Integrating New Approach Methodologies to Support Priority Setting and Risk Assessment under Canada’s Chemicals Management Plan: A Substituted Phenol Case Study

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Project Team

Health Canada

Santé Canada

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Outline

• Overview of the Chemicals Management Plan (CMP)
• Introduction to Collaborative Case Study
• Priority Setting under the CMP
  – Past Priority Setting Exercise
  – Moving Forward
    • Identification of Risk Assessment Priorities
    • New Approach Methodologies (NAM) for Priority Setting and Assessment
      – Part 1: Exploring HTS for Priority Setting and Assessment

• Risk Assessment under the CMP
  • CMP RA toolbox
  • NAM in Integrated Approaches to Testing and Assessment (IATA)
    – Part 2: Exploring the Utility of QSARs and HTS Data to Support IATA-based Hazard Characterization

• Wrap Up/Next Steps
Overview – CMP - Past Priority Setting Exercise

23,000 Substances on CEPA’s Domestic Substances List (DSL)

Greatest Potential for Human Exposure

Inherently Toxic to Humans

Persistent or Bioaccumulative

Inherently Toxic to Non-Humans

4,300 priority existing substances to be addressed

These substances were in Canada between January 1984 and December 1986

Categorization criteria for potential harm

Focus of CMP
Overview – CMP - Phases

**Ph3 - Currently in Planning Phase**
- Range of data availability (data rich to data poor)
- Many with limited data sets
- Opportunity to integrate emerging data & novel approaches

**Ph2 - Substance Groupings Initiative** (9 Groups)
- In silico
- Read-across
- Support risk assessment conclusions & recommendations
- Aromatic Azo & Benzidine-based substances, Phthalates, SDPAs, Flame Retardants

**Ph1- Challenge Initiative**
- Substance by substance risk assessment
- Used best available traditional toxicity data
- Limited use of alternative approaches

**Phase 3: 2016-2020**
4300 Existing Substances addressed by 2020

**Phase 1: 2006-2011**
1700 substances

**Phase 2: 2011-2016**
1500 substances
1064 substances

4300 Existing Substances addressed by 2020

*Approach for identification of chemicals and polymers as risk assessment priorities under Part 5 of the CANADIAN ENVIRONMENTAL PROTECTION ACT, 1999 (CEPA 1999)*
Collaborative Case Study - Motivation

Health Canada (HC) and U.S. EPA Collaboration

- Many remaining priorities for assessment under the Chemicals Management Plan (CMP) are considered data poor.

- Health Canada (HC) has an interest in establishing proof of concept for the integration of new approach methodologies into risk assessments and priority setting moving forward.

- The U.S. EPA National Center for Computational Toxicology (NCCT) has been actively exploring different contexts where HTS data can been effectively exploited, including:
  - Screening and prioritization;
  - Endocrine Disruption Screening Program (EDSP);
  - Systematic development and evaluation of chemical categories and their associated read-across.

- A collaborative case study has been developed in order to gain experience for moving this methodology forward for decision making both broadly as well as more specifically within Canada’s CMP.
Collaborative Case Study – Objectives/Elements

Objectives:
• To investigate the utility of new approach methodologies to support priority setting and risk assessment.
• To investigate the utility of combining new approach methodologies in an IATA-based hazard characterization to address data poor substances.

The case study investigates several key elements:

Part 1 Exploring the Bioactivity Exposure Ratio for priority setting and assessment
- Compare the bioactivity exposure ratio (BER) with traditional margin of exposure (MOE) techniques in order to examine the utility of HTS data to predict potential level of concern for human health effects for potential use in priority setting and risk assessment.

Part 2 Systematic approaches for identifying valid source analogues
Exploring the utility of QSARs and HTS data to support IATA-based hazard characterization to:
- Substantiate analogue selection for in vivo data read-across of estrogenicity;
# Risk Assessment under the CMP

## Risk Assessment Toolbox

### Type 1 Approach
- Addresses the substance/group with a science-based policy response
- Used when regulatory assessment conclusion under s.64 of CEPA 1999 is not suitable
- Examples include: Referring to a better placed program (e.g., foods); documentation of previous action under CEPA 1999

### Type 2 Approach
- Addresses substances using a broad-based approach, often based on low potential for exposure and conservative scenarios
- Substances do not meet criteria under s.64
- Examples include: Rapid Screening; Threshold of Toxicological Concern type approaches

