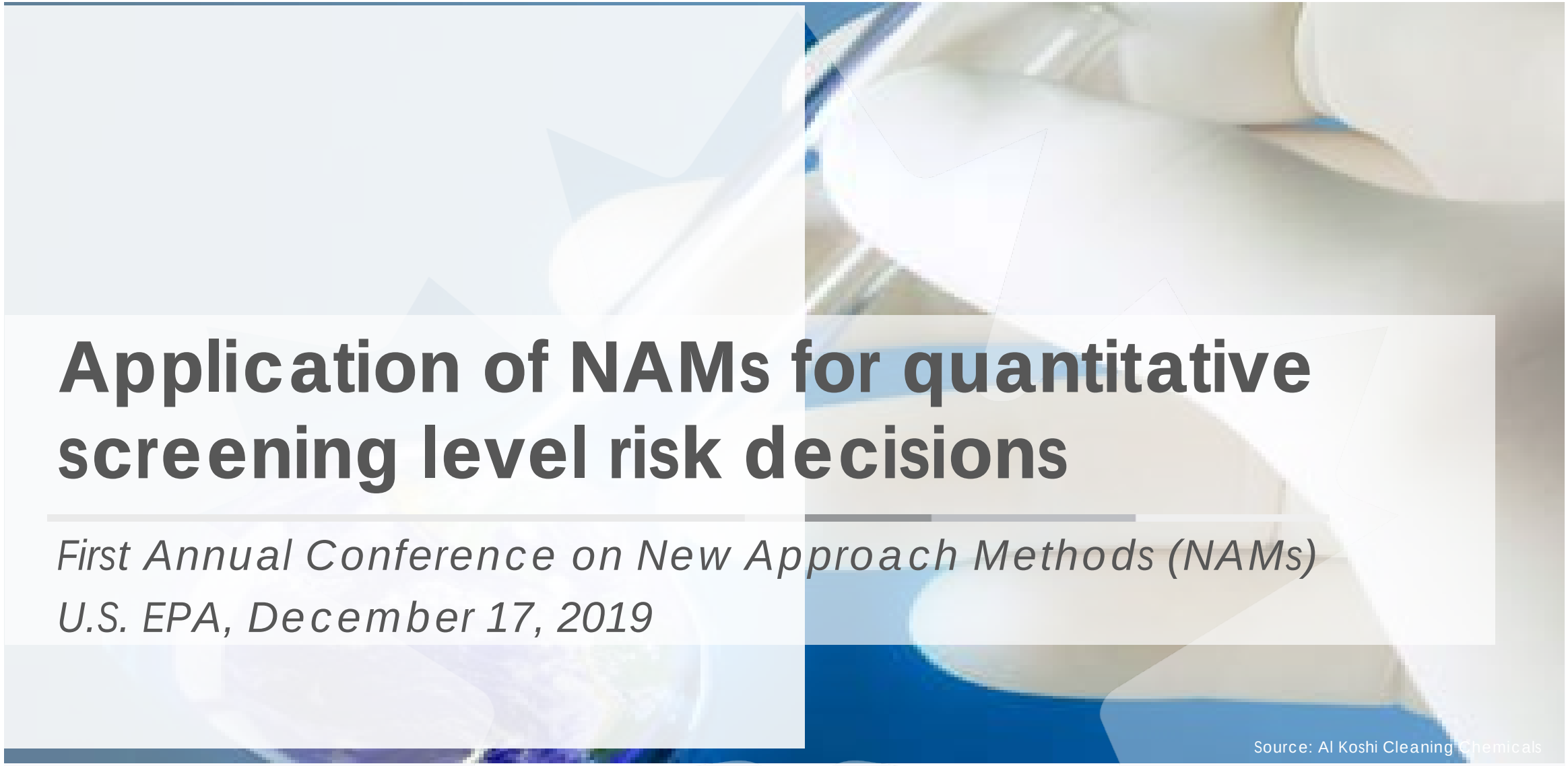
# Application of NAMs for quantitative screening level risk decisions

*First Annual Conference on New Approach Methods (NAMs)*

*U.S. EPA, December 17, 2019*



Source: Al Koshi Cleaning Chemicals

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

# Outline

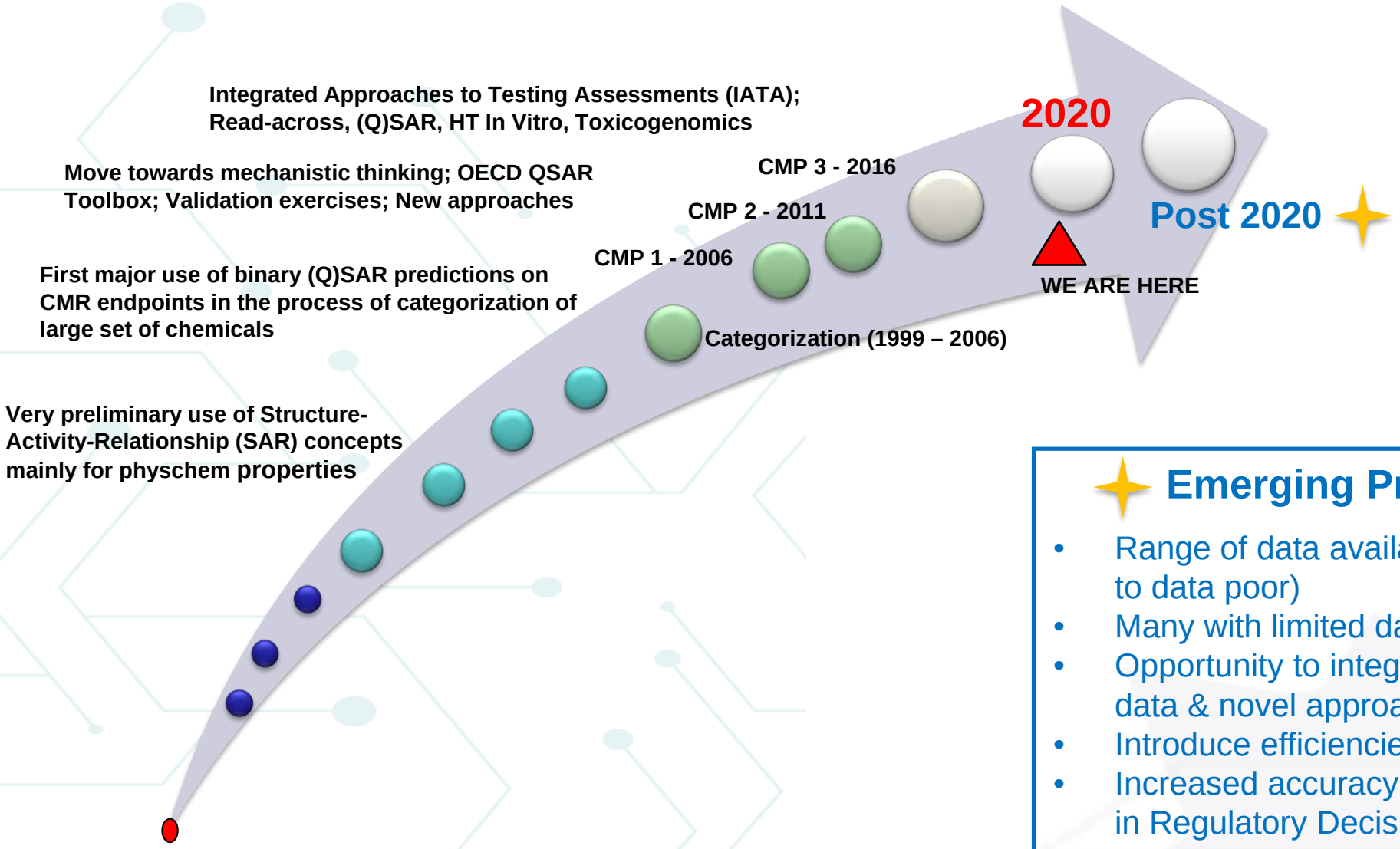
- Evolution of risk assessment under Canada's Chemicals Management Plan
  - Science Approach Documents
  - Risk Assessment Toolbox

