The Chemical Landscape of New Approach Methodologies for Exposure

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United States Environmental Protection Agency

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Exposure in the APCRA Initiative

- Identify available New Approach Methodologies (NAMs) for exposure-relevant domains
- 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 and provide recommendations
- Provide exposure metrics to support the APCRA inventory and hazard-focused case study activities

Contributors

US EPA Office of Research and Development Center for Computational Toxicology and Exposure	Health Canada	European Chemicals Agency
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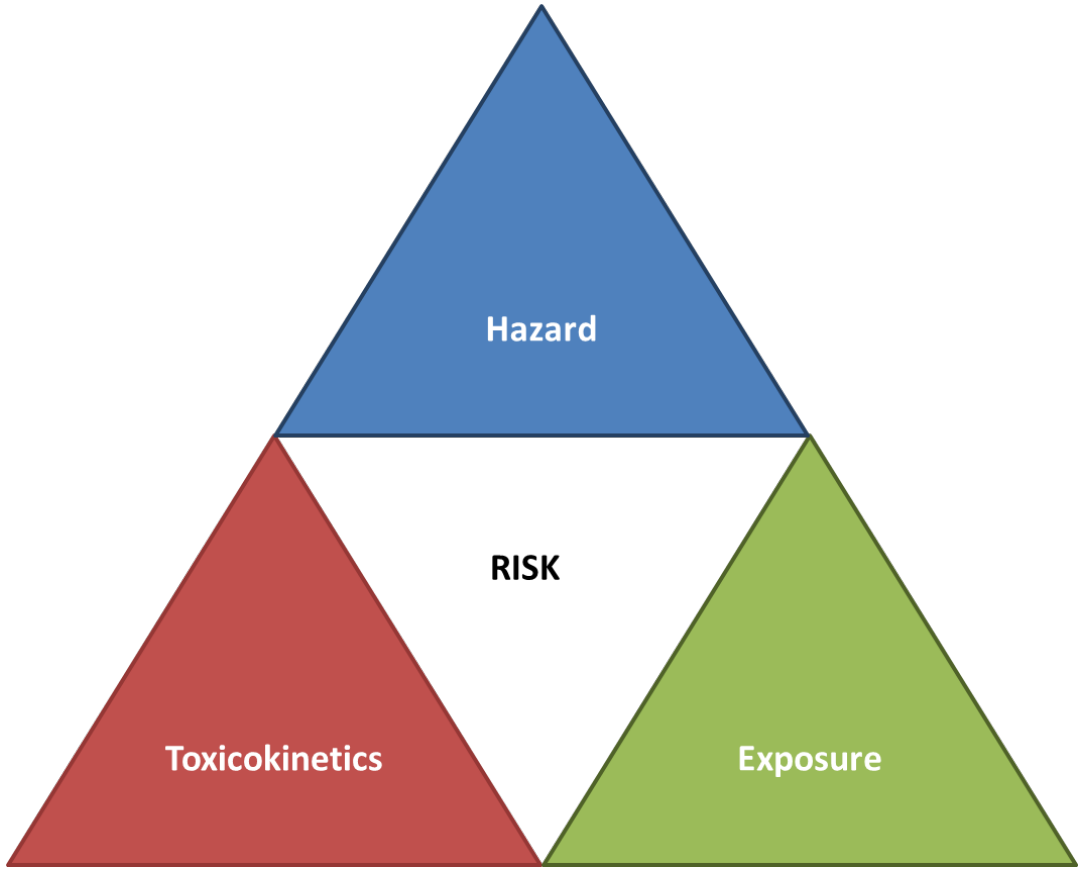
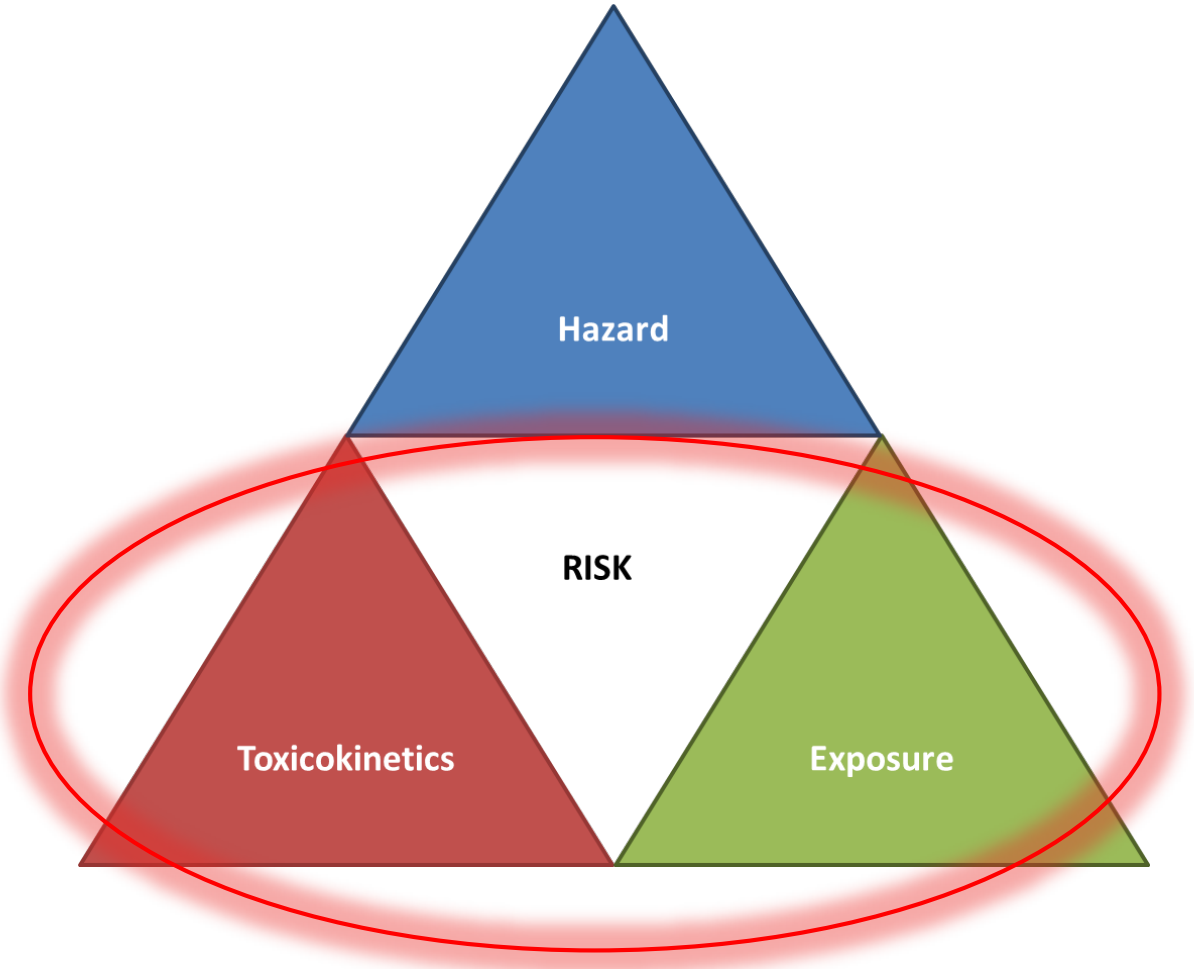
Risk is Multifaceted

