Development of a Tool for Systematic Integration of Traditional and New Approach Methods for Prioritizing Chemical Lists

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Introduction

Goal: Develop methods and tools to prioritize chemicals for further testing

Approach
- Develop databases of *in vivo, in vitro*, exposure and chemical property data
- Develop scoring schemes to merge different types of data
- Develop methods to fill or note data gaps
- Make data, scores, prioritization ranking available in a web-based tool

Current Applications
- Office of Pesticide Programs Inert Chemicals (OPP Inerts)
- Toxic Substances Control Act (TSCA) Active Inventory

Data Domains

***In Vivo* Human Hazard:**
- Mammalian toxicity studies – guideline-like, use Point-of-Departure (POD)
- System-specific *in vivo* data (Cancer, developmental)
- Models (QSAR) to predict POD and organ-specific effects
- Genotoxicity
- *In vitro*-derived endocrine disruption and neurotoxicity models

***In Vivo* Eco Hazard**
- Aquatic *in vivo* studies – POD
- Models (QSAR) of POD

Human Exposure
- Data on production volume and releases
- Quantitative biomonitoring data
- Predictions of oral and inhalation exposure

Eco Exposure
- Biomonitoring data
- Predictions of water concentrations

Physicochemical Properties
- Persistence and Bioaccumulation models (OPERA Models)

Data is divided into two broad categories
- Traditional Methods (primarily *in vivo*)
- NAM – New Approach Methods (primarily models, *in vitro*)

Scoring Strategy

Start with TSCA 2012 Prioritization Workplan:
https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-chemicals-assessments-2014-update

- For each chemical, each domain receives a score of 1 (Low), 2 (Moderate), or 3 (High) concern
- Hazard score = maximum of human and ecological hazard scores
- Exposure score = maximum of human and ecological exposure scores
- Total score = hazard score + exposure score + physchem score
- If no data is available for a domain, it is given the "missing data score", currently 1 (Low)
- Scoring can include or exclude NAM

Scoring Methods

Method 1: TSCA 2012
- Maximum score from human and ecological hazard: 1 – 3
- Maximum score from human and ecological exposure: 1 – 3
- Maximum score from persistence/ bioaccumulation (P/B): 1 – 3
- No NAM
- Add hazard, exposure, and P/B
- Categorical bins
  - High: 7-9
  - Moderate: 5-6
  - Low: 3-4

Method 2: NAM Equal
- Same as TSCA 2012 except NAM is incorporated with equal weighting in all domains
- Add hazard, exposure, and P/B
- Categorical bins
  - High: 7-9
  - Moderate: 5-6
  - Low: 3-4

Method 3: NAM Deferential
- Same as TSCA 2012 except human hazard NAM is incorporated in the absence of traditional *in vivo* studies
- In other domains, NAM is given equal weight.
- Add hazard, exposure, and P/B
- Categorical bins
  - High: 7-9
  - Moderate: 5-6
  - Low: 3-4

Method 4: Sum of Scores
- Sum all components (incl. NAM) from human and ecological hazard
- Sum all components (incl. NAM) from human and ecological exposure
- Sum all components (incl. NAM) from persistence/ bioaccumulation
- Add hazard, exposure, and P/B
- Categorical bins
  - High: >30
  - Medium: 10-30
  - Low: ≤10

Method 5: H/BER*
- Ratio of the minimum effect level from *in vivo* toxicity studies or the quantitative human hazard NAM data divided by the maximum oral exposure
- Categorical bins
  - High: $\leq 10^4$
  - Medium: $10^4 – 10^6$
  - Low: $\geq 10^6$

*Hazard/Bioactivity Exposure Ratio

Web-based Tool in Development

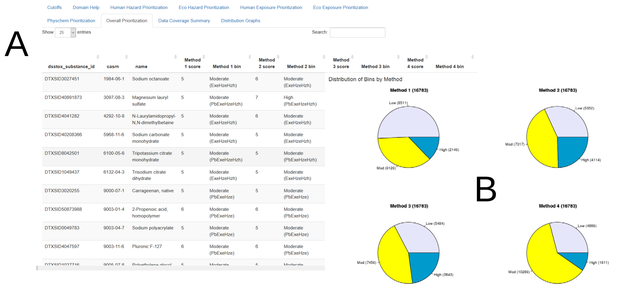

Figure 1: Views of the online tool (A) Overall scoring page; (B) fraction of chemicals in each bin; (C) Data coverage by domain – how many chemicals have that type of data from the TSCA active inventory

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domain	subdomain	count	pe
physchem	persistence	9757	58.1
physchem	bioaccumulation	9757	58.1
human hazard	er_qsar	9305	55.4
human hazard	erant_qsar	9305	55.4
eco hazard	min_pod_nam	8544	50.9
eco hazard	test_eco	7283	43.3
human exposure	cdr_child	7137	42.5
human exposure	cdr_commercial	7137	42.5
human exposure	cdr_consumer	7137	42.525174
human exposure	cdr_industrial	7137	42.525174
human exposure	cdr_manufacturing_sites	7137	42.525174
human hazard	min_pod_invivo_model	6875	40.964071

Example: OPP Inerts

Background: EPA received a public petition to evaluate the risk of a set of pesticidal inert ingredients. Our approach is being used to prioritize these chemicals for further assessment. Exposure is not of a primary concern, but here we evaluate priorities both with and without exposure
- 116 Pesticidal inert ingredients
- 30 "reference" chemicals – data rich chemicals that would score either high or low

Multiple scenarios were run, including / excluding different data domains. Ideally, the priority ranking would be somewhat insensitive to any one data set

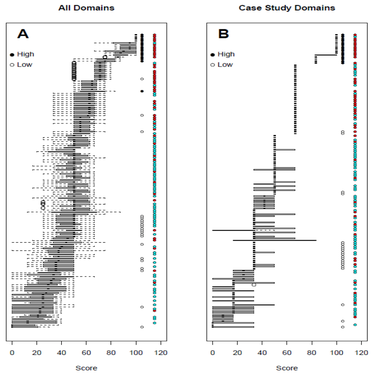

Figure 2: Summary of scores for all chemicals across all scenarios. (A) All domains were used; (B) Only human and eco hazard and Persistence/Bioaccumulation domains were considered. High-priority reference chemicals are indicated by black dots, and low-priority reference chemicals by white dots. Chemicals with an existing Tier 1 or Tier 2 RA are indicated by a red or cyan dot at the far right. If both types are available, a Tier 1 RA is indicated.

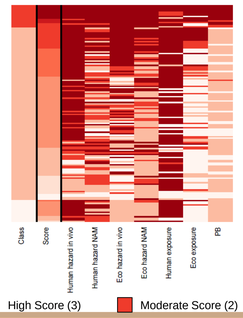

Figure 3: Heatmap showing individual scores for all domains. Rows are chemicals. The first column (Class) is red for the high priority reference chemicals, pink for the case study chemicals and white for the low priority reference chemicals. The Score column indicates the mean score for all domains, corresponding to Figure 2A.

Example: TSCA Pre-prioritization

Background: Under the revised TSCA, EPA must designate a set of high-priority chemicals for detailed risk assessment. This tool is one approach to help guide that selection.

The first example run prioritization for the TSCA Step 2 Workplan chemicals (344) and the SCIL (Safer Choice Ingredients List) chemicals (867)

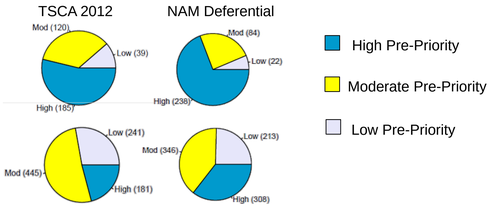

Figure 4: Distribution of High, Moderate and Low scoring chemicals in the two chemical sets

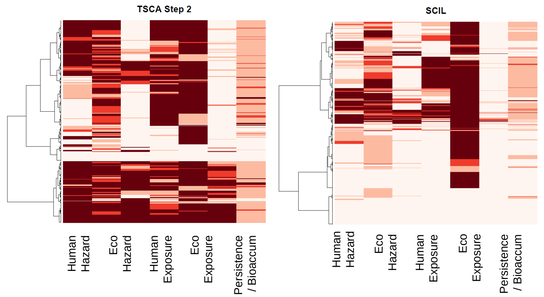

Figure 5: Heatmaps showing the domain-specific scores for the TSCA Step 2 and SCIL chemicals

Conclusions

We are developing a flexible web-based tool to allow prioritization of hundreds to thousands of chemicals
- Traditional and New Approach Methods data are included
- Domains are human and ecological hazard and exposure, plus physchem properties
- Multiple scoring schemes are being implemented
- All data and models are public
- The software application will be part of the CompTox tool suite (https://comptox.epa.gov) which will allow drill-down into the details of the data driving the prioritization scores