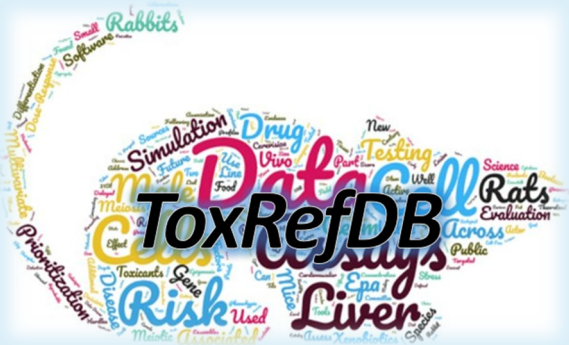


CompTox Chemicals Dashboard & Hazard Data

Introduction: Scarlett VanDyke

CompTox Chemicals Dashboard; Hazard Intro: Dr. Nisha Sipes

ToxValDB: Dr. Risa Sayre

ToxRefDB: Madison Feshuk, MPHTM

Outline & Disclaimer

- CompTox Chemicals Dashboard (CCD) Introduction
- Hazard Introduction
- Toxicity Values Database (ToxValDB)
  - CCD Demo: *Hazard and Batch Search*
- Toxicity Reference Database (ToxRefDB)
  - CCD Demo: *Hazard and Batch Search*

The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the US Environmental Protection Agency

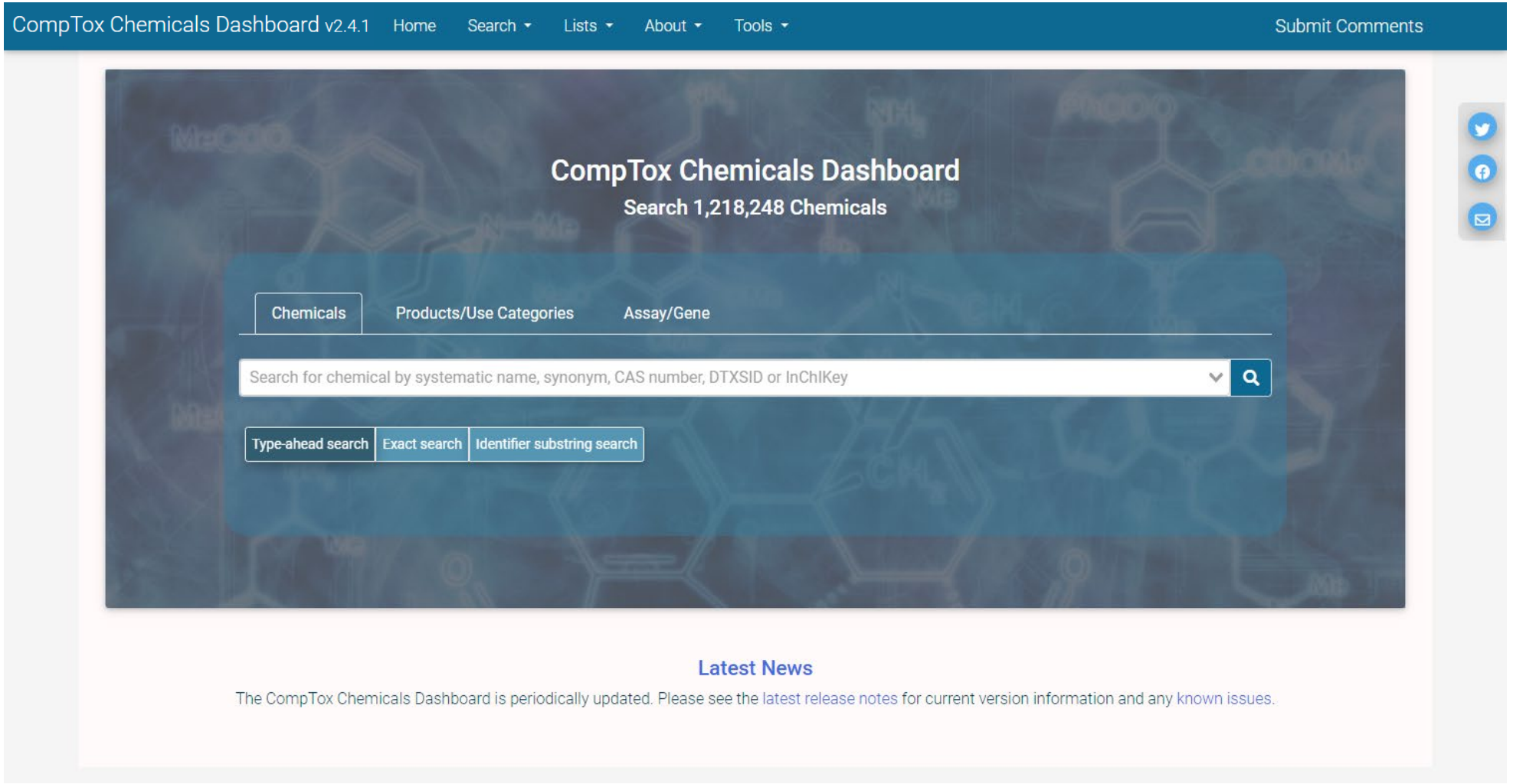
Company or product names do not constitute endorsement by US EPA

CompTox Chemicals Dashboard Introduction

Nisha Sipes

Dashboard Demonstration

https://comptox.epa.gov/dashboard/



Hazard Introduction

Nisha Sipes

What is hazard in toxicology?