- Translating case study findings into application
  - Focus on Bioactivity Exposure Ratio (BER) workflow development and implementation under the CMP

- Exploratory work to address data gaps

- Confidence building and broader application of NAMs within Health Canada framework

# Evolution in Using New Approaches(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

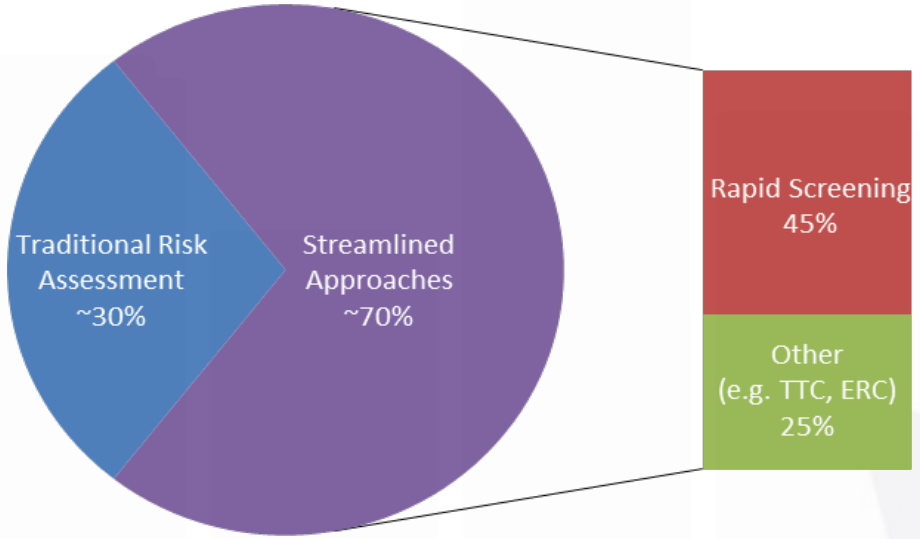
- ***A Science Approach Document (SciAD) describes a novel approach to evaluate the environmental or human health risk of substances***
- A SciAD does not include any regulatory conclusions but rather demonstrates the approach which can be used in future assessments or prioritization exercises
- Published 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 (BER) approach for prioritization and screening level assessment