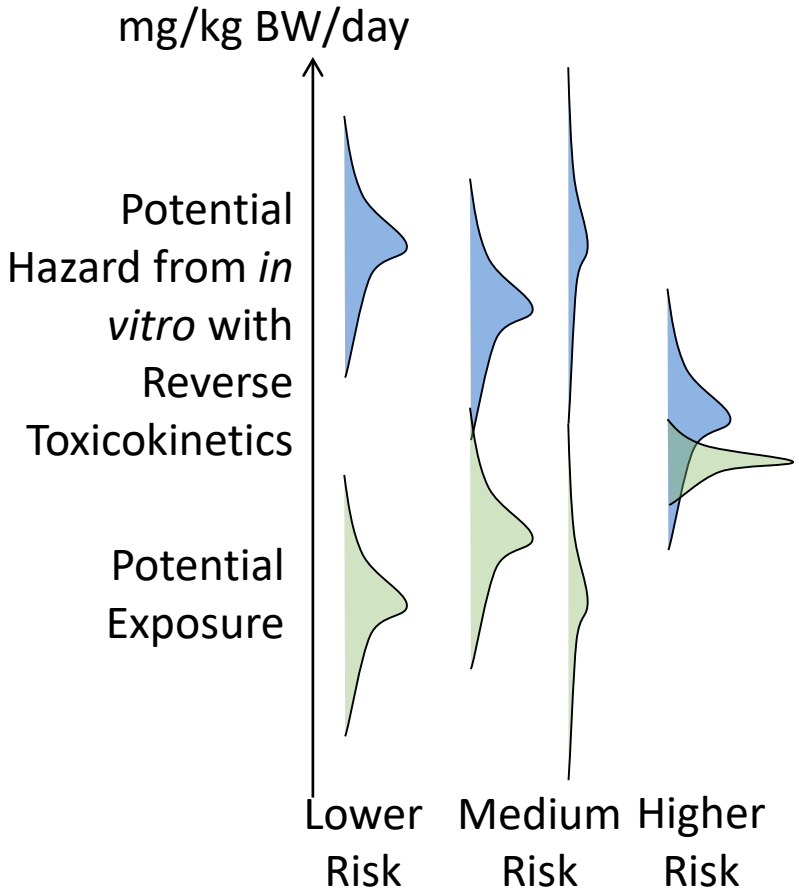


- Regulatory bodies are tasked with evaluating risks associated with 1000s of chemicals in commerce
  - For example, as of 2019 there were **~40,000** chemicals on EPA's TSCA Inventory
- Evaluating chemicals for risk to humans or the environment requires information on hazard and exposure potential
- 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?)