### Type 3 Approach

<table>
<thead>
<tr>
<th>Level of Complexity</th>
<th>Type 3-1</th>
<th>Type 3-2</th>
<th>Type 3-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Type 3-1**
  - Addresses the substance/group with a reduced amount of effort for streamlined hazard and/or exposure analysis
  - Examples include: Use of international hazard characterizations; use of biomonitoring data; qualitative assessment

- **Type 3-2**
  - Substance/group requires de novo risk assessment

- **Type 3-3**
  - A complex assessment is required for the substance/group that may require cumulative assessment approaches

RM actions for those meeting s.64; additional information gathering and source attribution may be required to inform risk management.
Collaborative Case Study - CMP Substituted Phenols

- Consists of a group of 22 substituted phenols to be addressed under CMP phase 3.
- Nine of these substances are considered data poor and lack traditional *in vivo* toxicity data.
- Certain substituted phenols:
  - are high volume substances of widespread use,
  - have the potential for direct exposure through consumer products.
- A human health related concern with phenols is that they can have the potential to be estrogenic.
- The group of CMP phenolic compounds contain substituents at various positions relative to the hydroxyl group. The type of substituent(s) and position(s) relative to the hydroxyl group is anticipated to have an impact on the estrogenic potential and potency.

Examples of CMP Substituted Phenols
Part 1: Exploring HTS for Priority Setting and Assessment

HTS data to predict potential level of concern for human health effects in priority setting or risk assessment: a Bioactivity Exposure Ratio (BER) approach

<table>
<thead>
<tr>
<th>Dose-Response Assessment</th>
<th>Exposure Assessment</th>
<th>Risk Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vivo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional Toxicity studies</td>
<td>NOAEL/LOAEL (mg/kg/day)</td>
<td></td>
</tr>
<tr>
<td><strong>In vitro</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTS Assays AC_{50} (µM) ↓</td>
<td>Oral Equivalent Dose (OED) (mg/kg/day)</td>
<td></td>
</tr>
</tbody>
</table>

**Exposure Estimates (mg/kg/day)**

**Risk Characterization**

- Margin of Exposure (MOE) = \( \frac{NOAEL/LOAEL}{\text{Exposure Estimates}} \)
- Bioactivity Exposure Ratio (BER) = \( \frac{\text{Oral Equivalent Dose}}{\text{Exposure Estimates}} \)
Part 1: Exploring HTS for Priority Setting and Assessment
Deriving the Bioactivity Exposure Ratio (BER)

HTS as a Basis for Tier 1 Decision-Making

1) Bioactivity as Points of Departure (Source: EPA ToxCast MySQL and R package – invtrodb_v2 / tcpl_1.0)
   - Most sensitive response in active calls across all assays (AC50)
   - Most sensitive response in active calls related to ER pathway (AC50)
2) HTTK-based Conversion to Oral Equivalent Dose – (Source: Wambaugh HTTK R package / Wetmore et al. 2012)
   - Human 0.95 Quantile from SimCYP Monte Carlo simulation
3) Exposure Estimates
   - ExpoCast calibrated upper 95% confidence interval (Source: Wambaugh et al. 2013)


1 https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data
2 https://cran.r-project.org/web/packages/httk/index.html
Data Availability for Deriving the Bioactivity Exposure Ratio (BER) for CMP Substituted Phenols

• Derivation of the BER requires:
  • HTS assay data
  • High-throughput toxicokinetics (HTTK) data
    • *In vitro* serum protein binding + hepatic microsomal clearance

• Three CMP substituted phenols have the required data to derive a BER

• An additional 10 have ToxCast/Tox21 HTS data but no HTTK data

• Health Canada is generating HTTK data for these additional substances via a contract with an external lab
  • Preliminary results are available as of March 31, 2016

• The following slides provide an example of the BER approach for one CMP substituted phenol
  • CAS RN 98-54-4
Part 1: Exploring HTS for Priority Setting and Assessment

Deriving the Bioactivity Exposure Ratio (BER) - CAS RN 98-54-4

Histogram of ToxCast Assay Activity
CAS RN 98-54-4

nhit = 56
min = -0.97 (0.11 µM)
med = 1.74 (55 µM)
mean = 1.59 (39 µM)

A – Assay with lowest AC50 across all activity
Considered **not suitable**: numerous flags and the result is deemed not reliable (i.e. Hit-call potentially confounded by overfitting; borderline active; only one conc above baseline, active).