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

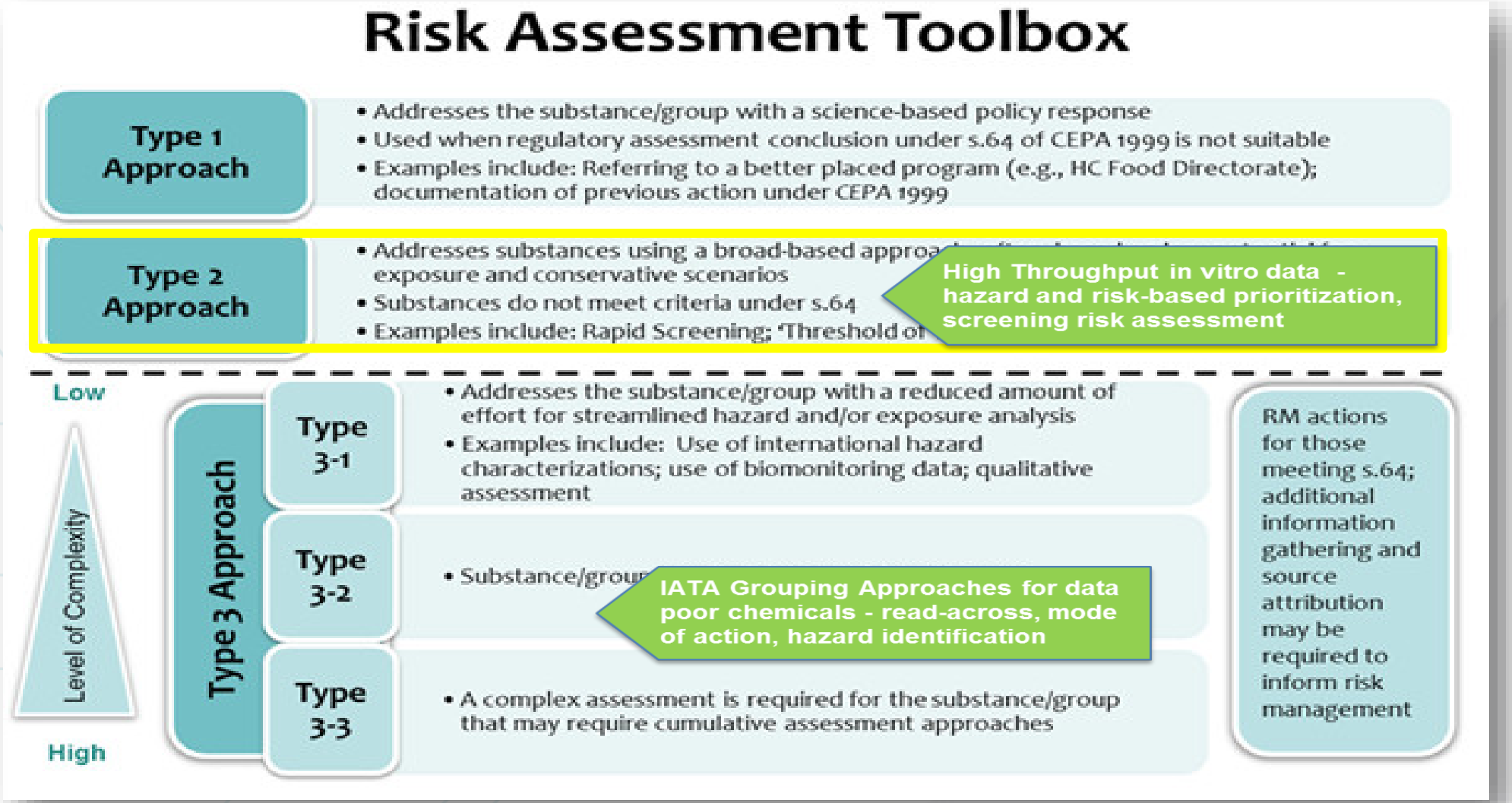



* Accounts for, at minimum, one department utilizing a streamlined approach
** For both departments utilizing a streamlined approach on the same set of substances, proportion is ~ 50 % streamlined approaches vs. ~ 50 % traditional risk assessments

# NAM to Support Risk-Based Priority Setting and Assessment

SciADs to date have generally described Type 2 Approaches

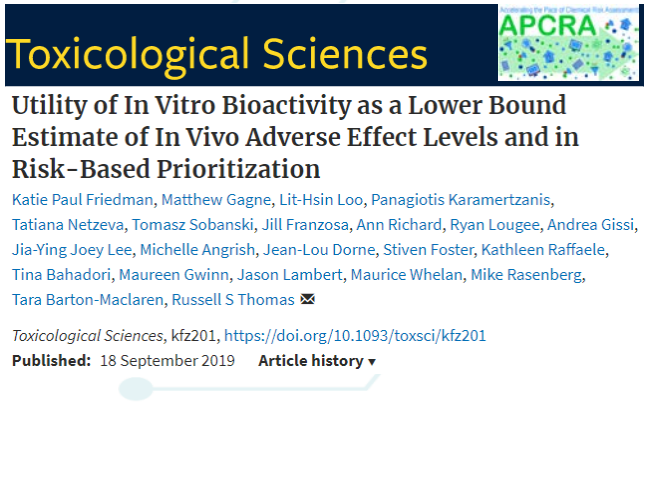
Exploring the utility of NAM data as an integrated element of more complex assessments




https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/chemicals-management-plan-risk-assessment-toolbox.html

# Translating Case Study Findings into Applications


*IN PROGRESS*



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 ✉

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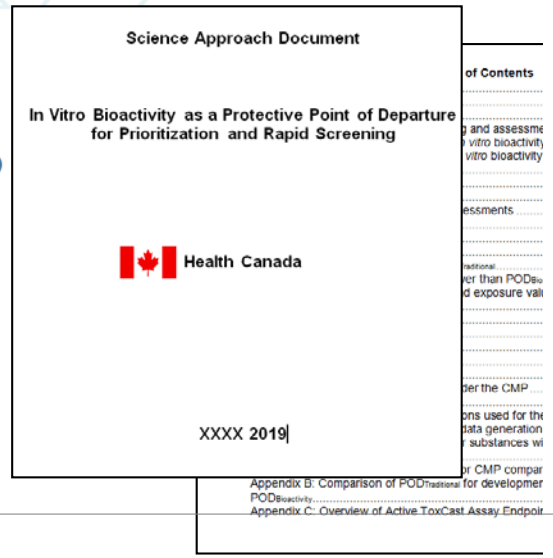