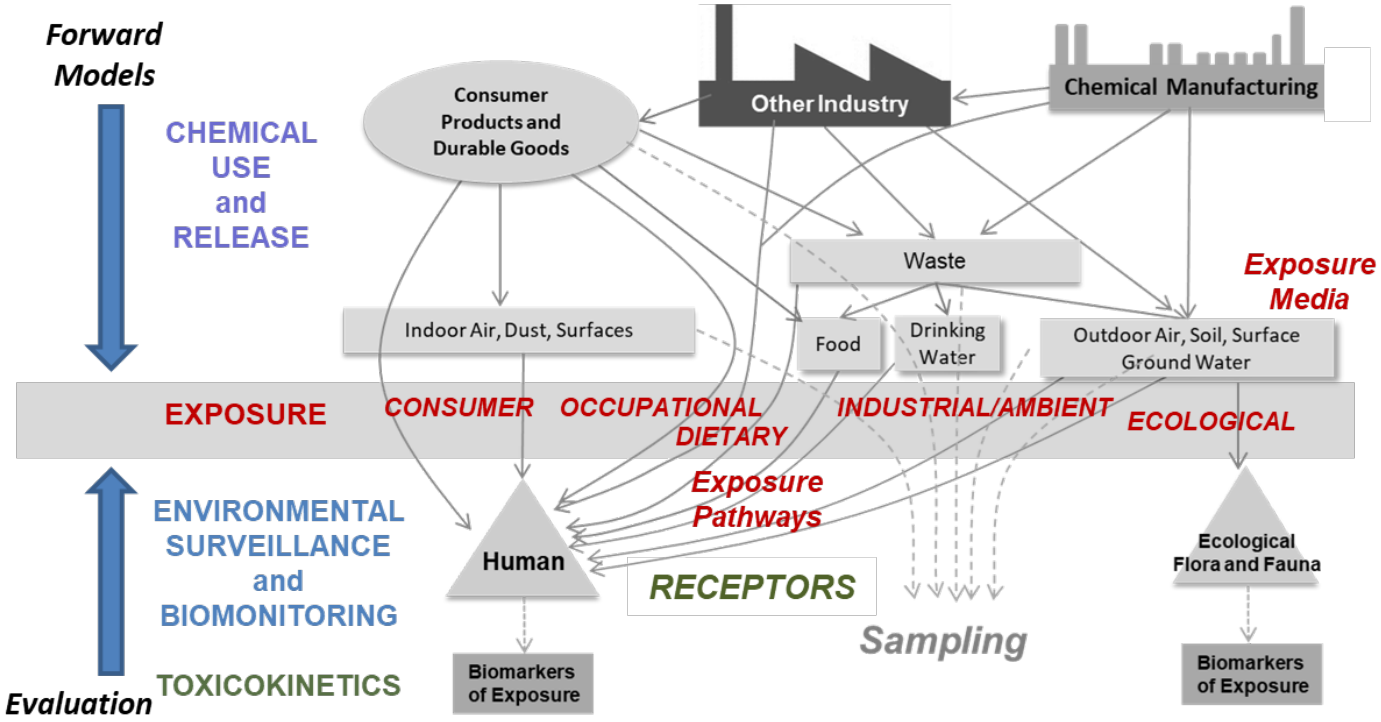
Risk is Multifaceted



EPA's ExpoCast Project



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.

Eight 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
- High-throughput approaches for measuring and predicting chemical ***toxicokinetics***
- New ***evaluation frameworks*** for integrating models and monitoring to provide consensus exposure predictions
- All these pieces together provide the tools for high-throughput ***chemical prioritization***

ELSEVIER

Current Opinion in Toxicology

Volume 15, June 2019, Pages 76-92

New approach methodologies for exposure science

John F. Wambaugh [1], Jane C. Bare [2], Courtney C. Carignan [3], Kathie L. Dionisio [4], Robin E. Dodson [5], Olivier Jolliet [6], Xiaoyu Liu [7], David E. Meyer [2], Seth R. Newton [4], Katherine A. Phillips [4], Paul S. Price [4], Caroline L. Ring [8], Hyeong-Moo Shin [9], Jon R. Sobus [4], Tamara Tal [10], Elin M. Ulrich [4], Daniel A. Vallero [4], Barbara A. Wetmore [4], Kristin K. Isaacs [4]

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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
  - Compiled 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

United States Environmental Protection Agency

* NAM dataset

Regulatory or agency data reporting of chemical use

Toxics Release Inventory

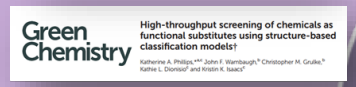
Voluntary Cosmetic Registration Program

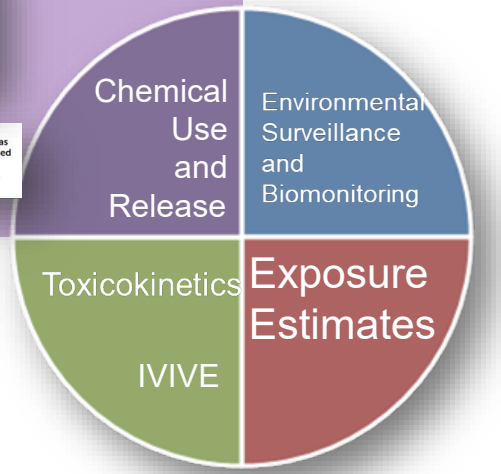
U.S Food and Drug Administration

Chemical Data Reporting

* **New quantitative and qualitative chemical use descriptors from EPA's Chemicals and Products Database (CPDat, Dionisio et al., 2018)**

* **Machine learning models for chemical function (Phillips et al. 2017)**





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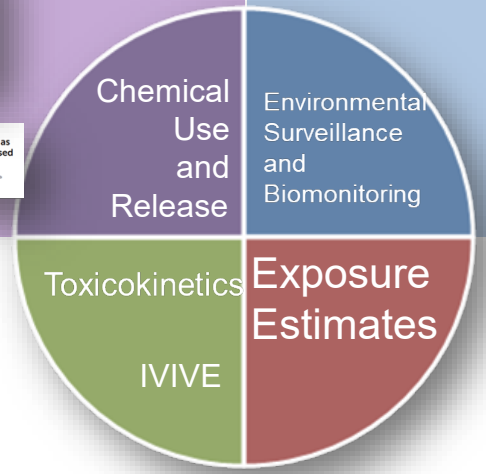
SCIENTIFIC DATA

OPEN | Data Descriptor: The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products

* Machine learning models for chemical function (Phillips et al. 2017)

Green Chemistry

High-throughput screening of chemicals as functional substitutes using structure-based classification models†



Traditional (targeted) monitoring data for various environmental media from publicly available monitoring databases

nhanes

ctd

IPCheM

USGS science for a changing world

Non-Targeted analysis studies for various environmental media from EPA and the EU (Newton et al. 2018, Rager et al. 2016, Sjerps et al. 2016, Phillips et al. 2018) *

Machine learning models for media occurrence *

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Chemical Use and Release

Environmental Surveillance and Biomonitoring

Toxicokinetics

IVIVE

Exposure Estimates

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Machine learning models for media occurrence *

U.S Food and Drug Administration

Cumulative Estimated Daily Intakes

Health Canada

Chemicals Management Plan Environmental and Consumer Assessments

EPA Reregistration Eligibility Decision (RED)

Publicly Available Traditional Assessments from Regulatory Bodies

Environmental Science & Technology

Consensus Modeling of Median Chemical Intake for the U.S. Population Based on Predictions of Exposure Pathways

Caroline L. Ring, Jon A. Arnot, Deborah H. Bennett, Peter P. Egeghy, Peter Fantke, Lei Huang, Kristin K. Isaacs, Olivier Jolliet, Katherine A. Phillips, Paul S. Price, Hyeong-Moo Shin, John N. Westgate, R. Woodrow Setzer, and John F. Wambaugh

DTU Danmarks Tekniske Universitet

High-Throughput Models for Various Pathways and Consensus Predictions from a Collaborative Modeling Study (Ring et al., 2019) *

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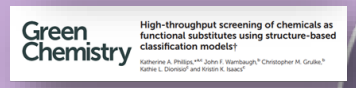

Environmental Surveillance and Biomonitoring

nhanes · ctd · USGS science for a changing world · IPCheM

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Machine learning models for media occurrence *

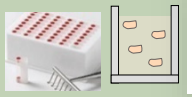
Toxicokinetics

In-vivo toxicokinetic parameters collected from the literature (Sayre et al., 2019)

* *In-silico* machine learning models for protein binding and clearance (Sipes et al. 2017, Ingle et al. 2018)

NIH National Institute of Environmental Health Sciences

* *In-vitro* protein binding and clearance (Wetmore et al. 2015, Pearce et al. 2017, Wambaugh et al 2019a.)