B – Assay with lowest AC50 for ER pathway
Considered **reliable**: no flags for this assay. The activity in the assay is outside the cytotoxicity region; related to the ER Pathway (effect of concern).
Part 1: Exploring HTS for Priority Setting and Assessment

Deriving the Bioactivity Exposure Ratio (BER) – CAS RN 98-54-4

B – Assay with lowest AC50 for ER pathway

ExpoCast Estimated Exposure, ToxCast/Tox21 AC50 Values, Oral Equivalent Dose (OED) and BER

<table>
<thead>
<tr>
<th></th>
<th>AC50 (µM)</th>
<th>OED (mg/kg bw/day)</th>
<th>ExpoCast upper 95% CI (mg/kg bw/day)</th>
<th>BER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest Activity for ER Pathway Assay</td>
<td>1.63$^1$</td>
<td>11.22</td>
<td></td>
<td>0.0543</td>
</tr>
<tr>
<td>Range of Activity for ER Pathway Assays</td>
<td>1.63 – 58.05</td>
<td>11.22 – 291.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$ Based on ER pathway assay with lowest AC50 (ATG_ERa_Trans_up)
### Study Type

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Effect Levels (mg/kg bw/day)</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterotrophic Assay (NICEATM DB) (Kleinstreuer et al. 2015)</td>
<td>LEL - 100</td>
<td>1.3 fold increase compared to control</td>
</tr>
</tbody>
</table>
Summary

• The bioactivity-exposure ratio (BER) provides a valuable metric linking activity of a substance to the estimated human exposure of that substance.

• The magnitude of the BER promises to be a useful indicator of the potential for concern arising from the detection of positive responses which can be integrated into decision-making.

• Ongoing activities are underway to:
  ❖ Establish further proof-of-concept for the use of HTS data in regulatory applications.
  ❖ Seek input on incorporating the approach for existing chemical assessment from the external CMP Science Committee Panel
  ❖ Continue to generate HTTK data for implicated CMP substances
  ❖ Communicate progress with other regulatory groups within Health Canada and other interested government departments

Part 1: Exploring HTS for Priority Setting and Assessment
Risk Assessment under the CMP

Risk Assessment Toolbox

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3. **Type 3-3**
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**Low**
- Level of Complexity

**High**
- RM actions for those meeting s.64; additional information gathering and source attribution may be required to inform risk management
Part 2: IATA Based Hazard Characterization

Analogue Selection – Analogue Source

• Investigate computational approaches for identifying structurally related substituted phenols with estrogenicity in vitro activity data.

• Analogues search was conducted using the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP) evaluation dataset

  ➢ High quality QSAR-ready dataset
    - Structure curation and standardization
    - Experimental data collected and cleaned

  ➢ ER pathway in vitro literature data reviewed and substances categorized
    - Data sources: Tox21; FDA EDKB; METI DB; ChEMBL DB
    - ER Binding
    - ER Agonist – reporter gene / transcriptional activation
    - ER Antagonist – reporter gene / transcriptional activation

1 Available from: https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data
### Part 2: IATA Based Hazard Characterization

#### Analogue Selection – Methods

- Several publically available structure descriptor approaches (Pubchem, Chemotyper and MoSS MCSS) were explored for identification and validation of analogues using Tanimoto index as a measure of similarity. The analogues were then screened to select relevant N = 10 analogues by filtering using:
  - Physchem properties of the analogue ($\text{LogP}_{ow}$ and Molecular Volume).
  - Number of literature sources as a marker for experimental data quality.

