

**Integrating New Approach Methodologies under Canada's Chemicals Management Plan
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Under Canada's Chemicals Management Plan (CMP), the Government of Canada is committed to addressing 4300 existing substances by 2020. Moving forward into the third phase of the CMP and beyond, a key challenge is assessing the potential for risk to human health of substances that have limited to no data. As such, Health Canada (HC) has an interest in establishing proof of concept for the integration of new approach methodologies into risk assessment activities under the CMP. At the same time, the US EPA National Centre for Computational Toxicology (NCCT) programme has been actively exploring different contexts where HTS data can be effectively exploited such as in the use of prediction models within the Endocrine Disruption Screening Program (EDSP) and more recently in the systematic development and evaluation of chemical categories and their associated read-across. A case study has been jointly developed by Health Canada and the US EPA NCCT programme in order to gain experience for moving this methodology forward for decision making both broadly as well as more specifically within Canada's CMP.

Substituted phenols are high volume substances of widespread use with the potential for direct exposure to the general population through consumer products. This case study uses a subset of 21 substituted phenols that will be addressed under phase 3 of Canada's CMP. A human health related concern with phenols is that they can have the potential to be estrogenic. The selected CMP phenolic compounds contain substituents at various positions relative to the hydroxyl group. The type of substituent and position relative to the hydroxyl group is anticipated to have an impact on the estrogenic potential and potency. This case study addresses several key elements including investigating systematic approaches for identifying valid source analogues and assessing their resulting read-across performance as well as exploring the utility of QSARs and HTS data to substantiate chemical categories formed and reducing uncertainties associated with the traditional read-across for apical effects.

The first step in the case study was to investigate computational approaches for identifying structurally related substituted phenols with *in vitro* estrogenicity activity data as taken from the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP) dataset that could be used to make read-across predictions. Several methods were explored including 3 different structure descriptor sets (PubChem, Chemotyper, and MoSS) with Tanimoto similarity or closest nearest neighbours as cut-offs. Several different data sources were used to populate data matrices for each of the three categories. The data matrices were structured in accordance with the templates devised by the OECD IATA work programme and refined based on the insights gained from the EU SEURAT programme. The data included *in vitro* assay data from ToxCast and Tox21 related to the ER pathway, literature data and QSAR model predictions for these targets as well as *in vivo* uterotrophic data where available. Ecotoxicological data related to endocrine disruption was also examined. For each category, the consistency in physicochemical properties, activity data as well as modelled toxicokinetic parameters across the category members was examined. An overall preliminary weight of evidence for the estrogenicity activity for the 3 target CMP substances was made. Where the required data was available for target CMP substituted phenols, the bioactivity exposure ratio (BER) was compared with traditional margin of exposure (MOE) techniques in order to further examine the utility of the HTS data to predict potential level of concern for human health effects for the purposes of screening and risk assessment.

The case study is still ongoing but work completed to date shows that the approach is promising for developing an IATA-based hazard characterization for the estrogenicity activity for the target CMP substituted phenols to support risk assessment activities under the Canadian Environmental Protection Act, 1999.

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