



The Chemical Landscape of New Approach Methodologies for Exposure

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*APCRA Public Webinar
March 11, 2020*

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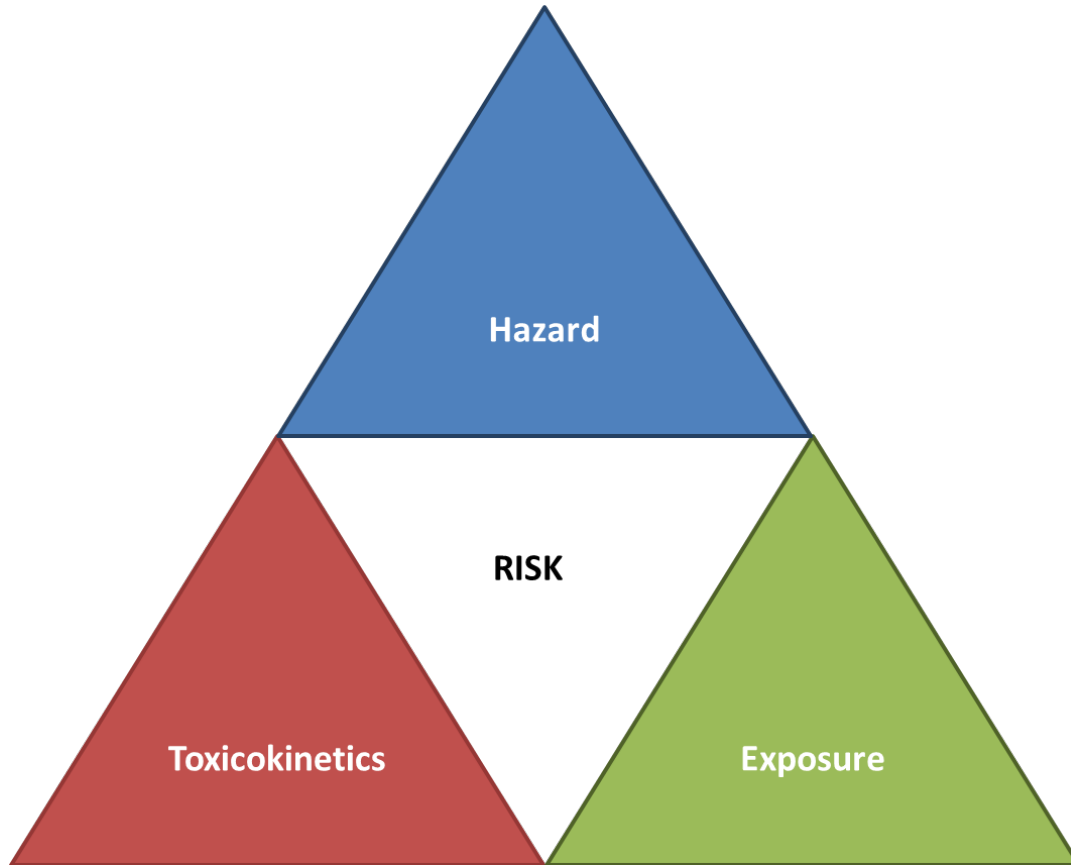
Triaging Chemical Exposure Data Needs and Tools for Advancing Next-Generation Risk Assessment

- Identify available New Approach Methodologies (NAMs) for exposure data streams
- Examine the landscape of exposure data (both traditional and NAMs) for an inventory of chemicals relevant to APCRA partners
- Identify key information or activities that would enable or enhance fit-for-purpose exposure estimates, predictions, or assessments
- Provide exposure metrics to support the APCRA inventory and hazard-focused case study activities
- Evaluate exposure NAMs against traditional methods to evaluate utility in different regulatory contexts

Contributors

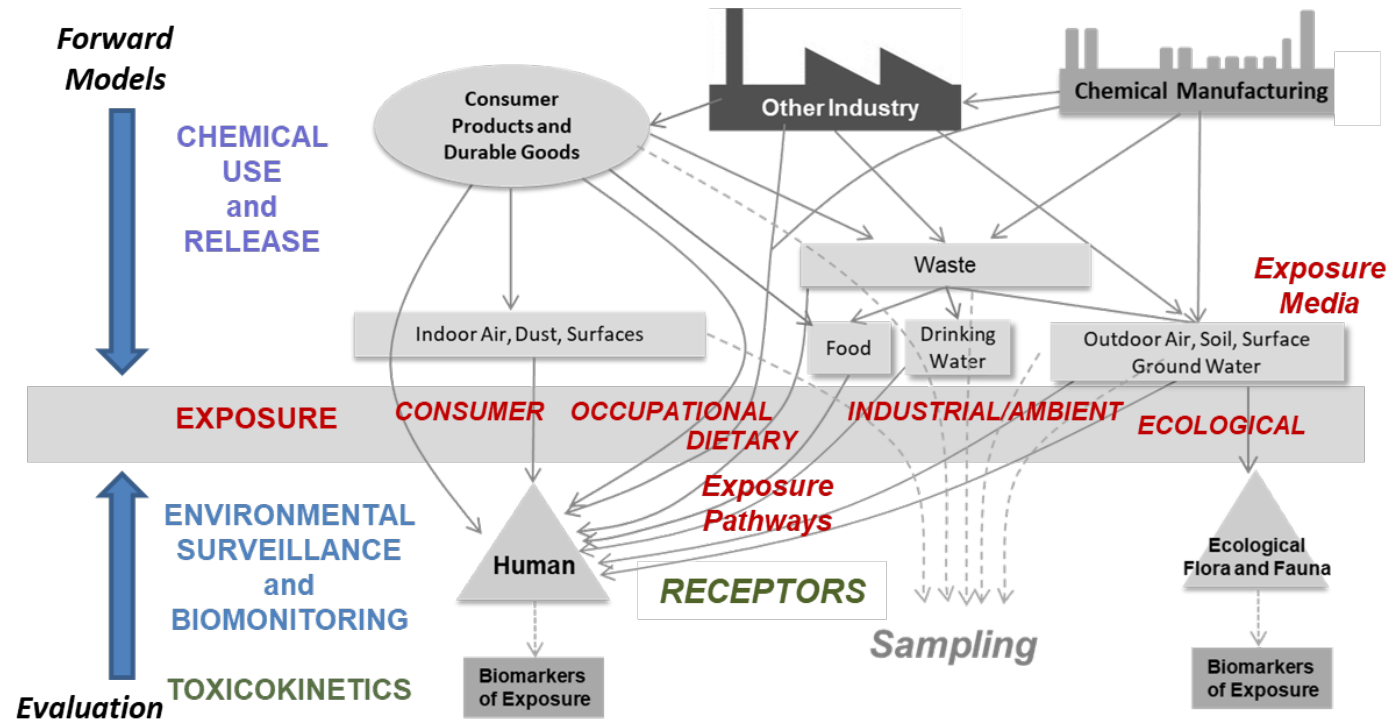
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Risk is Multifaceted