- A custom similarity metric was also developed that includes substituent position and chemical identity
  - Using a phenol scaffold, we decomposed the CMP compounds and CERAPP dataset into R-positions and set of fragments at each position.
  - For each R-position, we fingerprinted (Indigo) the fragments and calculated a pair-wise similarity matrix (including a penalty for different substitution patterns).
  - The global similarity matrix was taken as the product of the individual R-position similarity matrices.
  - The 10 nearest neighbors for each CMP substance were used to form the analogue set for each target.
  - The fingerprinting methods formed the preliminary basis for analogue selection/ group formation for each CMP target phenol.
Part 2: IATA Based Hazard Characterization

Analogue Selection – Methods

<table>
<thead>
<tr>
<th>Phenol Scaffold</th>
<th>Structures (3711)</th>
<th>Global similarity matrix</th>
<th>Analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>cutoff</td>
</tr>
<tr>
<td></td>
<td></td>
<td>product</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>fingerprint, similarity</td>
<td></td>
</tr>
</tbody>
</table>

Identical substitution pattern

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-buty1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>t-buty1</td>
</tr>
<tr>
<td>2</td>
<td>i-propyl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>i-propyl</td>
</tr>
</tbody>
</table>

| similarity | 0.75 | 1.0 | 1.0 | 1.0 | 0.75 |

Global similarity = 0.75 x 1.0 x 1.0 x 1.0 x 0.75 = 0.5625

Different substitution pattern

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-buty1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>t-buty1</td>
</tr>
<tr>
<td>2</td>
<td>i-propyl</td>
<td>H</td>
<td>i-propyl</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

| similarity | 0.75 | 1.0 | 0.0 | 1.0 | 0.0 |

Global similarity = 0.75 x 1.0 x 0.0 x 1.0 x 0.0 = 0.0
Part 2: IATA Based Hazard Characterization
Analogue Selection – Example of Potential Analogues

Closest CERAPP analogues with *in vitro* data, based on substituent position and identity
Part 2: IATA Based Hazard Characterization

ER Pathway Data Collection

• Collected empirical data and modelling results related to the ER Pathway for the CMP target and potential analogues.
• Data matrices were populated using a template devised by the OECD IATA work programme with planned refinements based on insights from the EU SEURAT programme.

• In vivo data
  • Uterotrophic (UT) Assay
    - Source: NICEATM UT Database of Guideline Studies (Kleinstreuer et al. 2015)
  • Female Pubertal Assay
    - Source: EPA Database of Studies (under development)
  • OECD Reproductive and Developmental Toxicity Guideline Studies
    - Source: Various EPA Databases; ECHA REACH website; Health Canada literature search

• In vitro data
  • ToxCast and Tox21 assays related to the ER pathway
    - Source: EPA EDSP21 Dashboard (http://actor.epa.gov/edsp21/)
  • CERAPP categorization result based on literature review
    - Source: CERAPP evaluation dataset

• Predictions and Alert Profilers
  • EPA ToxCast ER Pathway AUC Score (Agonist and Antagonist)
  • CERAPP Consensus Models
  • EPA rtER Expert System (within the OECD Toolbox)
  • Commercial Software: Derek Nexus; ACD Percepta; OASIS TIMES
**Part 2: IATA Based Hazard Characterization**

**Selection of Data Collected in Data Matrix**

Example of active ER Pathway agonist CMP substituted phenol and analogues
Non-Hindered Phenol (para-substituted)

<table>
<thead>
<tr>
<th>CMP Target</th>
<th>Uterotrophic Assay NICEATM DB</th>
<th>CERAPP in vitro literature data</th>
<th>ToxCast ER AUC Score</th>
<th>CERAPP Consensus QSAR</th>
<th>Other QSARa</th>
</tr>
</thead>
<tbody>
<tr>
<td>98-54-4</td>
<td>Active LEL - 100 mg/kg/day Result: 1.3 fold increase s.c. over 3 days Crj:CD(SD) Rat (PND 20)</td>
<td>Binding: <strong>Active</strong> (Very Weak) Agonist: ND Antagonist: Inactive</td>
<td>Agonist: 0.161 (<strong>Active</strong>) Antagonist: 0 (Inactive)</td>
<td>Binding: <strong>Active</strong> (Weak) Agonist: <strong>Active</strong> (Very Weak) Antiagonist: Active (Strong)</td>
<td>Binding: <strong>Active</strong> (Weak) (3/4) Derek Nexus: No Alert</td>
</tr>
<tr>
<td></td>
<td>ND</td>
<td>Binding: <strong>Active</strong> (Weak) Agonist: ND Antagonist: Inactive</td>
<td>Agonist: 0.282 (<strong>Active</strong>) Antagonist: 0 (Inactive)</td>
<td>Binding: <strong>Active</strong> (Weak) Agonist: <strong>Active</strong> (Weak) Antagonist: Active (Strong)</td>
<td>Binding: <strong>Active</strong> (Weak) (3/4) Derek Nexus: No Alert</td>
</tr>
<tr>
<td></td>
<td>ND</td>
<td>Binding: <strong>Active</strong> (ND) Agonist: ND Antagonist: Inactive</td>
<td>Agonist: 0.163 (<strong>Active</strong>) Antagonist: 0 (Inactive)</td>
<td>Binding: <strong>Active</strong> (Weak) Agonist: <strong>Active</strong> (Weak) Antagonist: Active (Strong)</td>
<td>Binding: <strong>Active</strong> (Weak) (4/4)</td>
</tr>
<tr>
<td></td>
<td>Active LEL - 200 mg/kg/day Result: 283% of control s.c. over 3 days SD Rat (PND 21)</td>
<td>Binding: <strong>Active</strong> (Weak) Agonist: <strong>Active</strong> (Moderate) Antagonist: Inactive</td>
<td>Agonist: 0.393 (<strong>Active</strong>) Antagonist: 0 (Inactive)</td>
<td>Binding: <strong>Active</strong> (Weak) Agonist: <strong>Active</strong> (Weak) Antagonist: Active (Strong)</td>
<td>Binding: <strong>Active</strong> (Moderate / Strong) (4/4)</td>
</tr>
</tbody>
</table>