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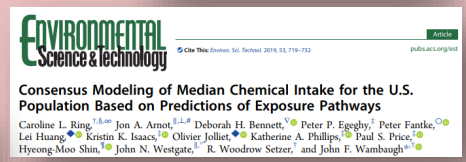
Exposure Estimates

FDA U.S Food and Drug Administration — Cumulative Estimated Daily Intakes

Health Canada — Chemicals Management Plan Environmental and Consumer Assessments

EPA Reregistration Eligibility Decision (RED)

Publicly Available Traditional Assessments from Regulatory Bodies



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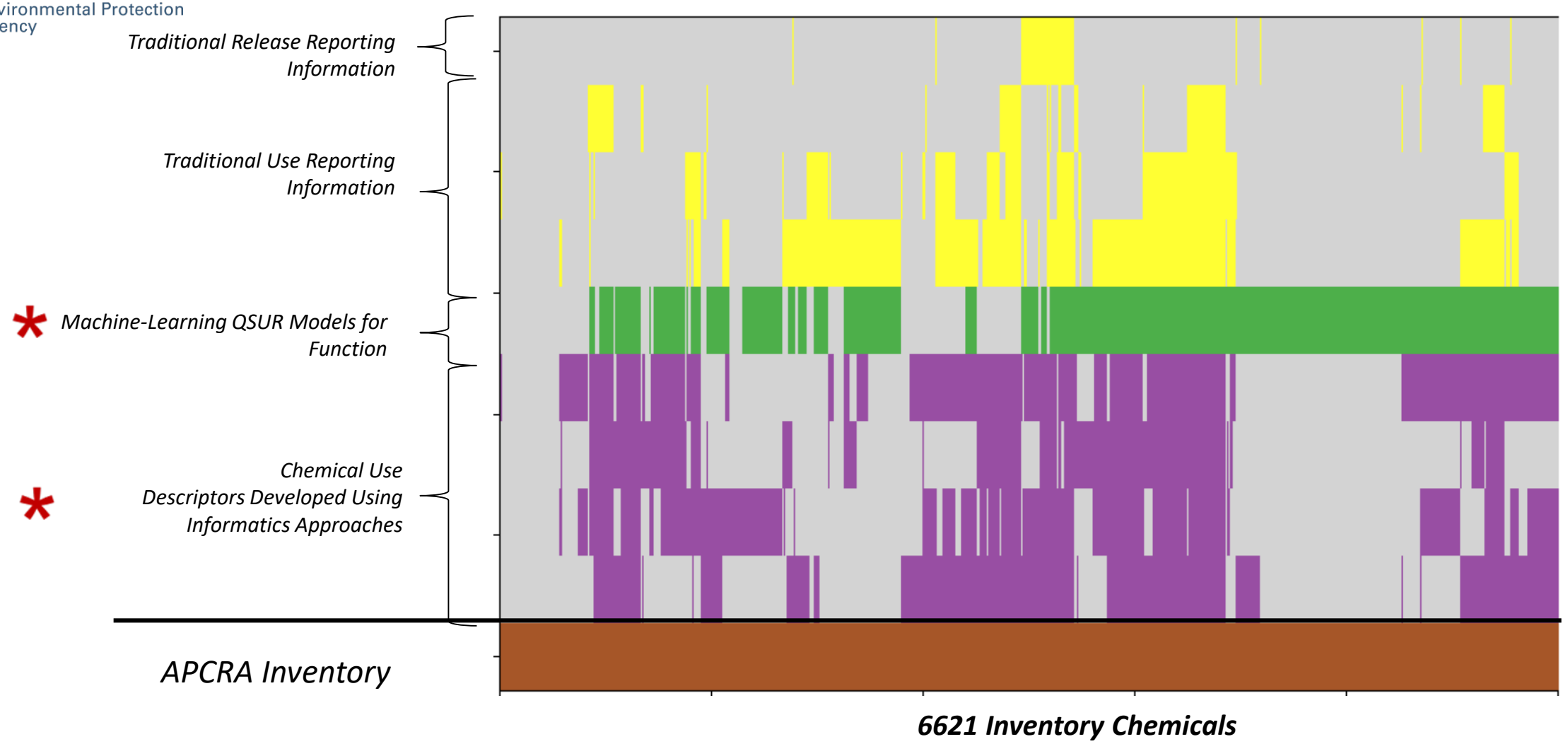