- Evaluating chemicals for risk to humans or the environment requires information on hazard and exposure potential
- Exposure potential quantifies the degree of contact between a chemical and a receptor
- Toxicokinetic information is required to bridge hazard and exposure (what real-world exposure is required to produce an internal concentration consistent with a potential hazard?)
- Regulatory bodies are tasked with evaluating risks associated with 1000s of chemicals in commerce. For example, as of 2019 there were ~40,000 chemicals on EPA's TSCA Active Inventory

Forecasting Exposure is a Systems Problem



Critical Exposure-Relevant Domains

- **Chemical use and release.** Provides critical information for identifying chemical sources, exposure pathways, and relevant predictive models for a given chemical.
- **Media occurrence, environmental surveillance, and biomonitoring.** Provides exposure data for evaluating predictive models.
- **Exposure estimates.** Predictions of chemical intake in mg/kg/day that can be compared with hazard information to inform risk.
- **Toxicokinetics.** Provides real-world exposure context to *in vitro* high-throughput screening data and biological receptor monitoring information.

Classes of NAMs for Exposure

- **Chemical descriptors** that provide information on chemicals in an exposure context (e.g., how chemicals are used)
- **Machine-learning approaches** that use these descriptors to fill gaps in existing data
- **High-throughput exposure models** for various pathways
- **High-throughput measurements** to fill gaps in monitoring data
- New **evaluation frameworks** for integrating models and monitoring to provide consensus exposure predictions
- High-throughput approaches for measuring and predicting chemical **toxicokinetics**
- All these pieces together provide the tools for high-throughput **chemical prioritization**

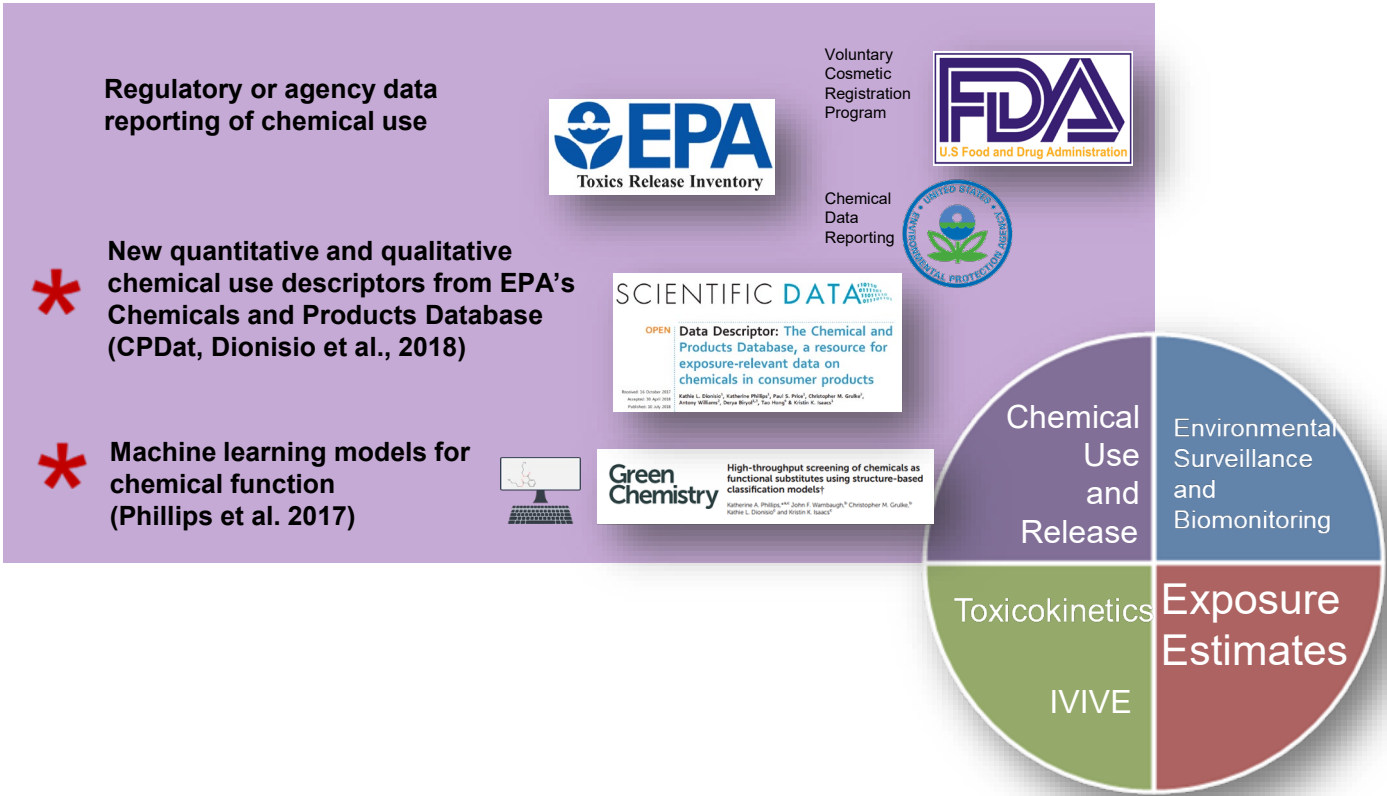


Characterizing the Chemical Landscape for Exposure NAMs

- “APCRA inventory” - case study chemical list
 - **6621** chemical substances compiled by APCRA partners for potential use in retrospective or prospective case studies- primarily single component
 - Selected from regulatory lists from EPA, Health Canada, ECHA, EFSA, NICNAS
- Investigated the coverage of this inventory
 - “Traditional” exposure data
 - Regulatory reporting
 - Targeted monitoring data
 - Regulatory exposure assessments
 - *In-vivo* toxicokinetic information
 - Exposure NAMs across all four domains