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*a Other QSAR – Oasis TIMES, ACD Percepta, Derek Nexus; EPA rtER
**Part 2: IATA Based Hazard Characterization**

**Selection of Data Collected in Data Matrix**

Example of non-active ER pathway CMP substituted phenol and analogues

Hindered Phenol (di-ortho-substituted) [*Conflicting literature data on CMP phenol*]

<table>
<thead>
<tr>
<th>CMP Target</th>
<th>128-37-0</th>
<th>2219-82-1</th>
<th>2409-55-4</th>
<th>1879-09-0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterotrophic Assay NICEATM DB</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>
| CERAPP in *vitro* literature data | Binding: **Active**
Agonist: ND
Antagonist: Inactive | Binding: **Inactive**
Agonist: **Inactive**
Antagonist: **Inactive** | Binding: **Inactive**
Agonist: **Inactive**
Antagonist: **Inactive** | Binding: **Inactive**
Agonist: ND
Antagonist: ND |
| ToxCast ER AUC Score | Agonist: 0 (**Inactive**)
Antagonist: 0 (**Inactive**)
| Agonist: 0 (**Inactive**)
Antagonist: 0 (**Inactive**)
| Agonist: 0 (**Inactive**)
Antagonist: 0.0164 | Agonist: 0 (**Inactive**)
Antagonist: 0 (**Inactive**)
|
| CERAPP Consensus QSAR | Binding: **Inactive**
Agonist: **Inactive**
Antagonist: **Inactive** | Binding: **Inactive**
Agonist: **Inactive**
Antagonist: **Inactive** | Binding: **Inactive**
Agonist: **Inactive**
Antagonist: **Inactive** | Binding: **Inactive**
Agonist: **Inactive**
Antagonist: **Inactive** |
| Other QSAR* | Binding: **Inactive** (2/3)
OECD TIMES: **Weakly active (due to metabolite)**
EPA rtER - **Inactive**
Derek Nexus – **No ER alerts** | Binding: **Inactive** (3/3)
OECD TIMES: **Inactive**
EPA rtER – **Inactive**
Derek Nexus – **No ER alerts** | Binding: **Inactive** (2/3)
OASIS TIMES - **Inactive**
EPA rtER – **V weakly active**
Derek Nexus – **No ER alerts** | Binding: **Inactive** (3/3)
OECD TIMES - **Inactive**
EPA rtER – **Inactive**
Derek Nexus – **No ER alerts** |

*Other QSAR – Oasis TIMES, Derek Nexus; EPA rtER*
Part 2: IATA Based Hazard Characterization

Selection of Data Collected in Data Matrix

Example of non-active ER pathway CMP substituted phenol and analogues
Partial Hindered Phenol (mono-ortho-substituted)