- The number of chemicals for which release data are available is still limited

NAM

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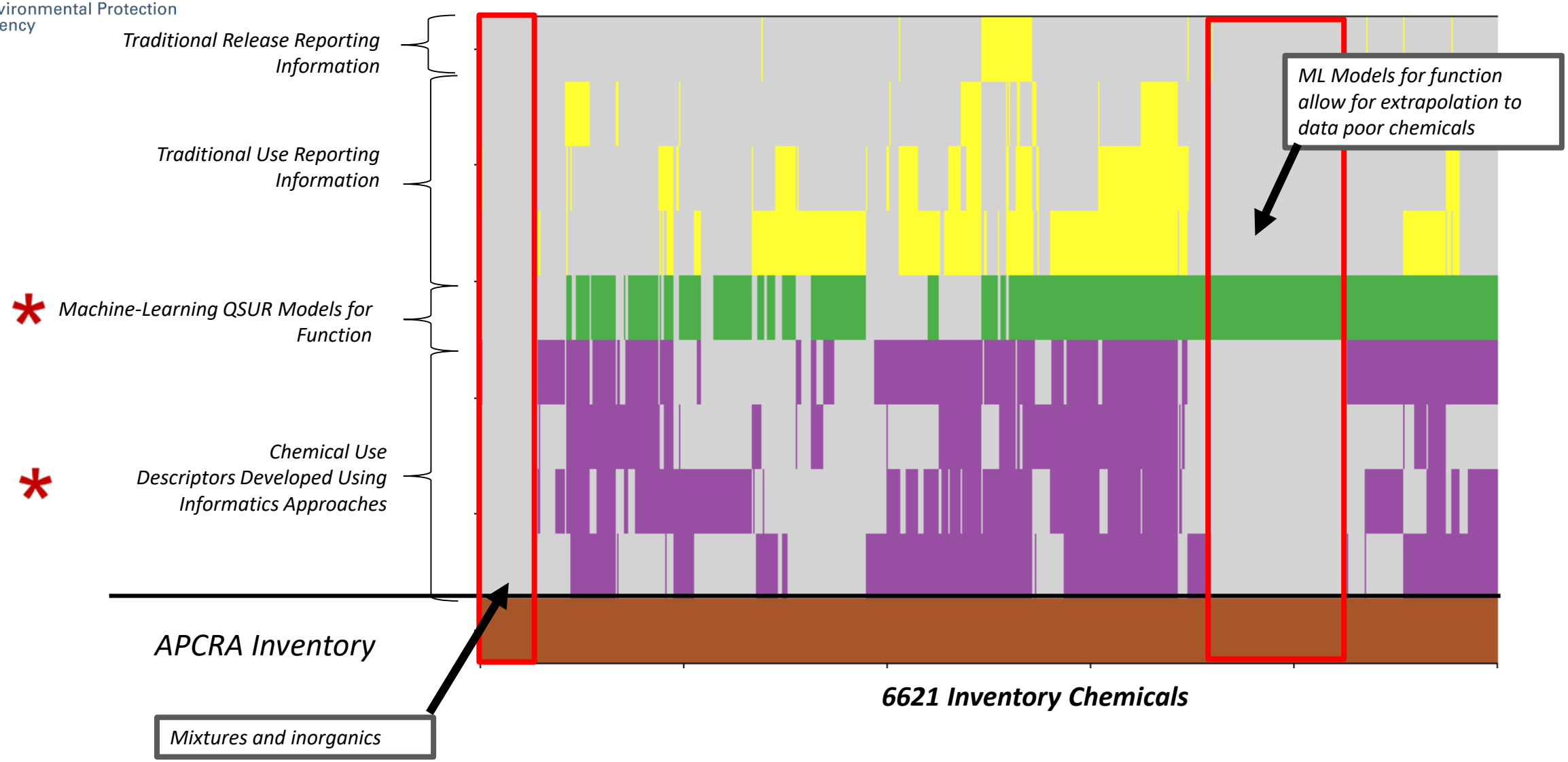

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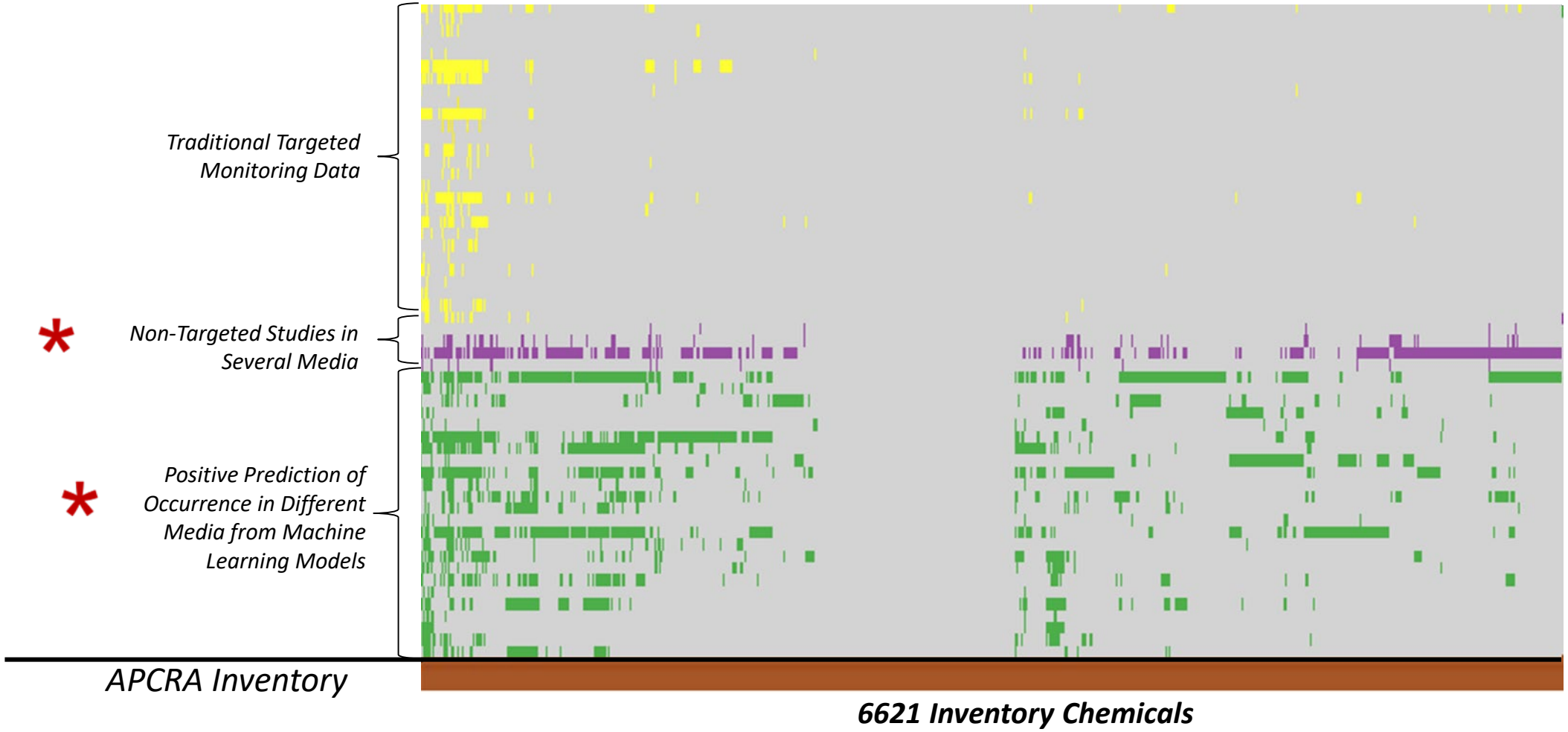
* NAM