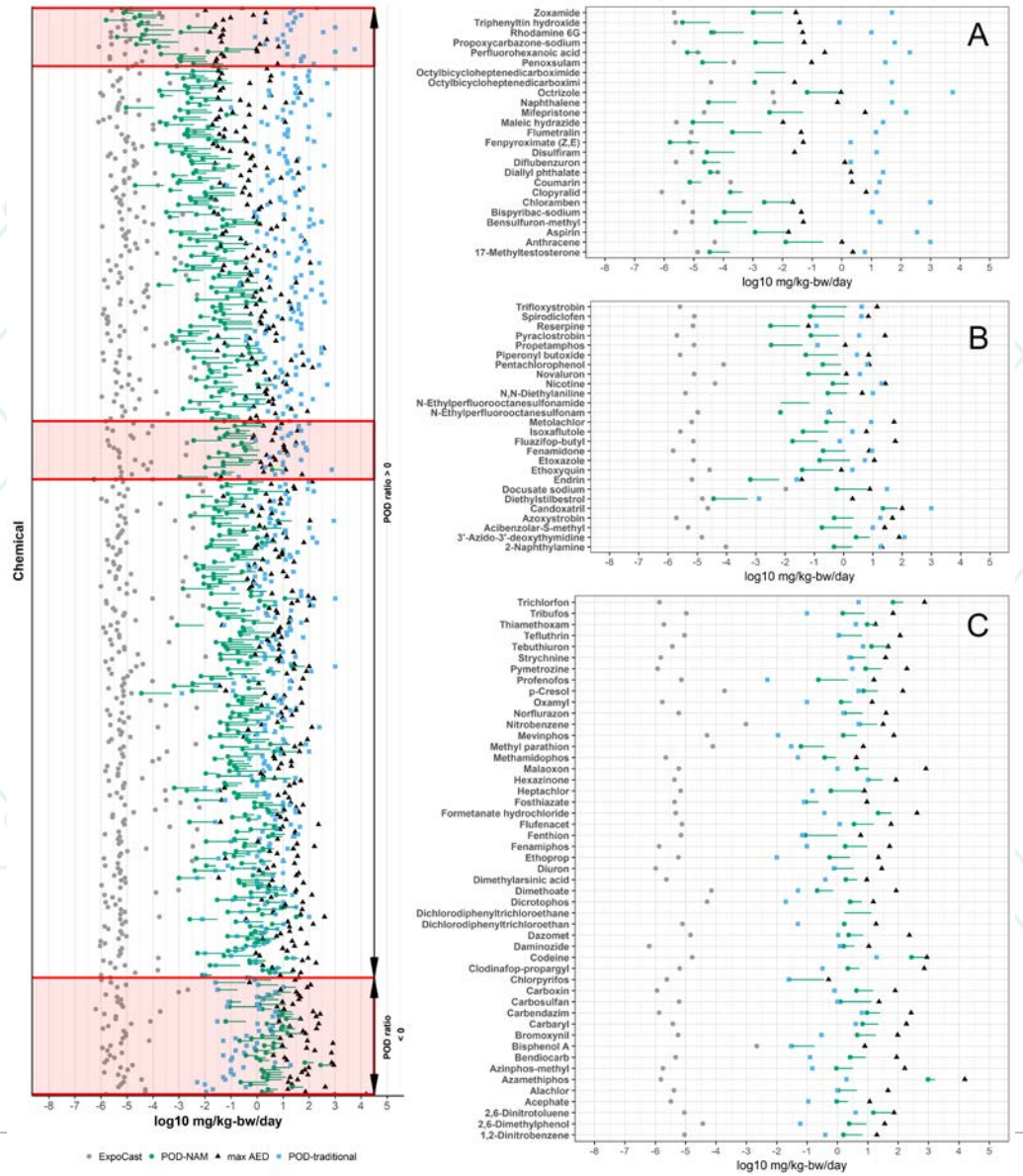
Science Approach Document

In Vitro Bioactivity as a Protective Point of Departure for Prioritization and Rapid Screening

Health Canada

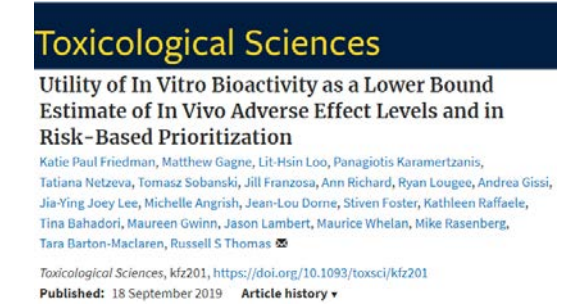
XXXX 2019

# 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
- The bioactivity PO protective metric r traditional toxicolc

**This collabo informs the r foundation fc in the H**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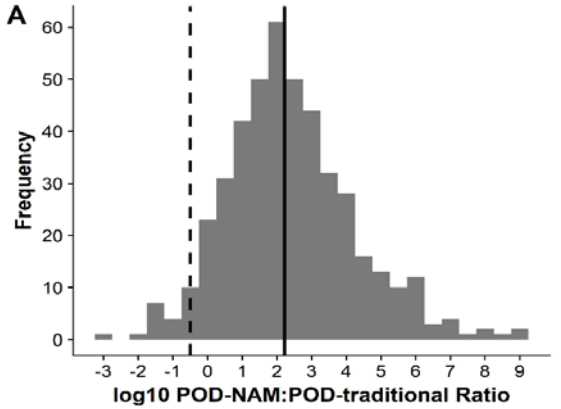



* APCRA – Accelerating the Pace of Chemical Risk Assessment

# 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 5$^{th}$ 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)

$POD_{Bioactivity}$

**Health Canada CMP Screening Assessments**

CMP Assessments (N=46)

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

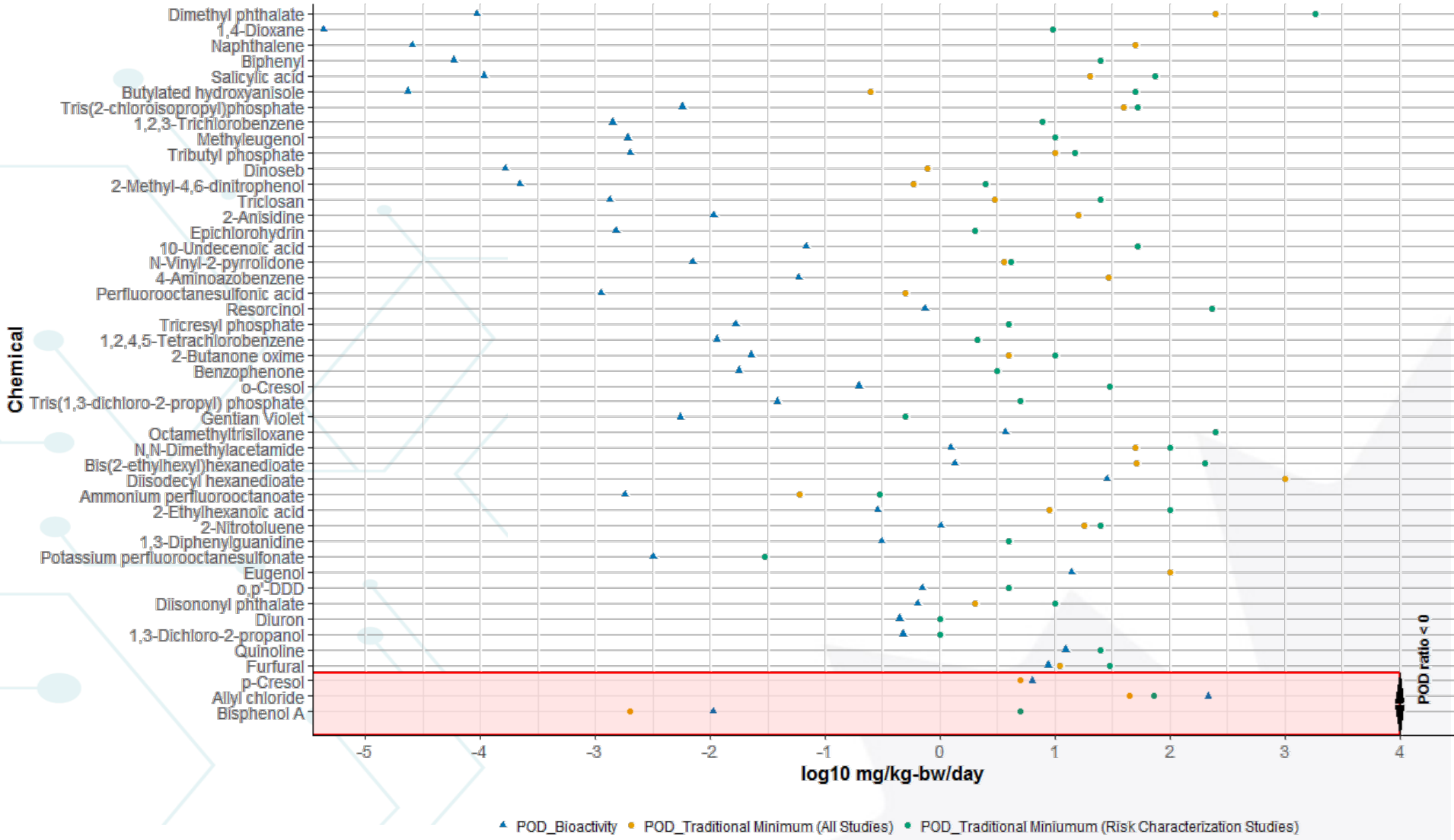
Label PODs:
- Minimum
- Risk characterization
- Effect Type
  - systemic
  - developmental
  - reproductive

$POD_{Traditional}$

"Comparison Case Study"

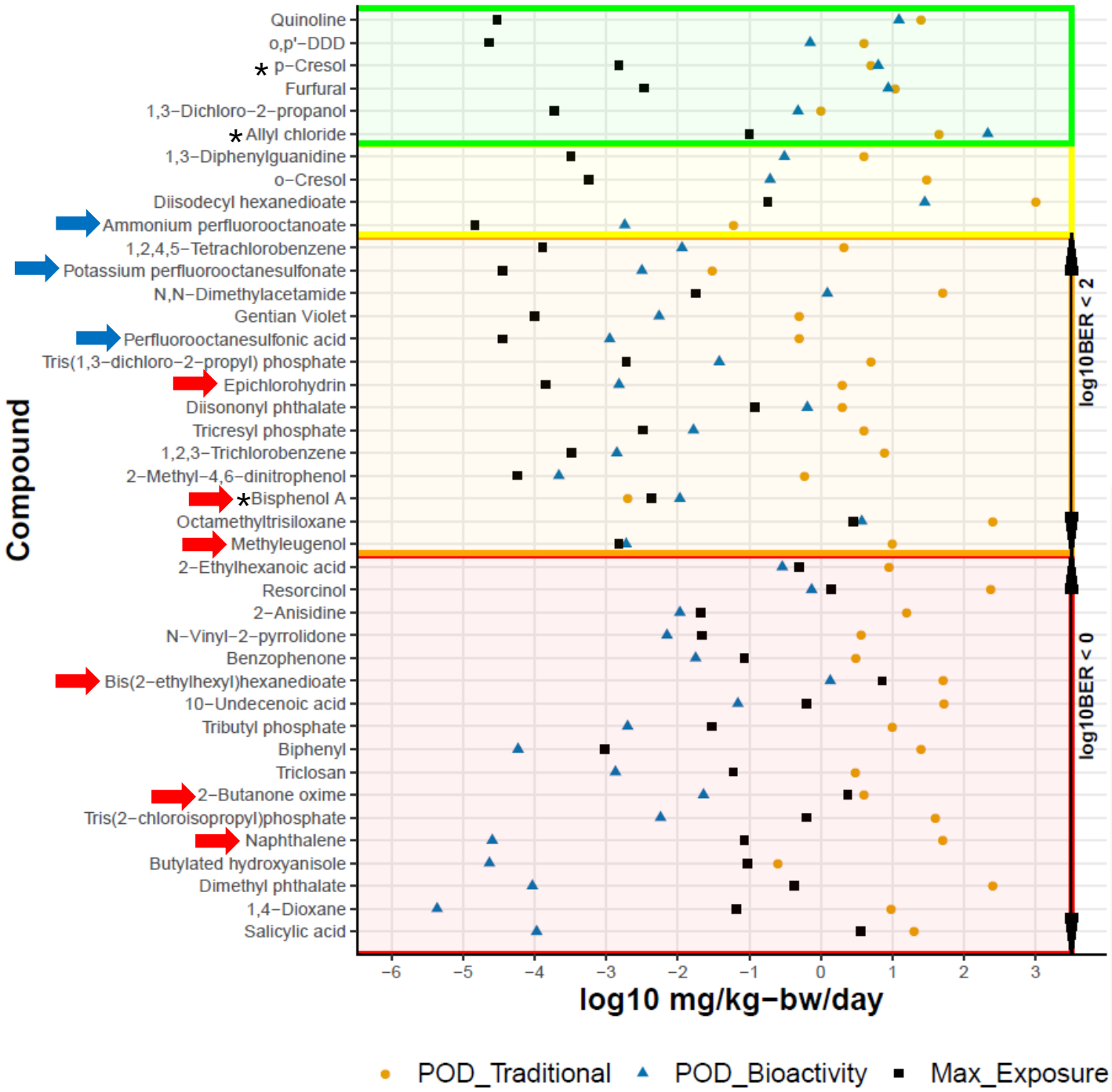
# $POD_{Bioactivity}$ is Protective of $POD_{Traditional}$ (minimum and risk characterization)

- $POD_{Bioactivity}$ less than $POD_{Traditional}$ 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

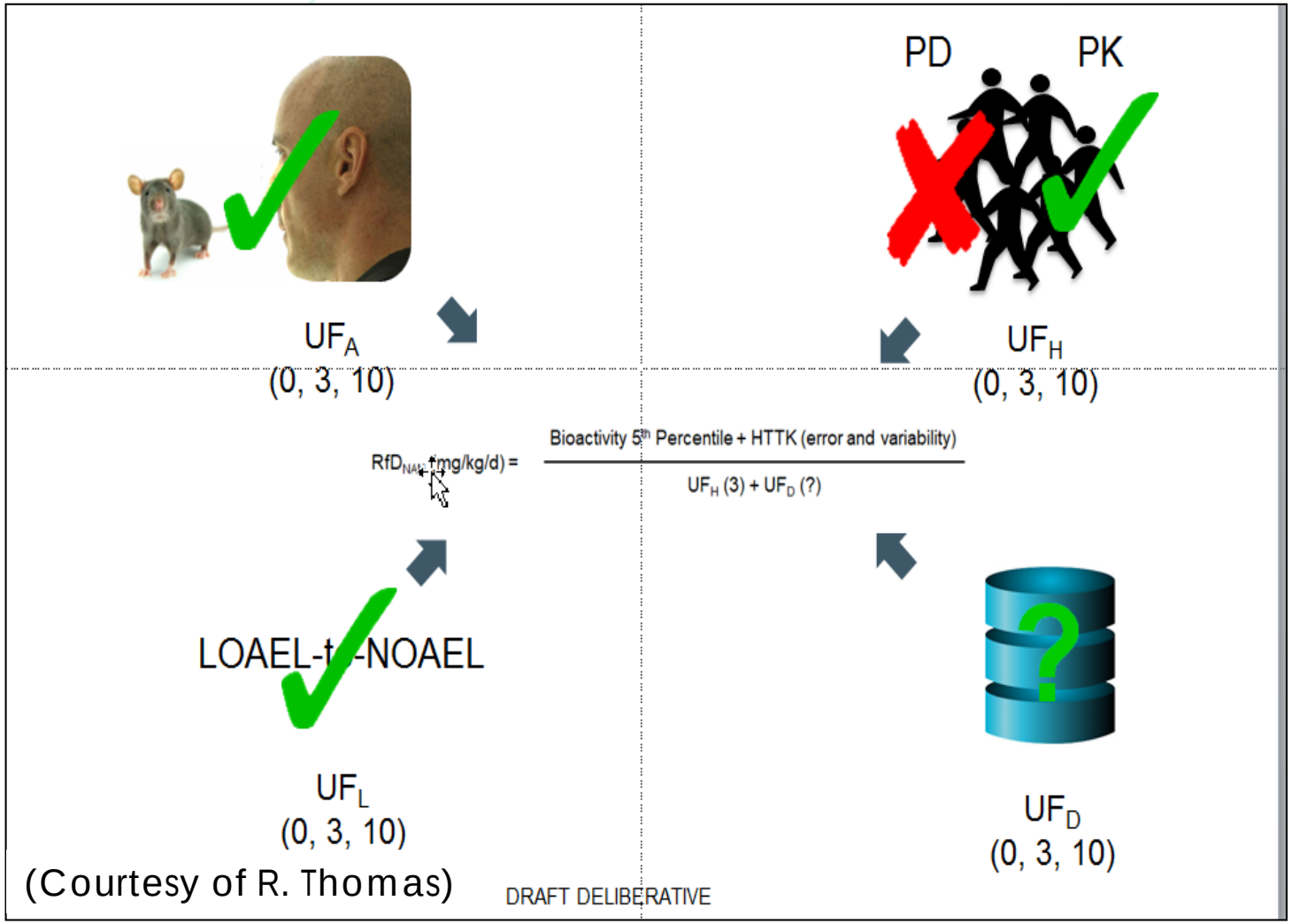
- $POD_{Bioactivity}$ was compared against maximum exposure value based on consumer products, environmental media, and biomonitoring data
- Using this approach, all six non-genotoxic compounds (red arrows) considered toxic to human health under CEPA section 64(c) had a log10BER < 2 (equivalent to MOE of 100)
- Substances considered ecotoxic under CEPA section 64(a) (blue arrows) had a log10BER <3
- *log10BER bins of <2 or <3 can be used to inform priority compounds



# Uncertainties and Variabilities Characterized

Health Canada Santé Canada

(Under Consideration)




(Courtesy of R. Thomas)

| Type | Factor | Rationale |
|---|---|---|
| **Deriving $POD_{Bioactivity}$ ($UF_{Bioactivity}$)** | **3** | Incomplete biological space covered by assays in ToxCast as well as limited metabolic competence. Uncertainties associated with the three compartment model to estimate $C_{ss}$ using in vitro toxicokinetic parameters. |
| **Immortalized Monocultures and Culture Conditions ($UF_{Cells}$)** | **3** | 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. |
| **Inter-individual Human Variability ($UF_{Human}$)** | **10** | Inter-individual variability related to toxicodynamics and toxicokinetics. Note this is likely conservative as HTTK model partially accounts for this. |
| **TOTAL** | **~100** | |

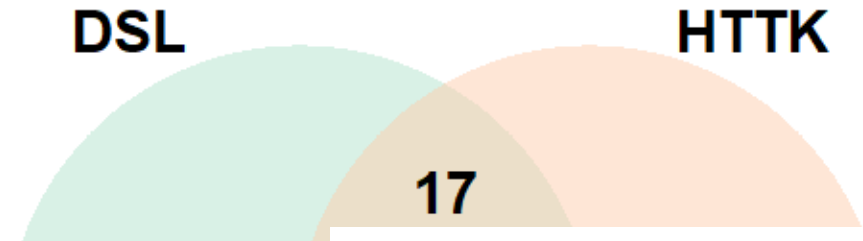
# Data Gaps Need to be Addressed for Broader Application

- 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 HTTK data

  2) The lack of intersection between DSL compounds and the current ToxCast database




* Canada's Domestic Substances List (DSL)

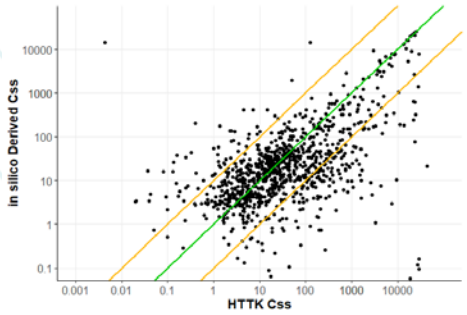
# Addressing Gaps Allows Quantitative Screening for Thousands of DSL* Chemicals

1) Lack of HTTK data (>2000)

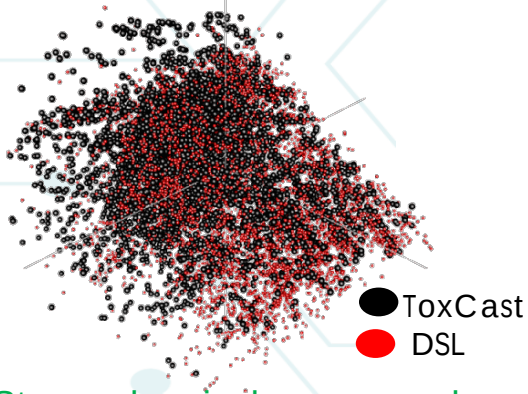
- HTTK data (intrinsic clearance, fraction unbound in plasma protein) not available for many compounds
- Addressed by *in silico* predictions

2) The lack of DSL and ToxCast intersection

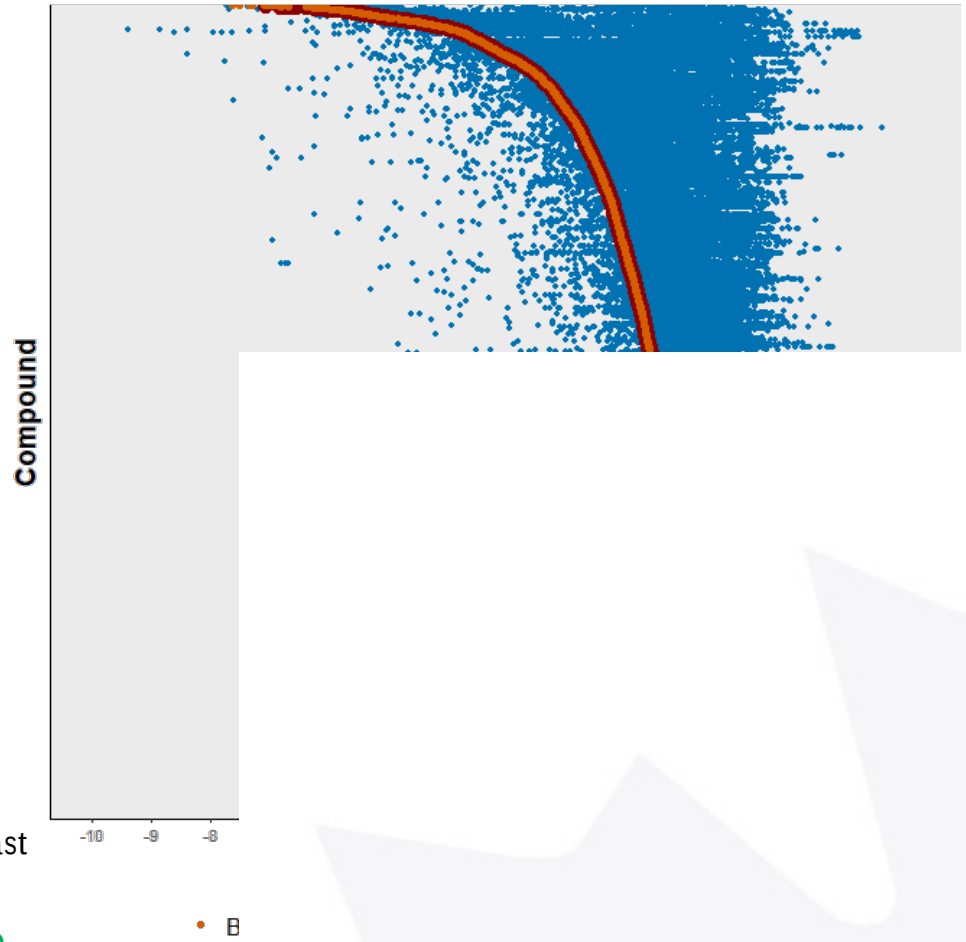
- Exploring read-across to address bioactivity data gaps as early tier screening tool
- Under development for >6000 substances




