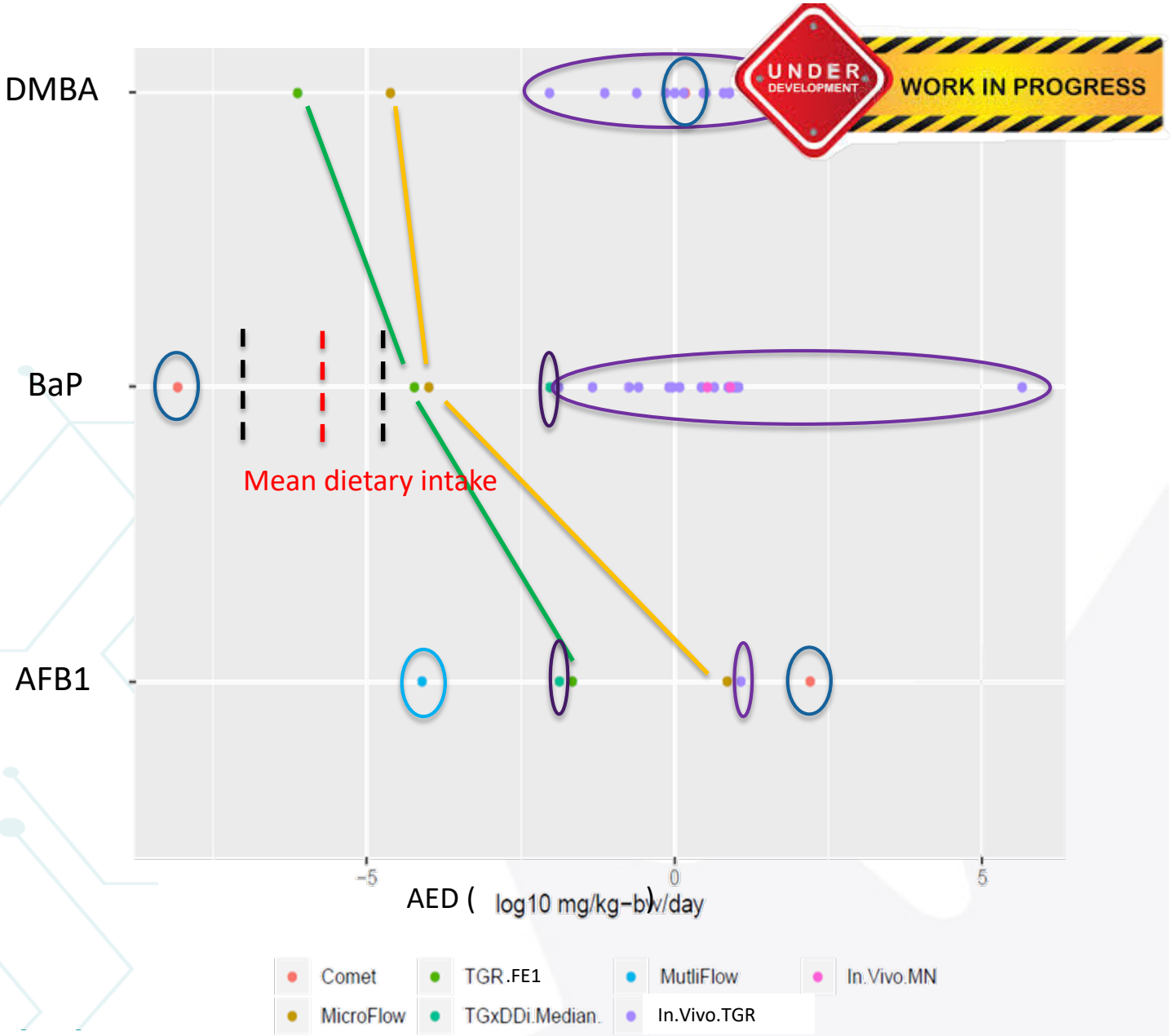
Courtesy of Drs. Julie Cox, Alexandra Long, and Paul White

Preliminary Vision & Exploration




**BER** $= \frac{AED}{Estimated\ Exposure\ Dose}$

Bioactivity-Exposure Ratio



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- Julie Cox
- Alexandra Long
- Paul White

Agency for Science, Technology and Research SINGAPORE

ECHA EUROPEAN CHEMICALS AGENCY

efsa European Food Safety Authority

JRC EUROPEAN COMMISSION

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

- Katie Paul Friedman
- Russell Thomas
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# Questions?