Media Occurrence, Environmental Surveillance, and Biomonitoring



- Traditional monitoring very limited

* NAM

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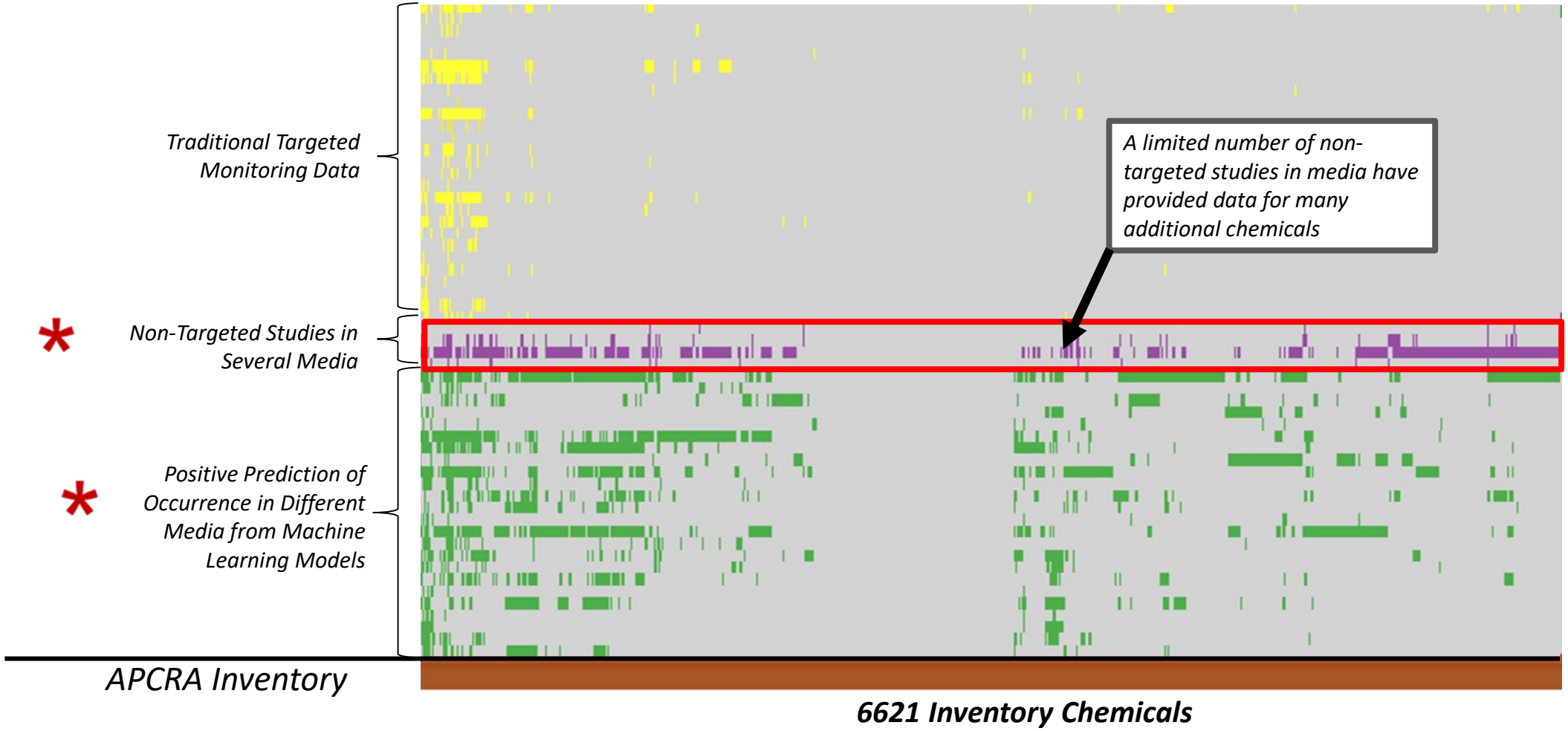