<table>
<thead>
<tr>
<th></th>
<th>96-76-4</th>
<th>2934-05-6</th>
<th>96-70-8</th>
<th>105-67-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterotrophic</td>
<td>Inactive</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Assay NICEATM</td>
<td>Max Dose</td>
<td>Max Dose</td>
<td>Max Dose</td>
<td>Max Dose</td>
</tr>
<tr>
<td>DB</td>
<td>s.c. 1000 mg/kg/day</td>
<td>over 3 days</td>
<td>Crj:CD(SD) Rat (PND 20)</td>
<td>Crj:CD(SD) Rat (PND 20)</td>
</tr>
<tr>
<td>CERAPP in vitro</td>
<td>Binding:</td>
<td>Binding:</td>
<td>Binding:</td>
<td>Binding:</td>
</tr>
<tr>
<td>literature data</td>
<td>Active (V. Weak)</td>
<td>Inactive</td>
<td>Active (Weak)</td>
<td>Active (ND)</td>
</tr>
<tr>
<td></td>
<td>Agonist: Inactive</td>
<td>Agonist: Inactive</td>
<td>Agonist: ND</td>
<td>Agonist: ND</td>
</tr>
<tr>
<td></td>
<td>Antagonist: ND</td>
<td>Antagonist: Inactive</td>
<td>Antagonist: Inactive</td>
<td>Antagonist: Inactive</td>
</tr>
<tr>
<td>ToxCast ER AUC</td>
<td>Agonist: 0 (Inactive)</td>
<td>Agonist: 0 (Inactive)</td>
<td>Agonist: 0.019 (Inactive)</td>
<td>Agonist: 0 (Inactive)</td>
</tr>
<tr>
<td>Score</td>
<td>Antagonist: 0 (Inactive)</td>
<td>Antagonist: 0 (Inactive)</td>
<td>Antagonist: 0 (Inactive)</td>
<td>Antagonist: 0 (Inactive)</td>
</tr>
<tr>
<td>Other QSARa</td>
<td>Binding: Inactive</td>
<td>Binding: Inactive</td>
<td>Binding: Inactive</td>
<td>Binding: Inactive</td>
</tr>
<tr>
<td></td>
<td>(4/4)</td>
<td>(3/4)</td>
<td>OASIS TIMES - Inactive</td>
<td>(3/4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Derek Nexus - No Alert</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACD Percepta - Active</td>
<td></td>
</tr>
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a Other QSAR – Oasis TIMES, ACD Percepta, Derek Nexus; EPA rtER
Part 2: IATA Based Hazard Characterization

Early findings

• Integrating the analogue approach along with *in vitro* HTS data and (Q)SAR predictions show promise in facilitating an IATA-based hazard characterisation for estrogenicity of CMP substituted phenols.

  - ToxCast ER Pathway AUC Scores agree with higher tier tests (e.g. Uterotrophic Assay) where examined
  - ToxCast ER Pathway AUC Scores discriminate activity between hindered and non-hindered phenols where examined
  - QSAR results for some models are mixed for CMP phenols and respective analogues and do not always agree with empirical data
    - Requires examination of underlying algorithm to determine if model accounts for steric hindrance around phenol (e.g. OASIS Times)
    - Limitation of current CERAPP Consensus model. Development of local QSAR models for phenols a possible solution being explored by others.
Wrap-up / Next Steps

• Rapidly advancing technologies and the need to address large inventories of substances with a range of data availability presents an opportunity to integrate novel approaches and methodologies into Canada’s risk assessment program.

• Investigations to date on the application of NAM under the CMP suggests:
  ❖ in vitro HTS data coupled with other exposure and hazard characterization approaches can support chemical risk assessment;
  ❖ NAM can provide a basis supporting substance groupings and read-across;
  ❖ emerging data and technologies provides support for moving toward an IATA strategy.

• Work continues for the remaining CMP Substituted Phenols and associated analogues
  ❖ To expand on the results presented today to more CMP substituted phenols
  ❖ Including comparative outcomes of IATA-based hazard characterization and the BER approach to low tier screening assessments.

• Increase awareness and communication of a new set of uncertainties in the scientific process:
  • Maintain communication of scientific rigour and precautionary approach
  • Communicate uncertainties present in both the current and proposed emerging scientific tools

• Advisory Bodies – CMP Science Committee; Health Canada Science Advisory Board
Further Information

- Chemical Substances website:
  - [www.chemicalsubstanceschimiques.gc.ca](http://www.chemicalsubstanceschimiques.gc.ca)
  - Launch Announcement
  - Group Profile Documents
  - Link to stakeholder engagement form

- Website subscription provides the latest news: