Approaches to Identifying Potential Candidate Chemicals for Prioritization:
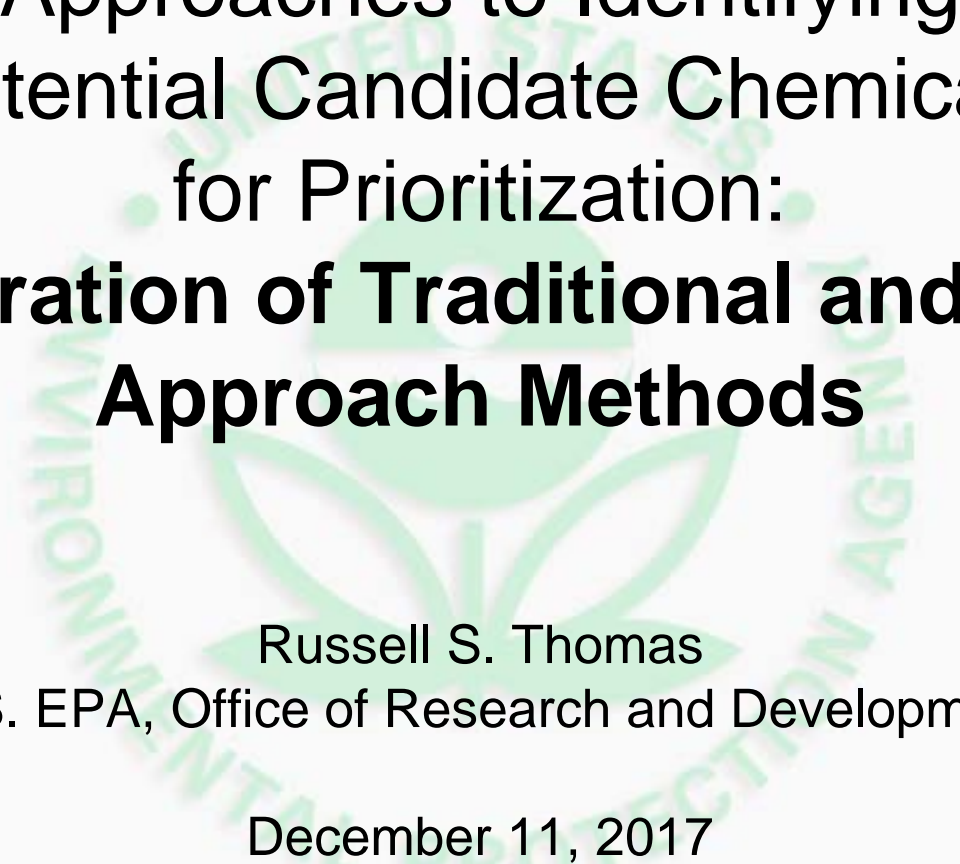## Integration of Traditional and New Approach Methods

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Outline

- Objectives
- Chemicals
- Methods
  - New Approach Methods
  - Scoring Methods
- RapidTox Workflow
- Results
- Summary
- Additional Progress
- Benefits and Caveats

Objectives

- Develop a web-based, decision support workflow to provide a transparent process for chemical pre-prioritization and allow users to flexibly explore the relative impact of different approaches

- Integrate new approach methods (NAM)[*] with traditional toxicological, exposure, and persistence/bioaccumulation data to fill information gaps

*New approach methods (NAM) are any *in vitro*, *in silico*, or *in chemico* techniques used to provide data or information for regulatory decision making (ECHA, 2016).

Disclaimer

The chemicals and scoring methods are for illustration purposes only and are intended to demonstrate applicability of the tool in the candidate selection process. They do not represent final candidate selection decisions.

Chemicals

List	Definition	Number of chemicals
TSCA2	The TSCA Step 2 chemicals	344*
SCIL	Safer Chemicals Ingredients List	867
TSCA2 / SCIL	Unique set of chemicals from the merged TSCA Step 2 and SCIL lists	1184

*The TSCA Step 2 chemicals number 344 instead of the original 345 due to consolidation with another category (EPA, 2016).

New Approach Methods

- Human Hazard
  - LOAEL/NOAEL – Computational model using chemical structure and bioactivity (Truong et al., In Press); ToxCast bioactivity (Wetmore et al., 2013; HC, 2016)
  - Endocrine – ToxCast Estrogen Receptor (ER) and Androgen Receptor (AR) models (Judson et al., 2015; Kleinstruer et al., 2016); CERAPP ER QSAR model (Mansouri et al., 2016)
  - Subchronic, Chronic, Developmental/Reproductive, Neurotoxic Effects – Generic Read Across (GenRA) models (Shah et al., 2016)

- Human Exposure
  - Exposure pathway prediction
  - Quantitative exposure estimates – Systematic Empirical Evaluation of Models (SEEM)(Wambaugh et al., 2014) and Stochastic Human Exposure and Dose Simulation-High-Throughput (SHEDS-HT)(Isaacs et al., 2014)

- Persistence and Bioaccumulation
  - Environmental half-life – OPERA QSAR model
  - Bioaccumulation factor – OPERA QSAR model

Methods

Method 1: TSCA 2012
- Maximum score from human and eco hazard: 1 – 3
- Maximum score from human and eco 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 eco hazard
- Sum all components (incl. NAM) from human and eco exposure
- Sum all components (incl. NAM) from persistence/ bioaccumulation
- Add hazard, exposure, and P/B
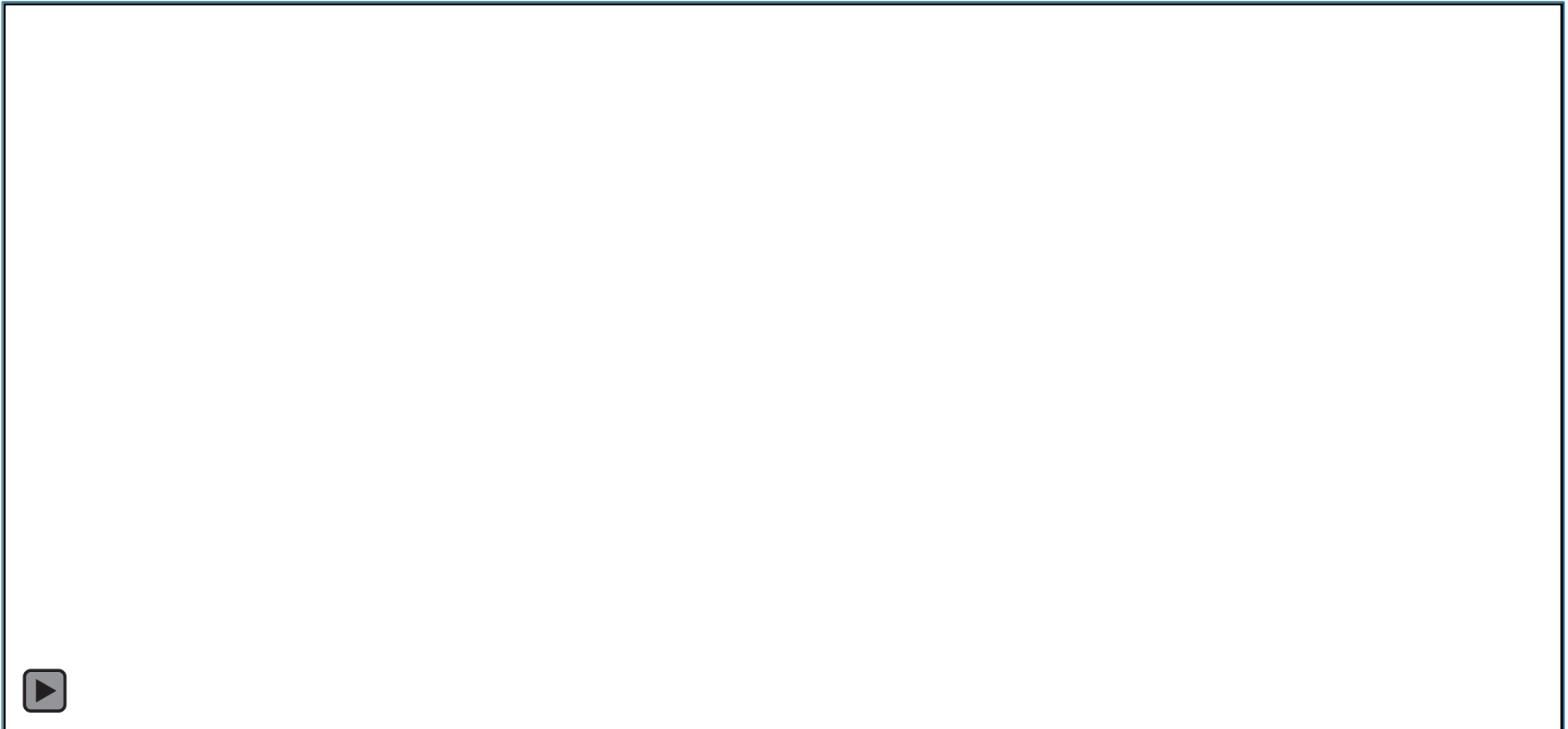- Categorical bins
  - High: >30
  - Medium: 10-30
  - Low: ≤10

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

RapidTox Workflow Integration
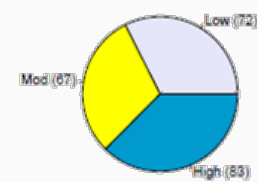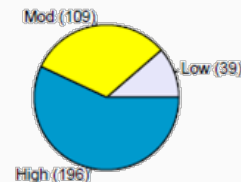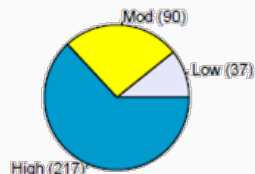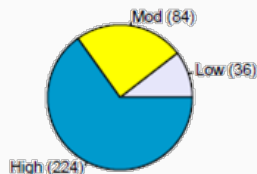
Pre-Prioritization Binned Breakdown

Chemical Scores and Data Landscape

TSCA Step 2

SCIL

Chemicals

Human Hazard | Eco Hazard | Human Exposure | Eco Exposure | Persistence / Bioaccum

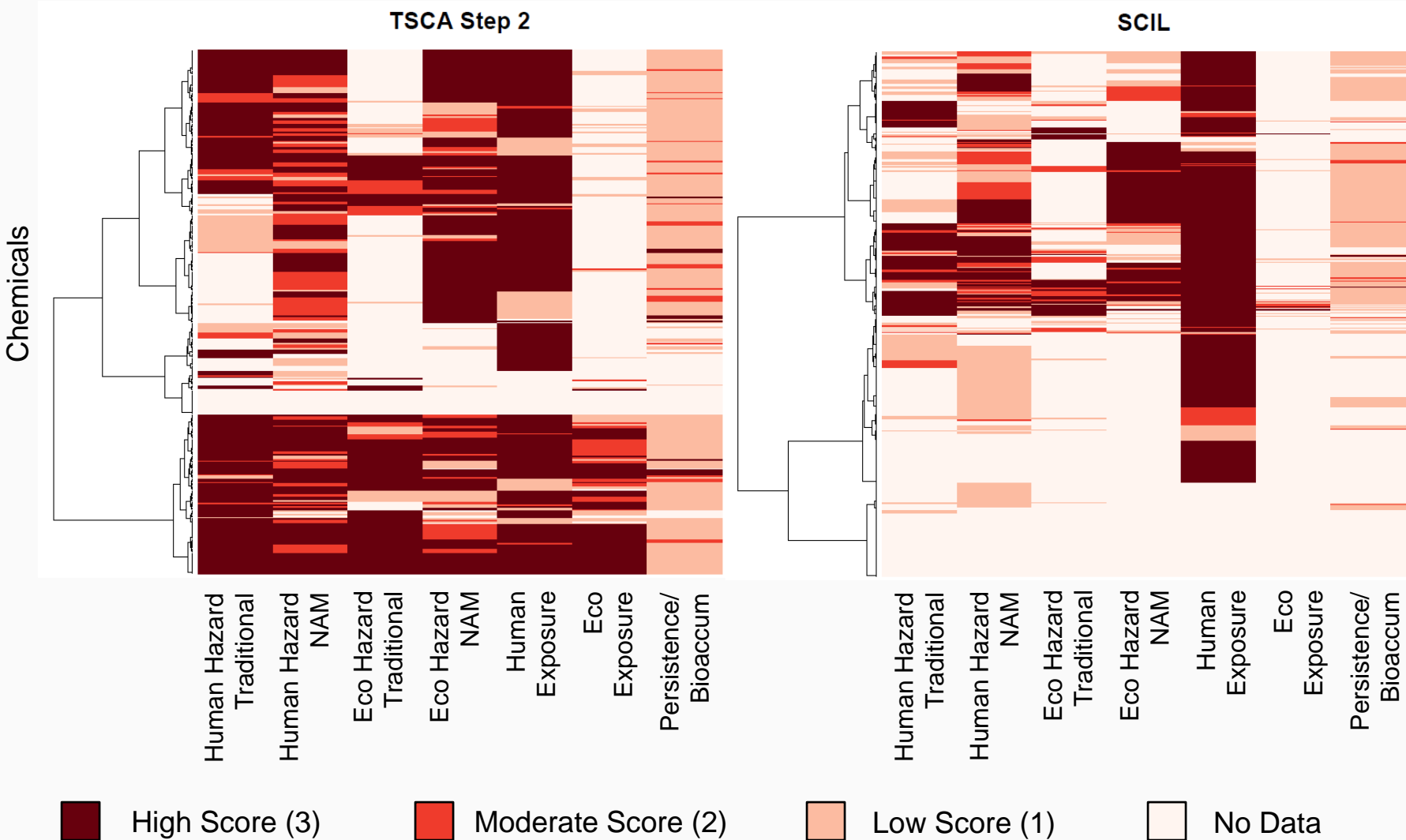High Score (3) Moderate Score (2) Low Score (1) No Data
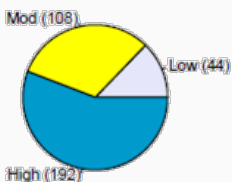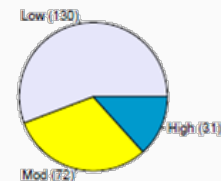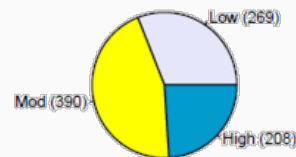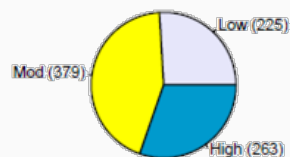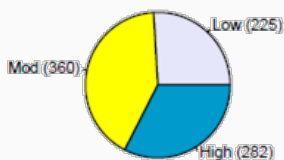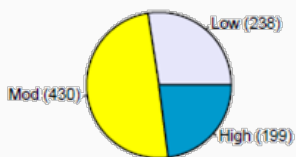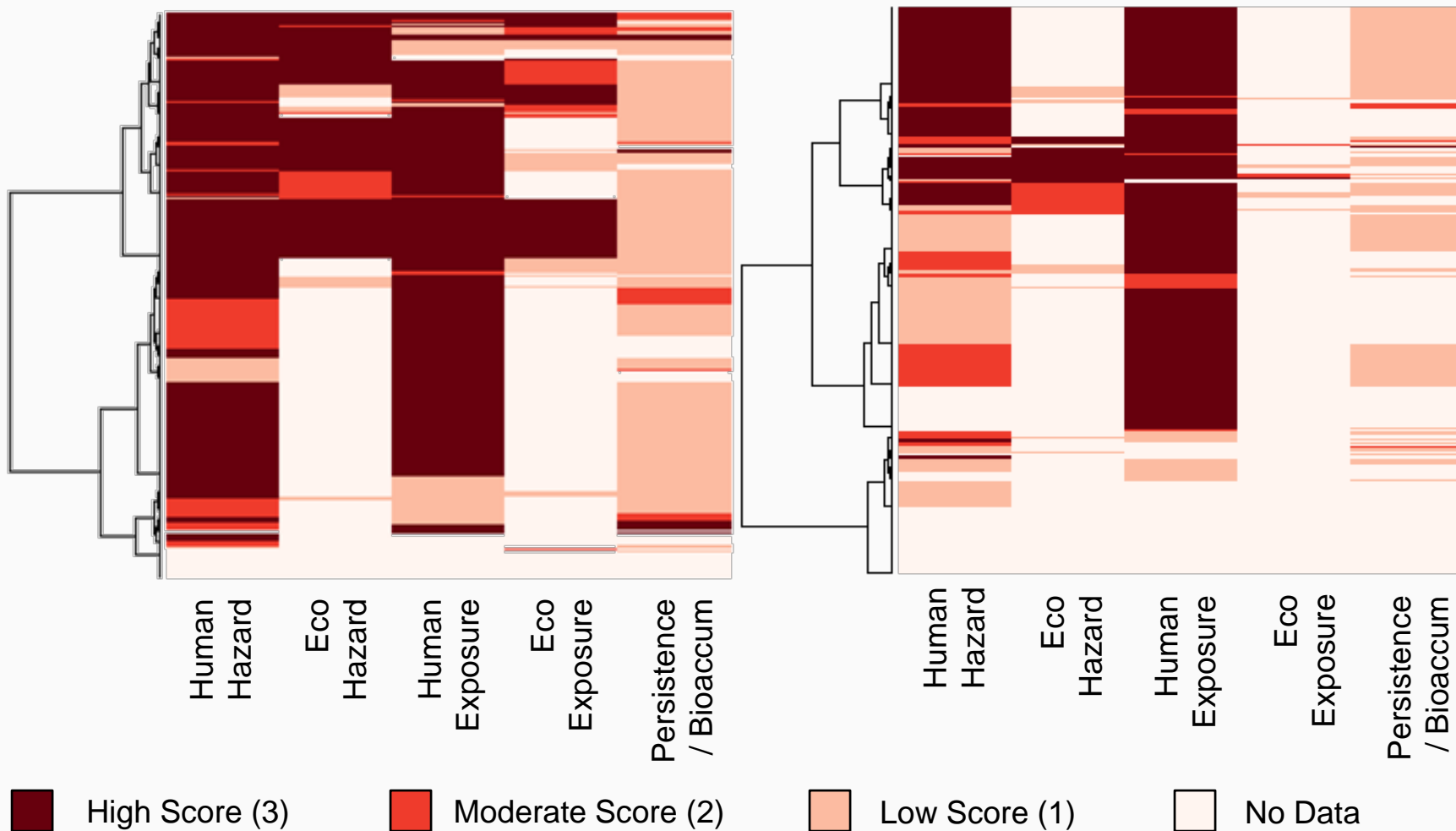
Quick Summary

- The RapidTox workflow enabled identification of data that contributed most to candidate selection and allowed flexible exploration of prioritization methods

- Each method resulted in more high pre-priority chemicals for TSCA Step 2 than SCIL

- Incorporation of NAM data changed 22% of the TSCA Step 2 chemicals and 31% of SCIL chemicals, either by adding data or by changing the overall bin (Low, Moderate, High)

- Similar distributions across Low, Moderate, High bins were observed for Methods 1 – 4, while Method 5 (BER) resulted in lower proportion of High pre-priority chemicals

- The data landscape was poor for ecological hazard and exposure, but no NAM data were incorporated

Progress Since Discussion Document Release

- Human Hazard
  - Added more acute studies

- Ecological Hazard
  - Added zebrafish embryo assay data to estimate aquatic toxicity
  - Added Toxicity Estimation Software Tool (TEST) and Ecological Structure Activity Relationships (EcoSAR) predictions for aquatic toxicity

- Ecological Exposures
  - Added limited number of high-throughput water model predictions (Barber et al., 2017)

- Identification of Common High Pre-Priority Chemicals
  - Evaluated overlap of high pre-priority chemicals among methods

Updated Chemical Scores and Data Landscape

TSCA Step 2 | SCIL

Chemicals

Human Hazard Traditional | Human Hazard NAM | Eco Hazard Traditional | Eco Hazard NAM | Human Exposure | Eco Exposure | Persistence/ Bioaccum

High Score (3) | Moderate Score (2) | Low Score (1) | No Data
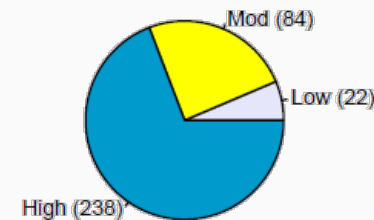
Updated Pre-Prioritization Binned Breakdown

Old Database

Updated Database

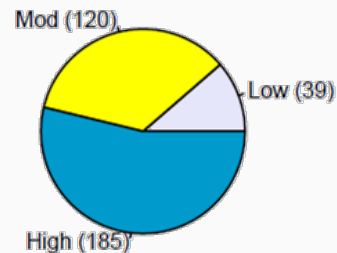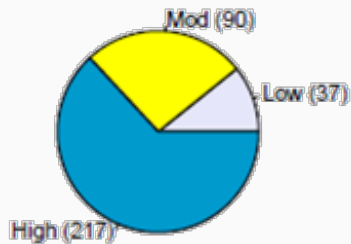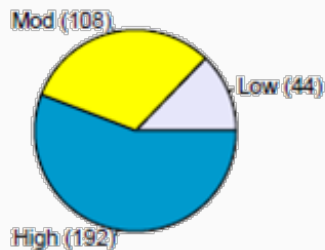TSCA 2012   NAM Deferential   TSCA 2012   NAM Deferential

TSCA Step 2 (344)

Mod (108), Low (44), High (192)

Mod (90), Low (37), High (217)

Mod (120), Low (39), High (185)

Mod (84), Low (22), High (238)

SCIL (867)

Low (238), Mod (430), High (199)

Low (225), Mod (379), High (263)

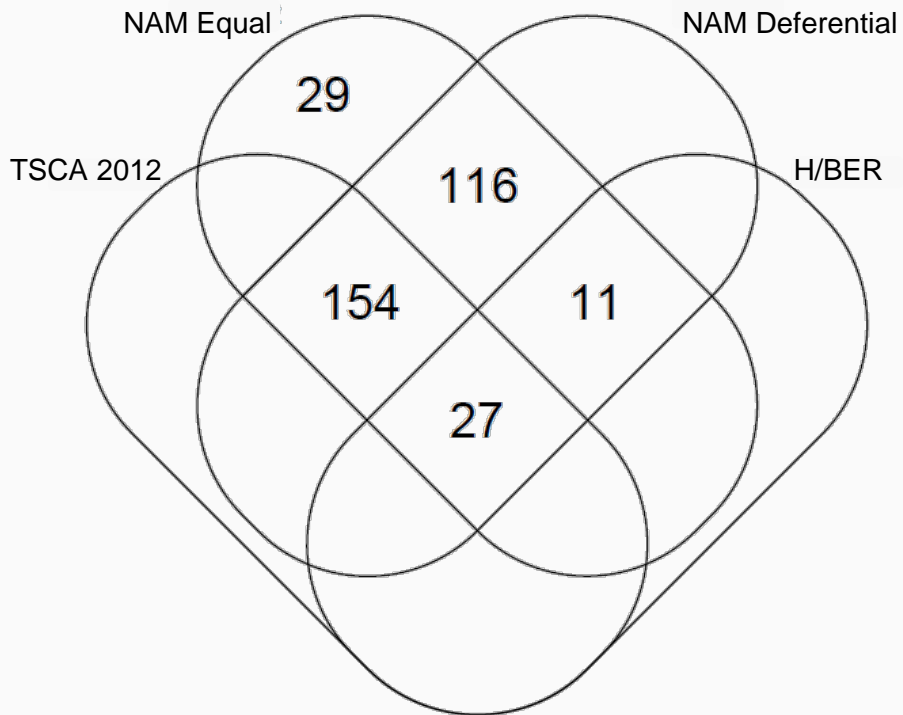Low (241), Mod (445), High (181)

Low (213), Mod (346), High (308)
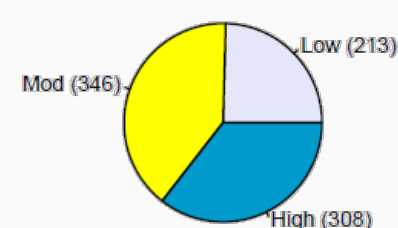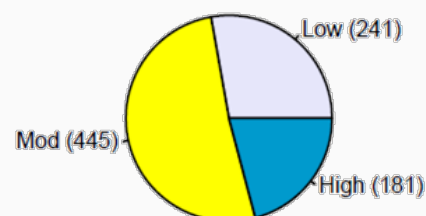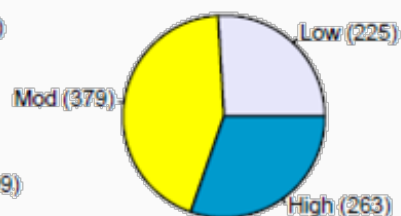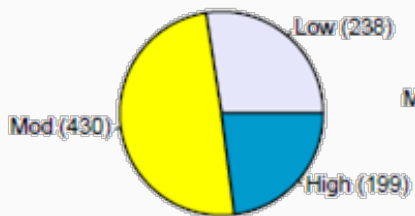
- ■ High Pre-Priority
- ■ Moderate Pre-Priority
- ■ Low Pre-Priority

Overlap of High Pre-Priority Chemicals

TSCA Step 2

SCIL

NAM Equal

NAM Deferential

TSCA 2012

H/BER

7

47

125

6

2

60

NAM Equal

NAM Deferential

TSCA 2012

H/BER

29

116

154

11

27
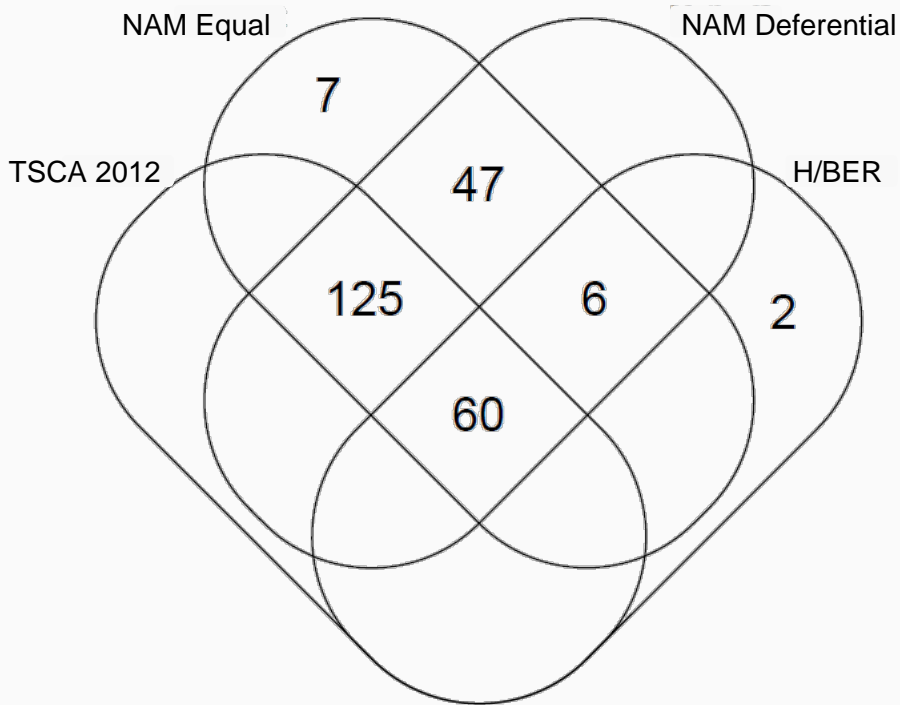
Quick Summary of Progress

- Ongoing efforts have filled specific data gaps, but have had marginal effects on numbers of chemicals in pre-priority bins

- Significant overlap in high bin chemicals across methods highlight potential consensus chemicals for pre-prioritization

Benefits of Approach

- Transparency and reproducibility for the candidate selection process

- Systematic examination of data domains that contribute most to candidate selection

- Utilizes large collections of existing traditional and NAM data for hazard, exposure, persistence, and bioaccumulation

- Accommodates new methods and data when available

- Incorporates cost-effective NAM for collecting data on thousands of chemicals to fill gaps in traditional data

- Enables focused data requests to stakeholders

Caveats of Approach

- Ongoing data cleaning and curation
- Ecological hazard endpoints currently limited to acute and chronic aquatic toxicity
- No quantitative estimates for occupational exposure
- No respiratory sensitizer data in current database
- No experimentally measured persistence and bioaccumulation data in current database
- Limited media and chemical coverage for quantitative ecological exposure
- Scoring criteria in this approach do not account for Safer Choice use restrictions (e.g., strong acids as pH modifiers), or some SCIL criteria (e.g., rate of biodegradation to mitigate aquatic toxicity)

Ongoing and Future Efforts

- Systematically addressing caveats in proceeding slide (e.g., experimental data for persistence/ bioaccumulation, ecological toxicity data)

- Incorporating inhalation studies into the H/BER method

- Progressively adding additional NAM data relevant to regulatory endpoints and chemicals of concern
  - Hazard (e.g., neurotoxicity, developmental toxicity)
  - Chemicals (e.g., volatiles)

- Improve RapidTox workflow to increase flexibility and provide preliminary assessment of data sufficiency for risk evaluation

Thank you