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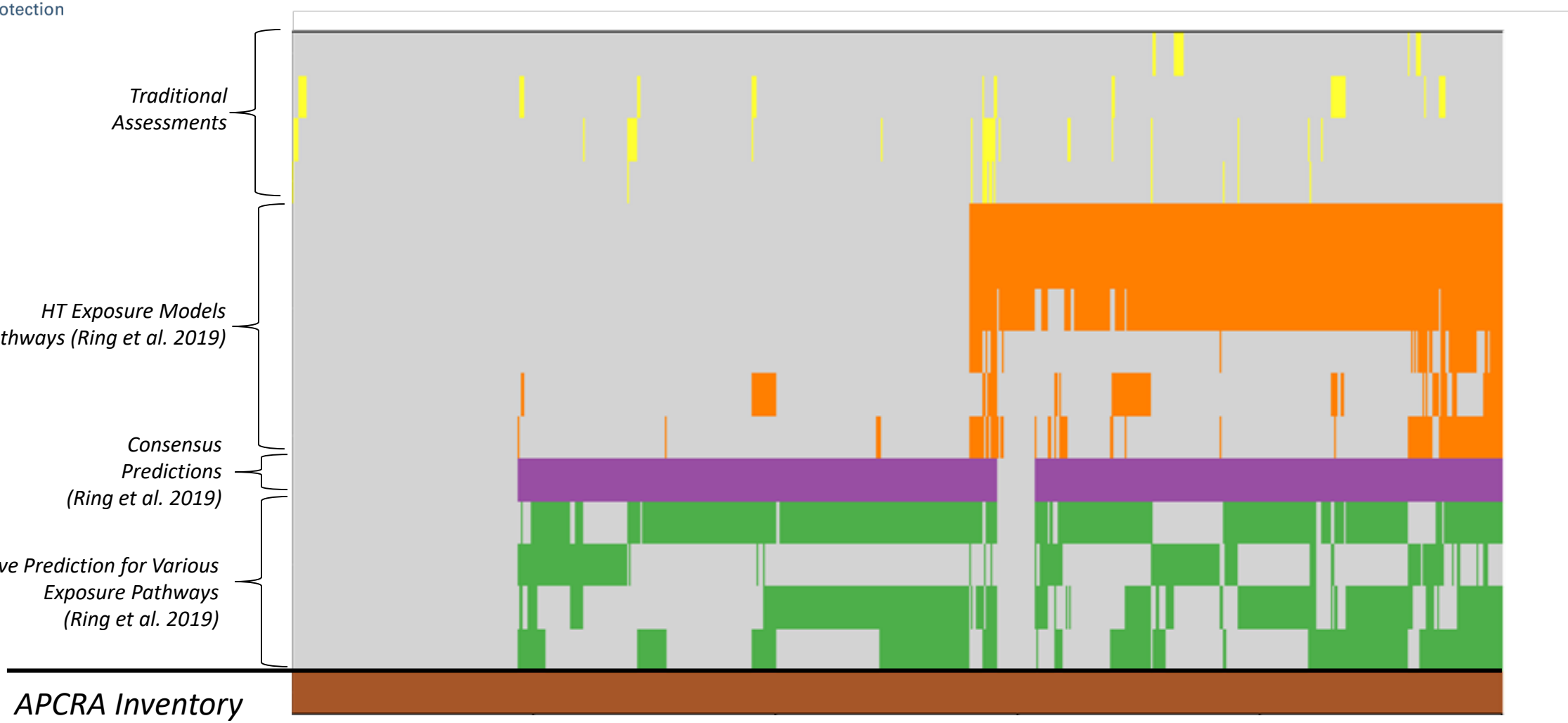
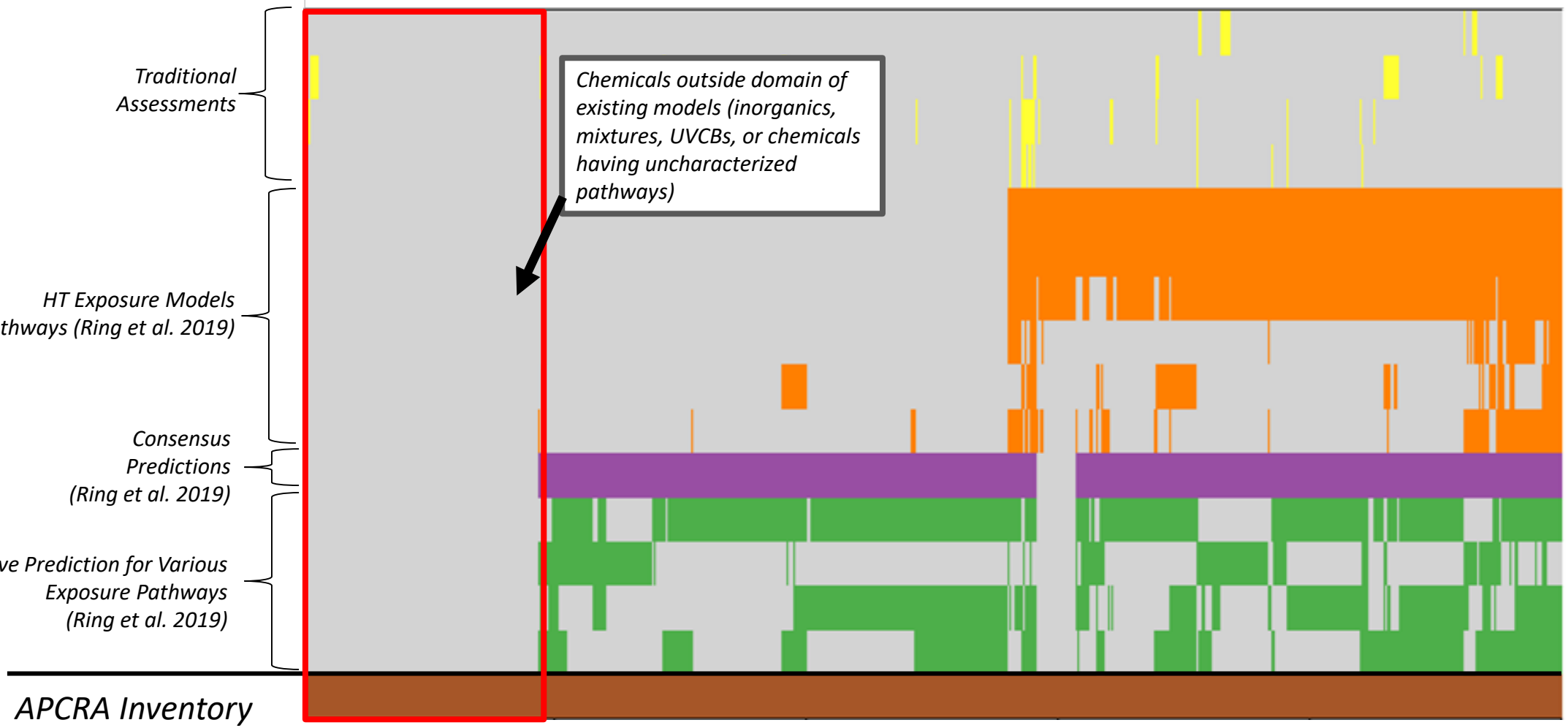
Exposure Predictions