96% within 100-fold




Strong chemical space overlap



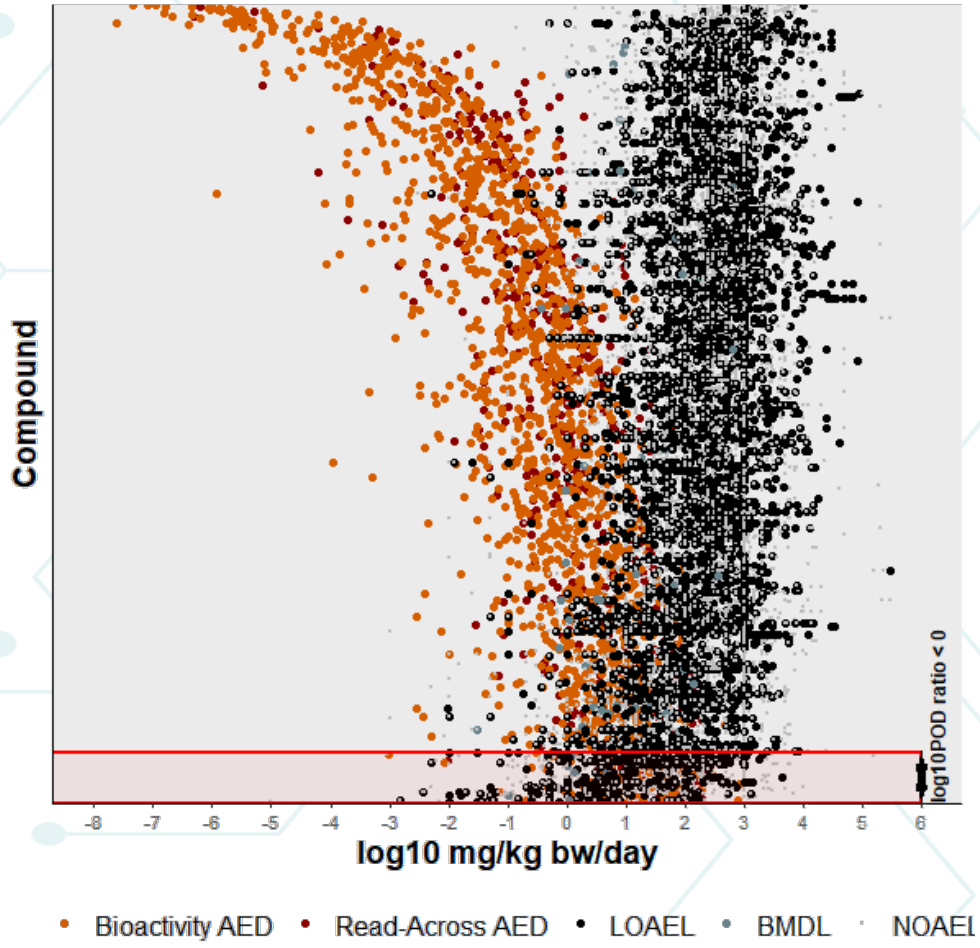

❖ Hazard predictions can be compared to exposure estimates to explore application to support rapid risk-based prioritization decisions

* Canada's Domestic Substances List (DSL)

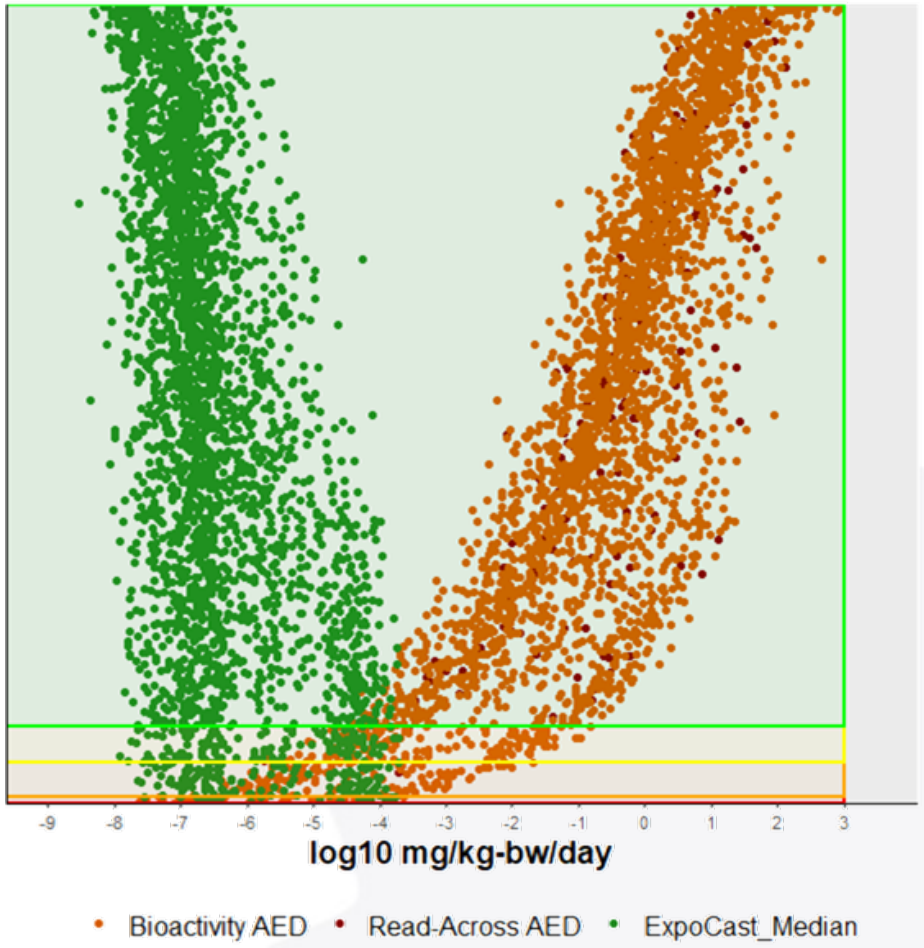
# Additional Data Comparisons Build Confidence

WORK IN PROGRESS

1947 of 2080 bioactivity PODs were lower than traditional PODs based on ToxValDB *in vivo* data




Application of SciAD-recommended bins and UFs identifies a subset of chemicals for closer examination



# 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
- Data availability often limited for the chemical space of regulatory interest
  - Advancements in *in silico* predictions are quite good relative to empirical measurements in most cases

# Future Challenges

- Assessing chemicals at the boundaries of the domain of applicability
  - Low molecular weight, highly volatile substances, etc.
- Assessing chemicals with intermittent exposures or that bioaccumulate
  - Consider alternative toxicokinetic approaches (i.e., Max Concentration vs. steady-state)

# Implementation

- Science Approach Document under Canada's CMP
  - Expanded application may be achieved through use of bioactivity based on nearest neighbours (or structural features) and *in silico* HTTK parameters (i.e. for data poor chemicals)
  - Broad risk-based quantitative approach to support rapid screening of chemicals that are of lower potential for concern
  - Support triaging efforts for chemicals of greater concern
  - Trigger information gathering and/or data generation

- The BER approach may be applied to "bin" substances for consideration for future prioritization activities
  - ie. <1, 1-100, 100-1000, >1000

- Anticipate that the approach will evolve to incorporate additional sources of NAM data
  - As further *in vitro* and high content assays advance, these technologies, and the data generated, will be considered as available for the ongoing expansion of the approach and rapid screening of substances

# Building Confidence through Collaboration

# Acknowledgments


Health Canada Santé Canada

- Matthew Gagné
- Marc Beal
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- Andy Nong
- Cathy Campbell
- Angelika Zidek

United States Environmental Protection Agency

- Katie Paul Friedman
- Russell Thomas
- Maureen Gwinn
- Jason Lambert

Accelerating the Pace of Chemical Risk Assessment APCRA


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# Questions?