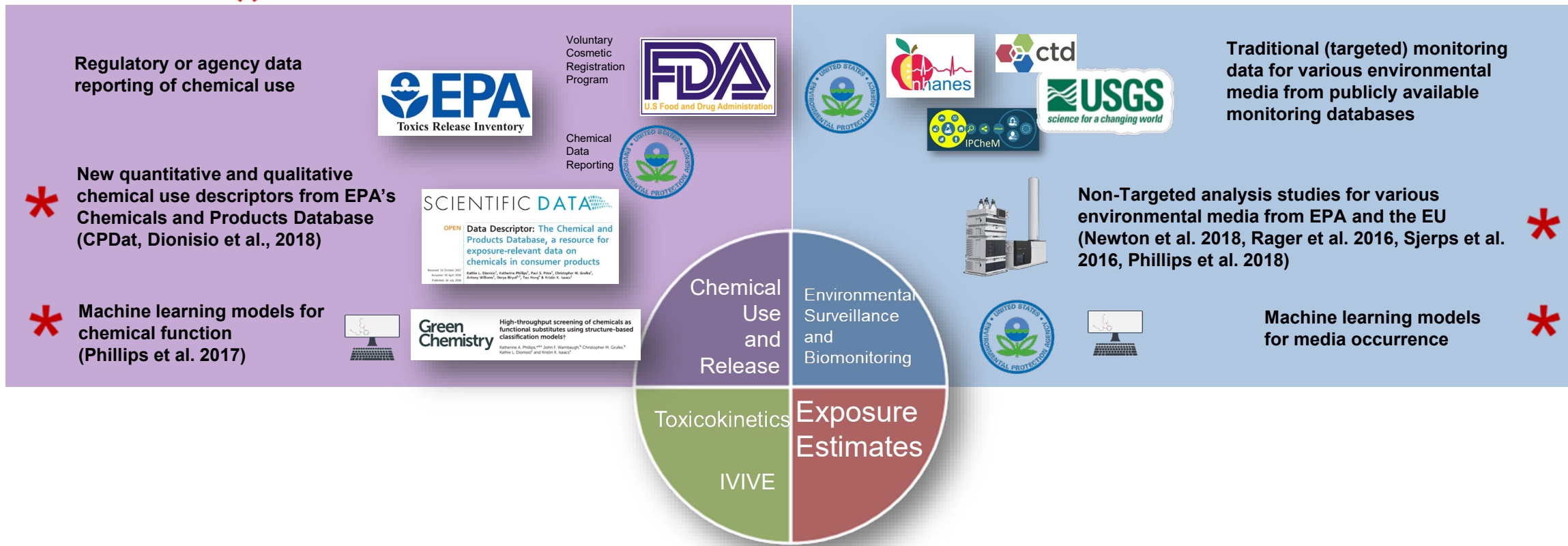
Traditional and NAM Exposure Datasets

*** NAM dataset**



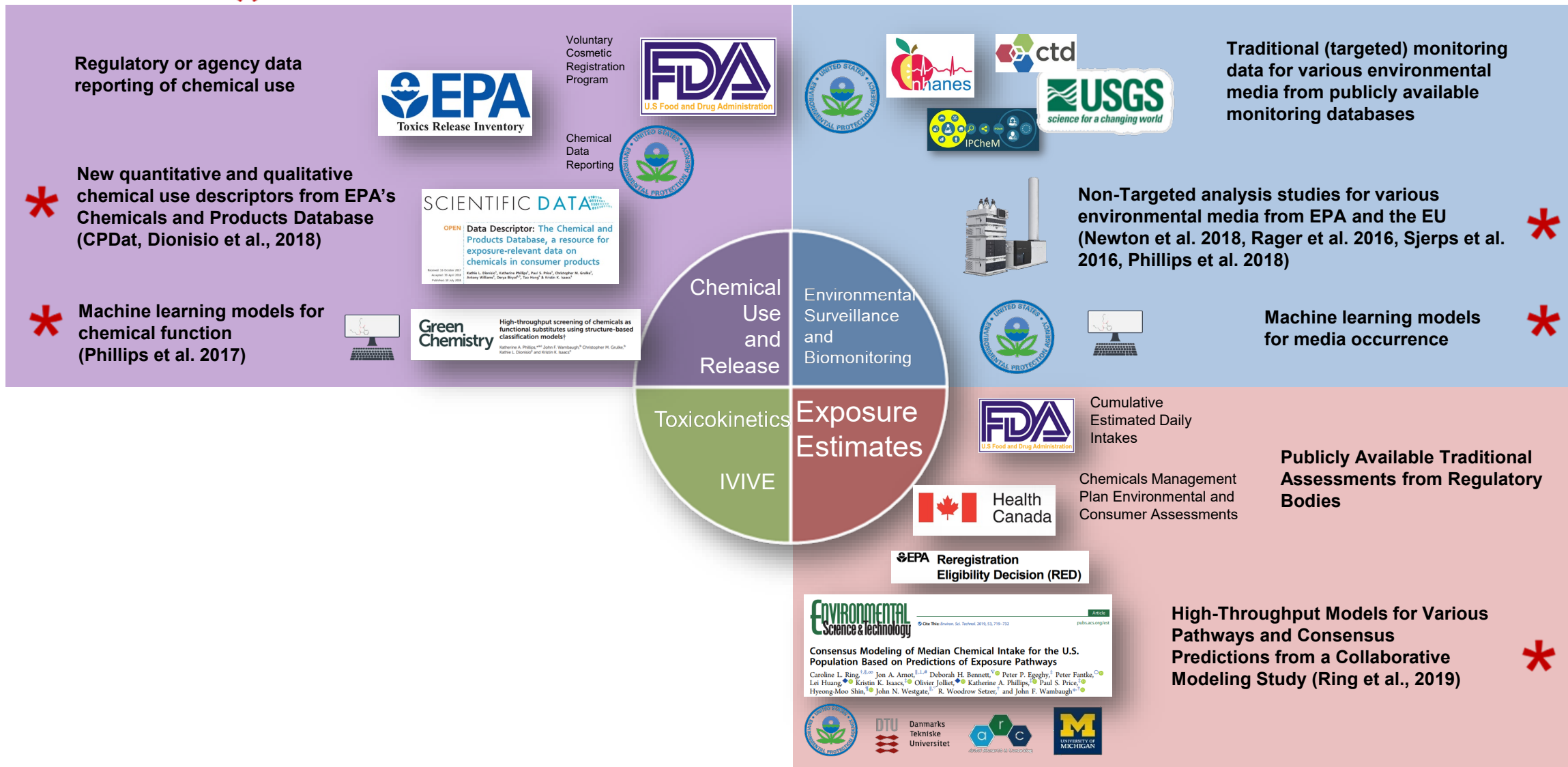
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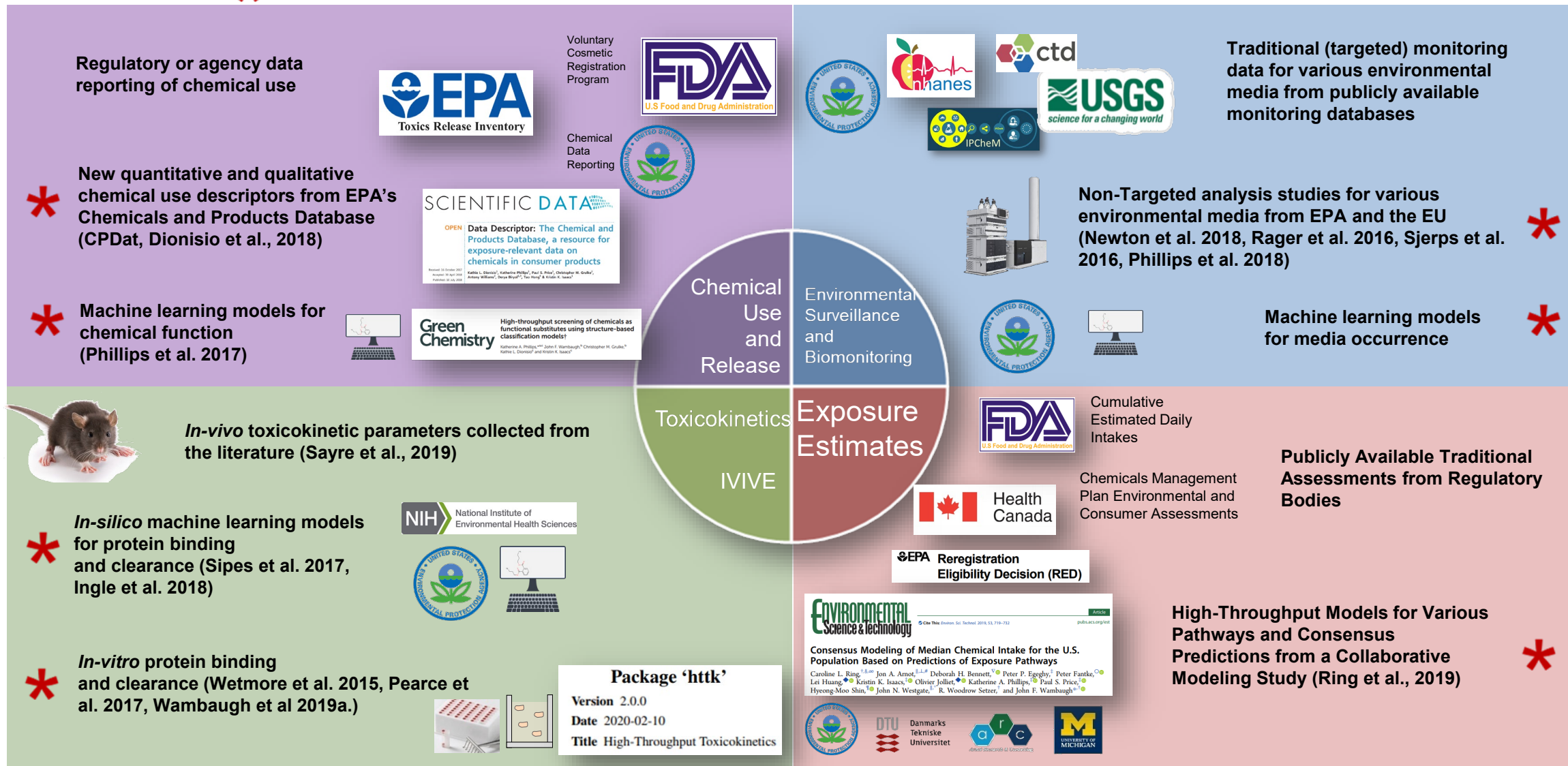
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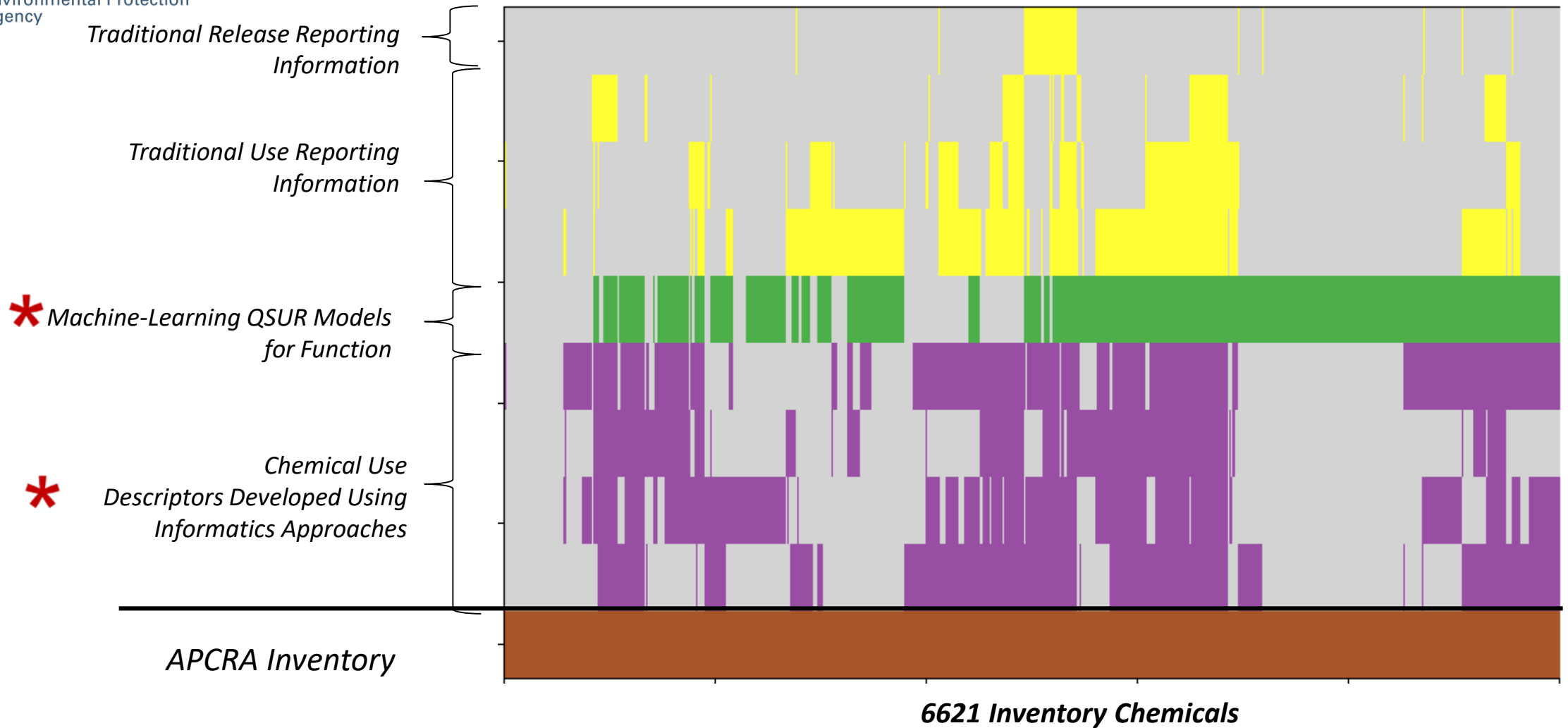


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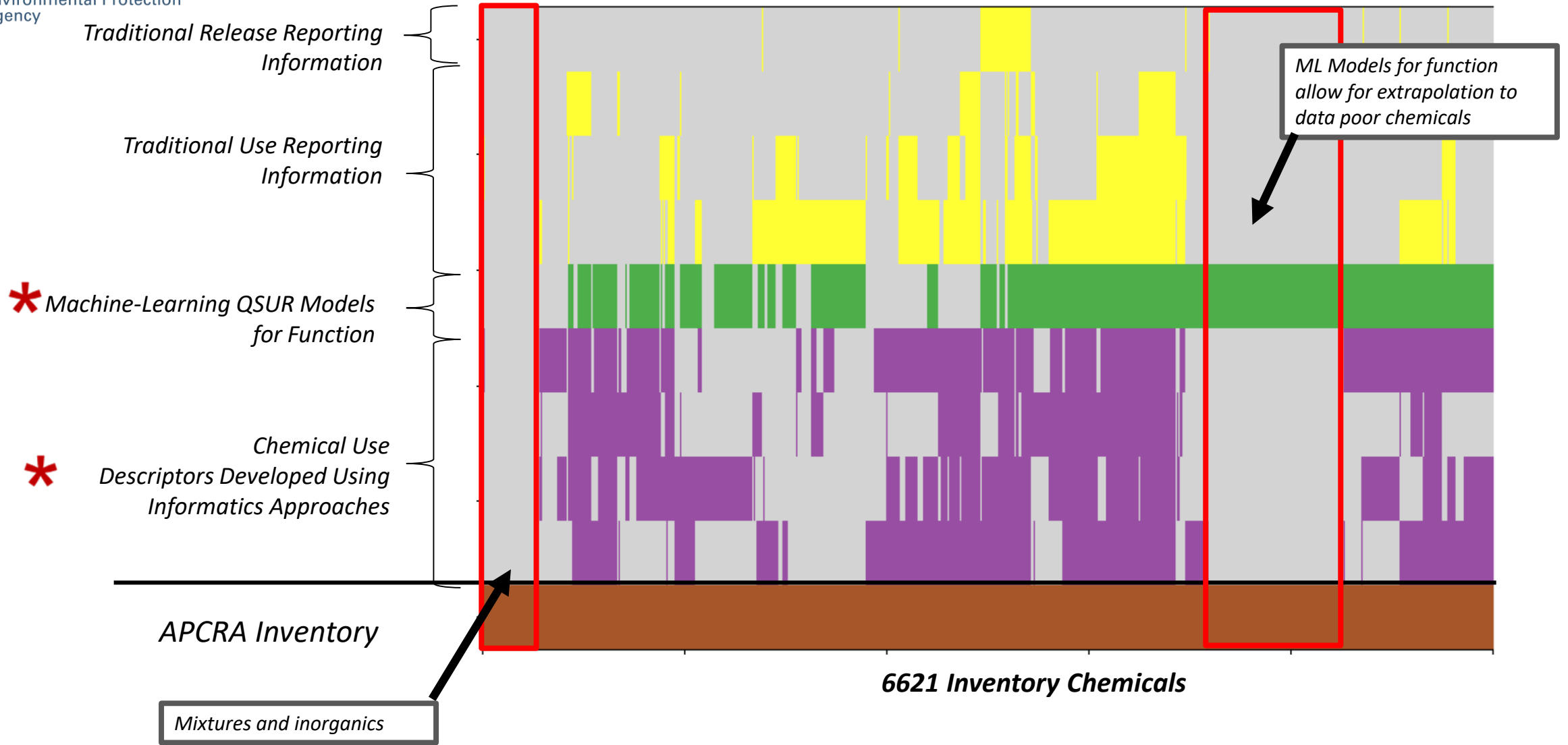


Chemical Use and Release



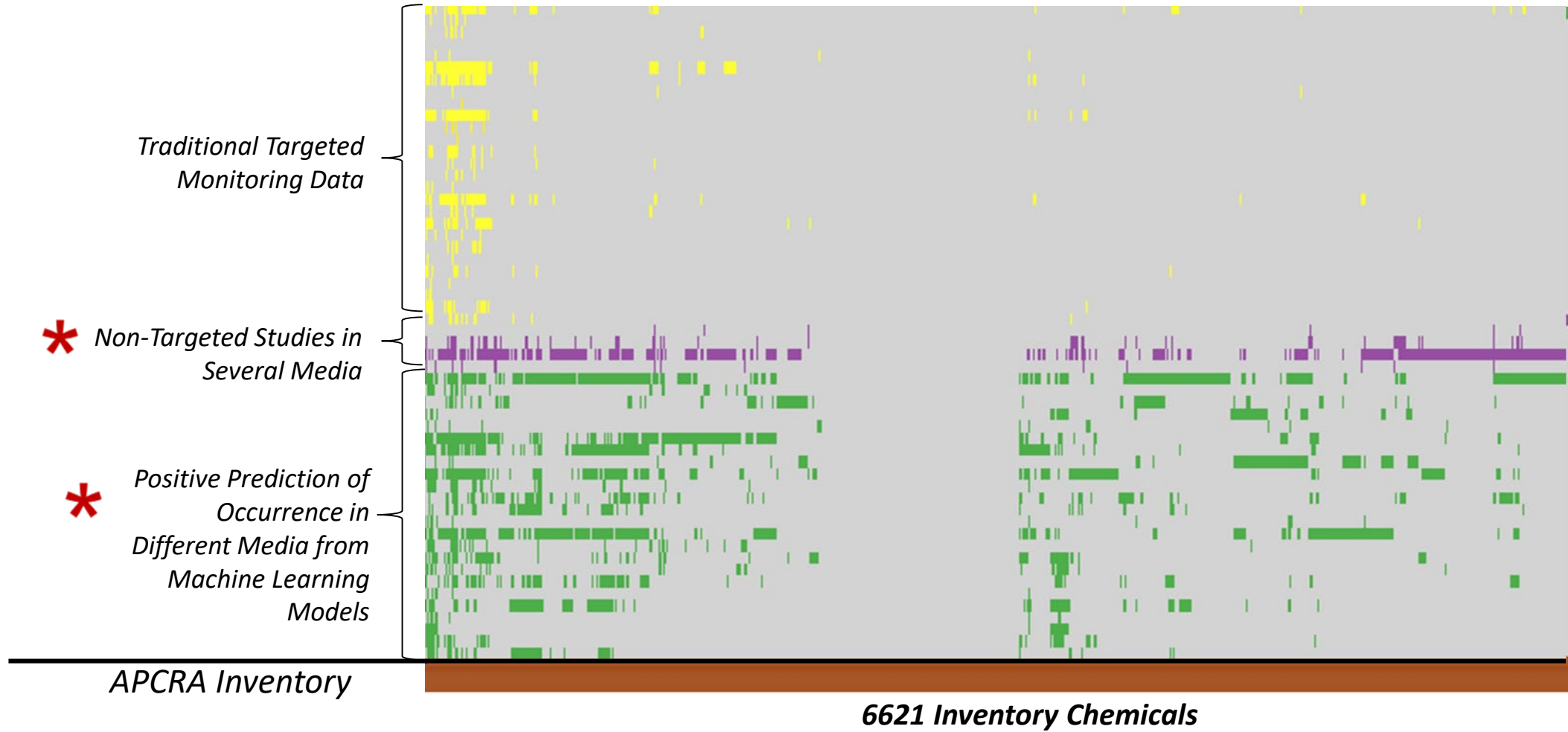
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Chemical Use and Release

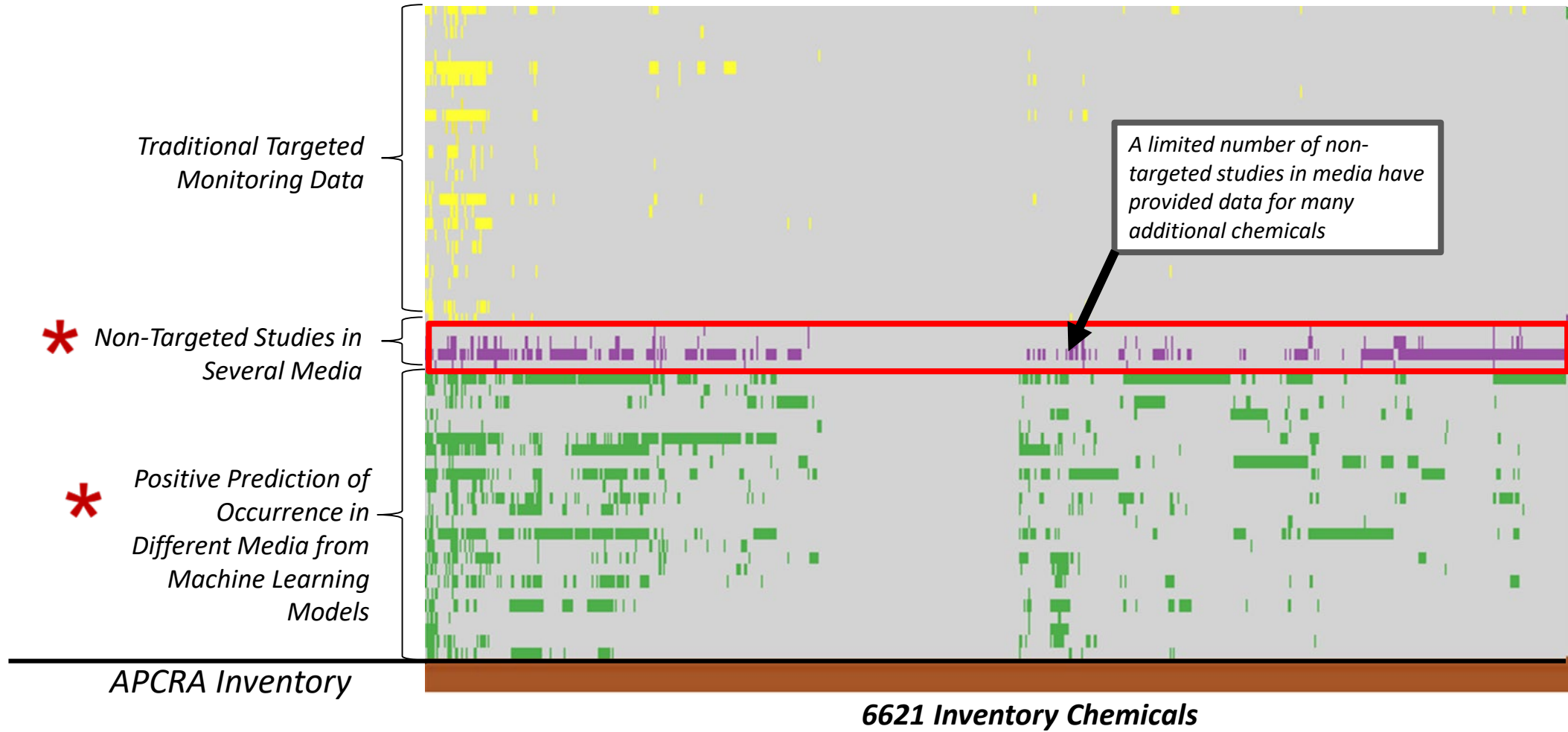


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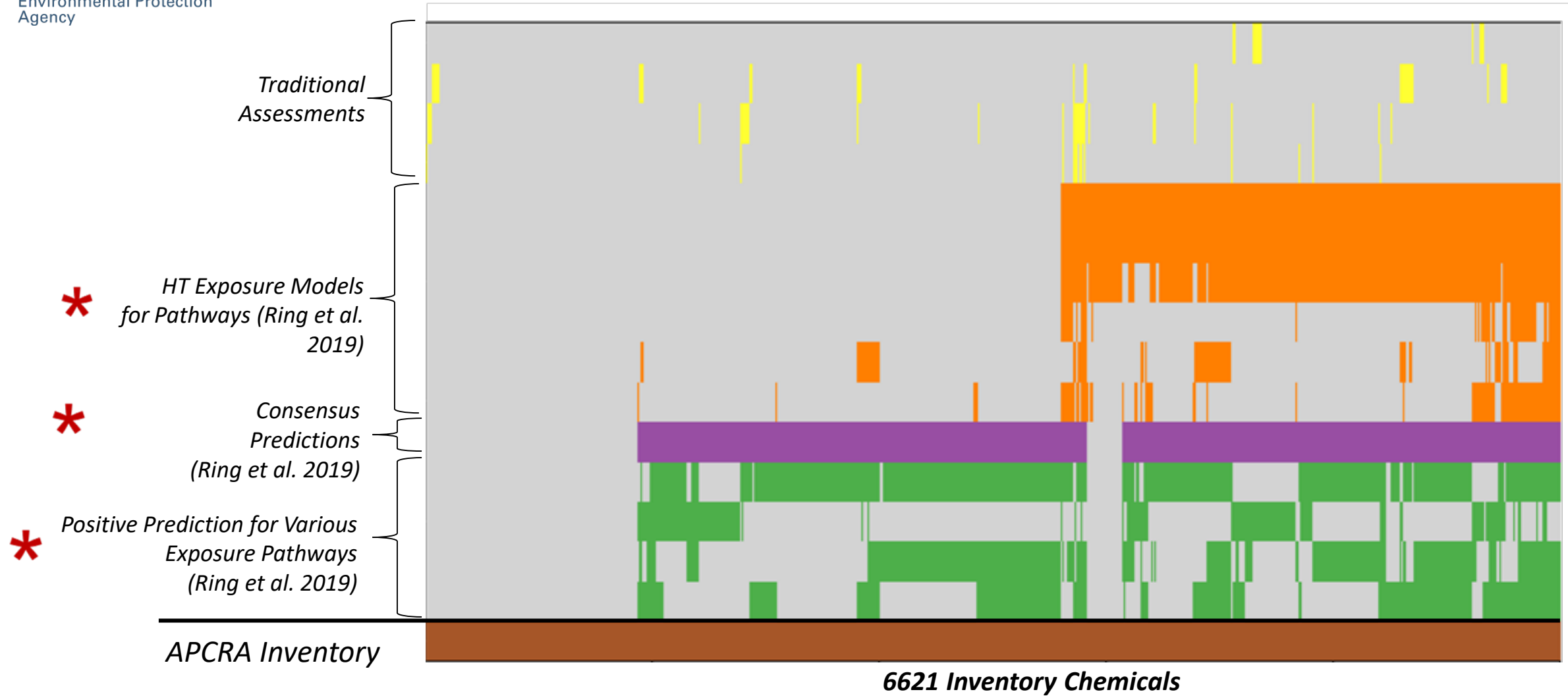
Media Occurrence, Environmental Surveillance, and Biomonitoring



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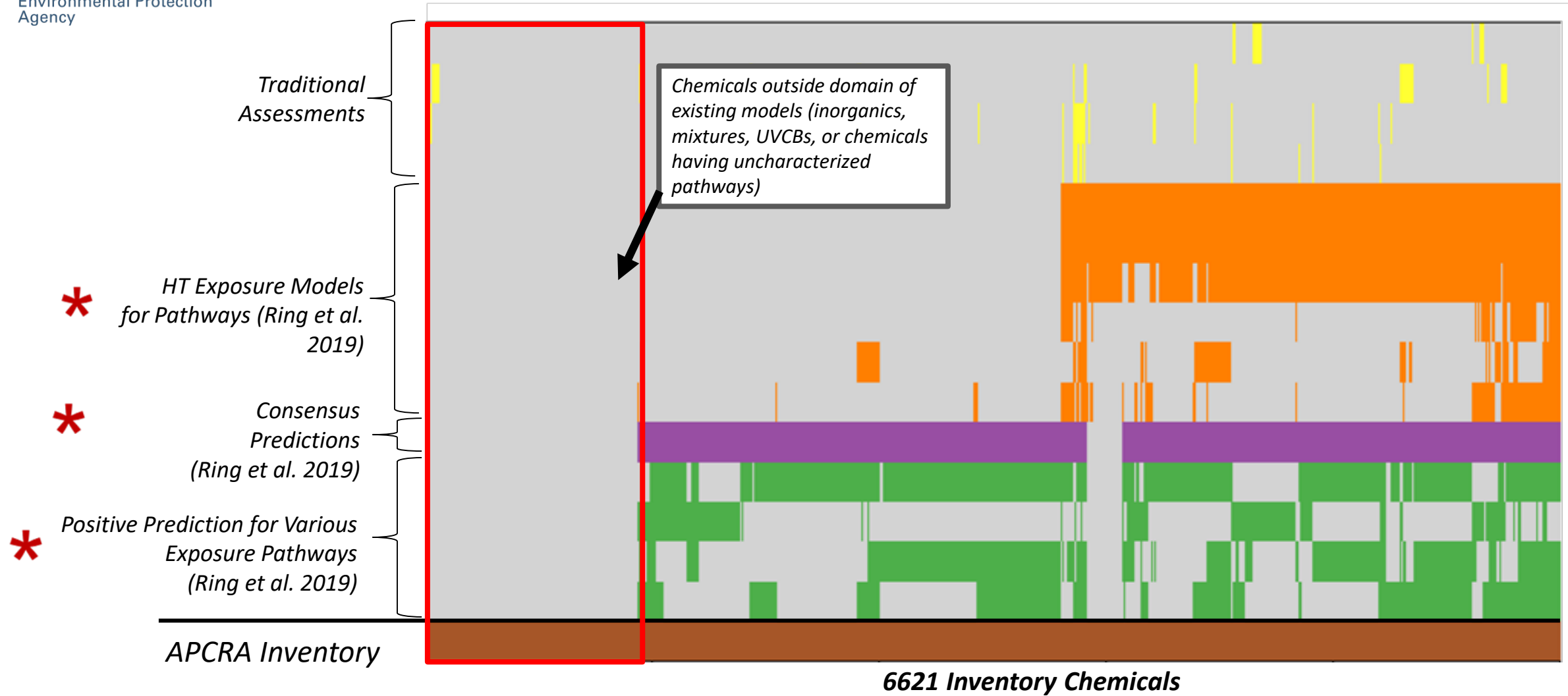


Exposure Predictions



- High-throughput exposure models covering different exposure pathway classes have generated exposure estimates for large numbers of chemicals compared to traditional assessments.

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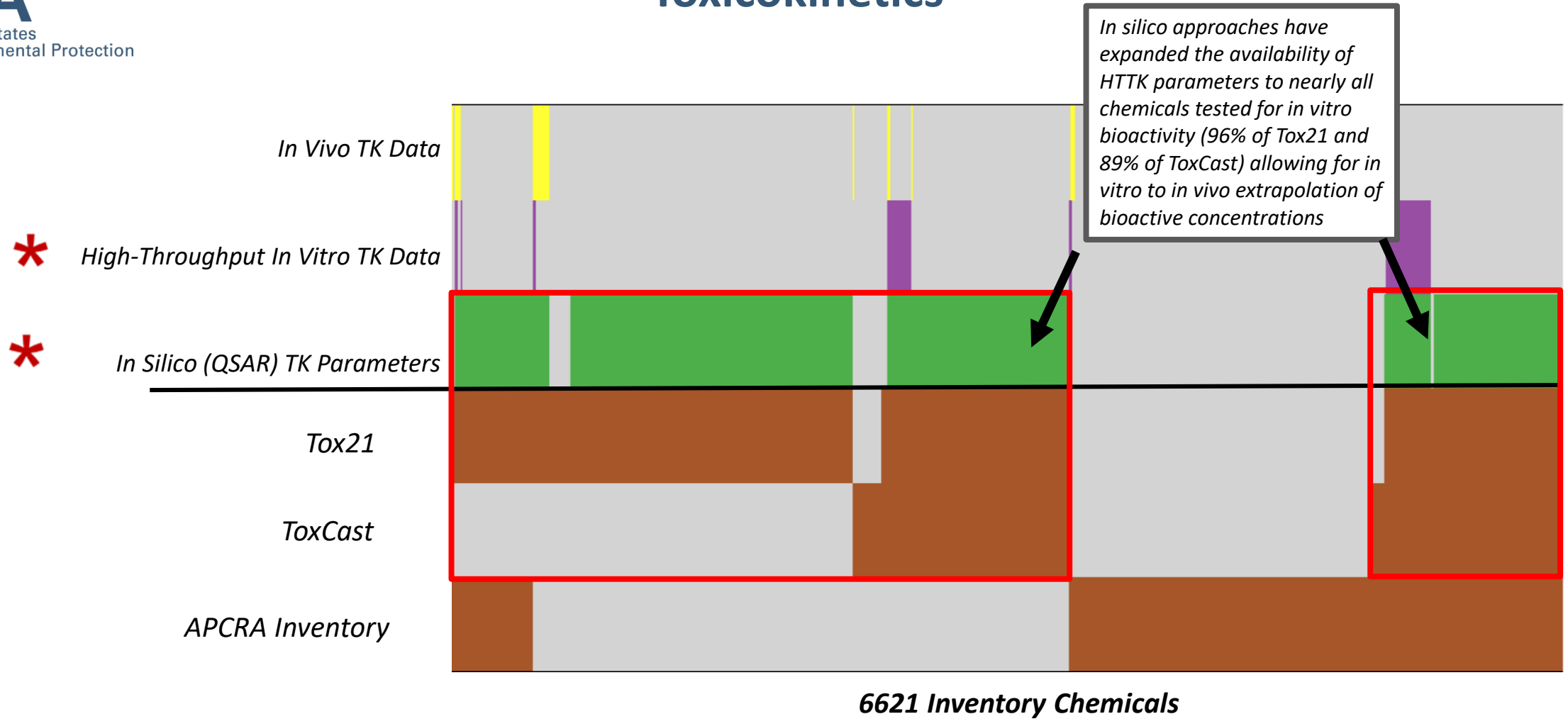
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Toxicokinetics



- *High throughput* in vitro measurement of toxicokinetics has expanded the quantity and domain of chemicals with data, allowing for the development or refinement of *in silico* models

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Landscape Summary

- In all exposure-relevant domains, high-throughput NAMs have substantially increased the number of chemicals for which data are available and improved coverage of chemical inventories.
- Methods for estimating chemical releases (quantitative estimates of emission into different environmental compartments) are needed; predictions for releases can reduce uncertainty in HT exposure models that currently rely on production volume as surrogates for emission rates.
- Methods should be developed for addressing mixtures or UVCBs. Approaches are needed for identifying representative compositions or structures for multicomponent substances, and for making use of this information in *in silico* modeling (i.e., QSAR) frameworks.
- Measurement NAMs (i.e., non-targeted approaches) have the potential to substantially increase the scope of evaluation datasets for predictive exposure models.
- **Continuing to develop and refine NAMs for exposure and toxicokinetic domains will improve the quality of and expand the scope of risk-based metrics available for chemical prioritization.**

Ongoing Exposure NAM Evaluation Activities

- Will aid in assessing fit-for-use of exposure NAMs in various regulatory contexts (classification and labelling, prioritization, first-tier versus full assessments)
- Comparison of Quantitative Use Relationship (QSUR) models for chemical function with industry reported data
 - EPA's Chemical Data Reporting for Industrial Uses (Public)
 - ECHA Plastics Additives Initiative (PLASI)
 - Health Canada Chemicals Management Plan Information Gathering
- Comparison of traditional exposure assessments (Health Canada Chemicals Management Plan) to high-throughput model predictions
 - Consumer Assessments
 - Environmental media (i.e., ambient/far-field)

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