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

* NAM

Exposure Predictions



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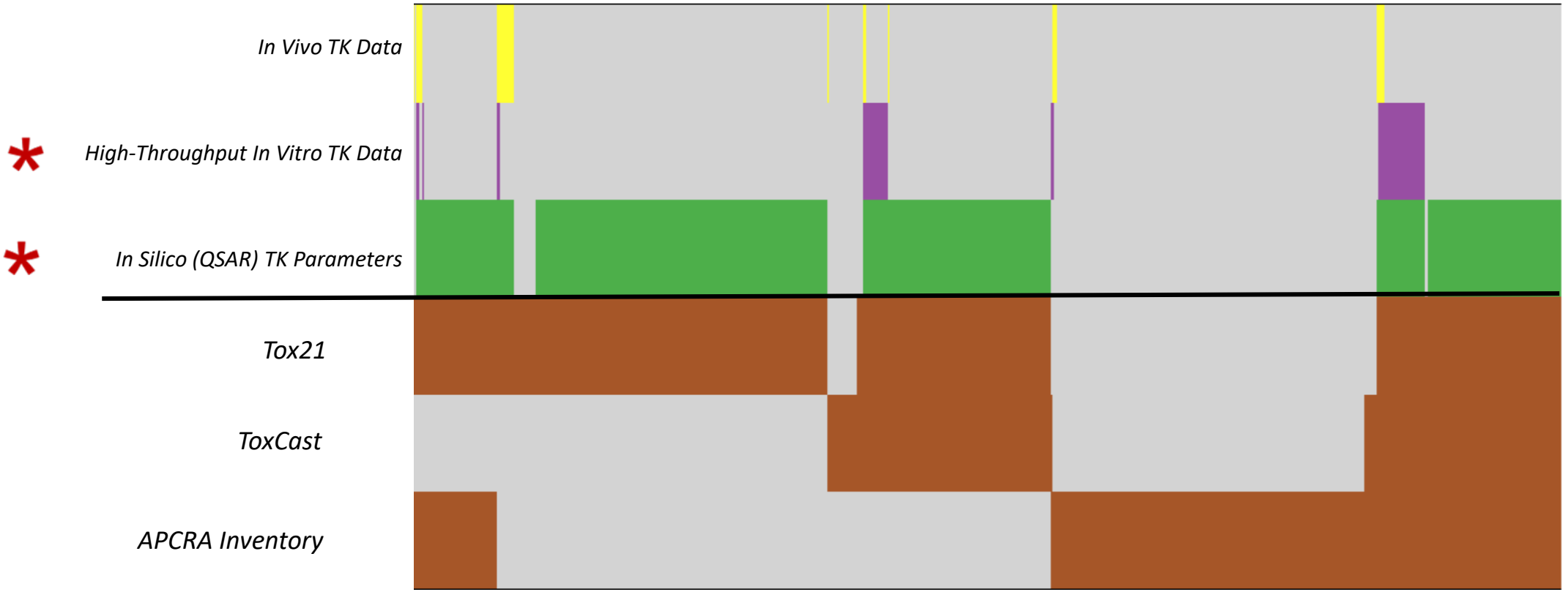
Toxicokinetics

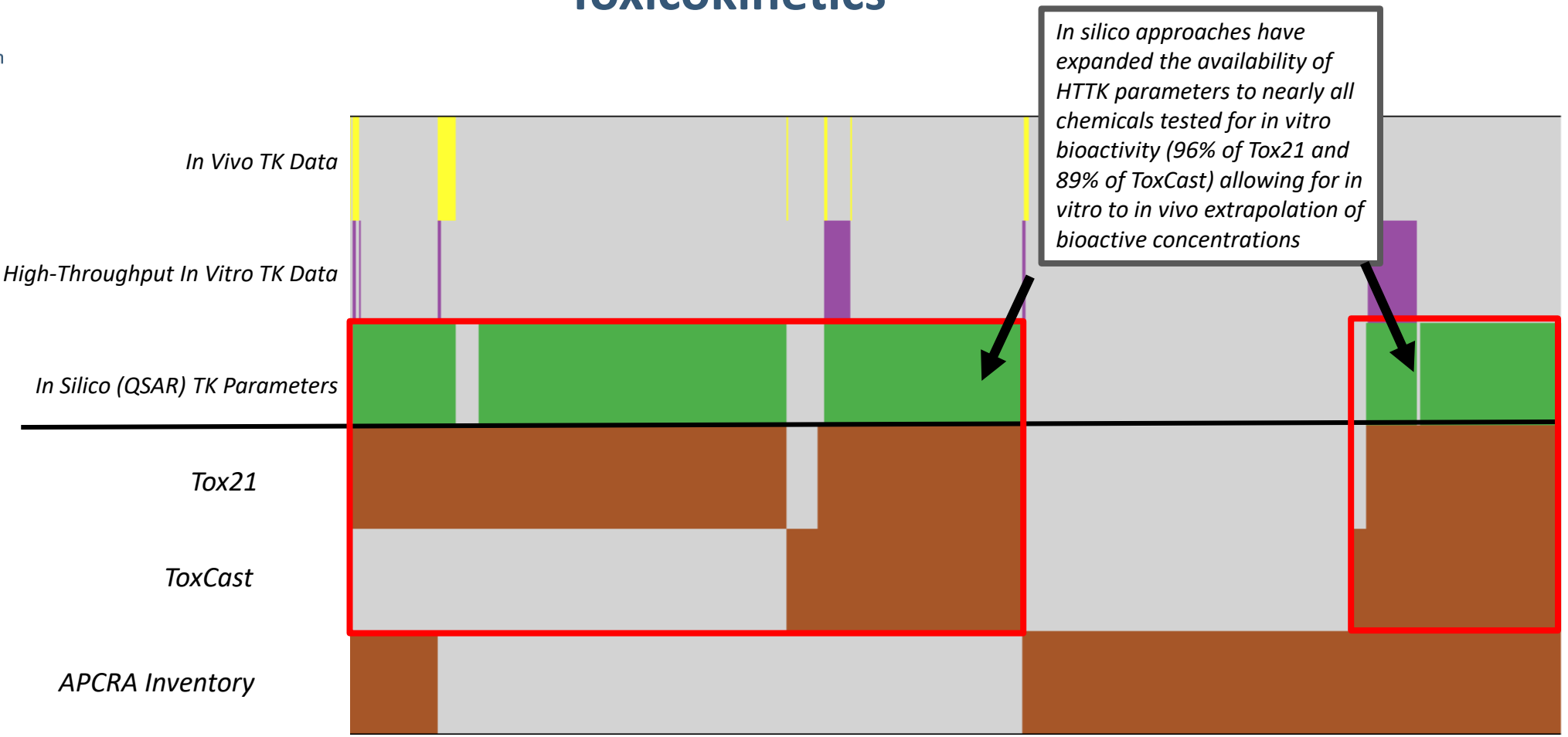


6621 Inventory Chemicals

- *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

* *NAM*

Toxicokinetics



6621 Inventory Chemicals

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* *NAM*

United States Environmental Protection Agency

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)

United States Environmental Protection Agency

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