Hazard

Something with the potential to cause biological harm

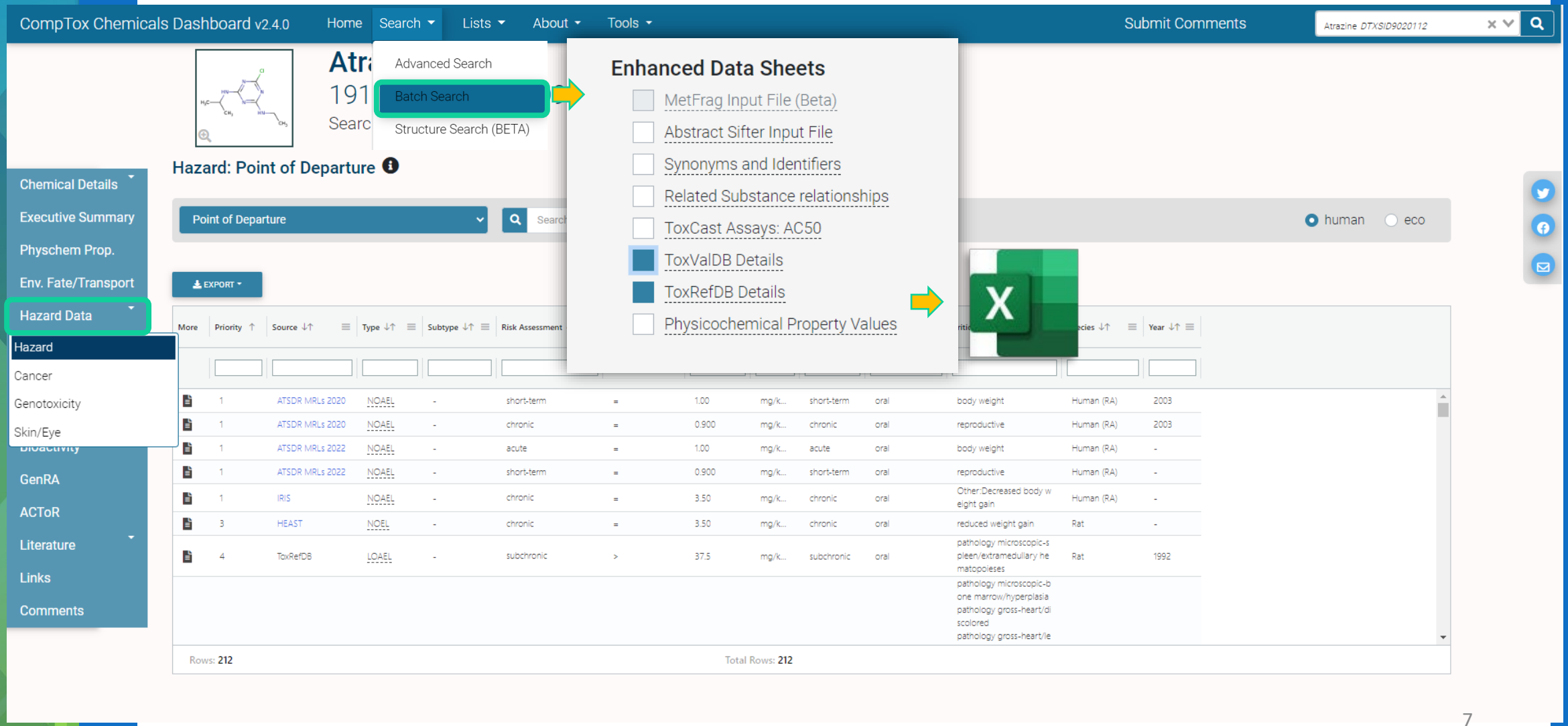
Common *in vivo* hazards of interest for regulatory toxicology

- Acute
- Repeated dose/ systemic
- Genotoxicity
- Carcinogenicity
- Developmental and reproductive toxicity
- Neurotoxicity
- Immunotoxicity

The *in vivo* animal test data are interpreted as both

- predictive of specific apical responses
- protective of general, non-specific effects

CompTox Chemicals Dashboard: Hazard Data



“Traditional” Hazard Resources

- Today’s session will explore two of EPA resources available for legacy animal toxicity information:
  - The **Toxicity Values Database (ToxValDB)** is a compilation of information sourced from multiple public datasets, databases and open literature, and includes data on thousands of chemicals from tens of thousands of records, with an emphasis on quantitative estimates of relevant points-of-departure from *in vivo* toxicology studies, such as NOAELs and LOAELs, screening levels, RfDs, tolerable daily intakes, etc.
  - The **Toxicity Reference Database (ToxRefDB)** contains *in vivo* study data from over 5900 guideline or guideline-like studies for over 1100 chemicals.

- For more information & data download:
  https://www.epa.gov/comptox-tools/downloadable-computational-toxicology-data#AT

- This traditional hazard data
  - Combined with exposure information can inform risk
  - Are used in regulatory applications for predicting and ultimately protecting human health
  - Can aid in the validation of *in vitro* high-throughput chemical screening
  - Can support retrospective and predictive toxicology applications

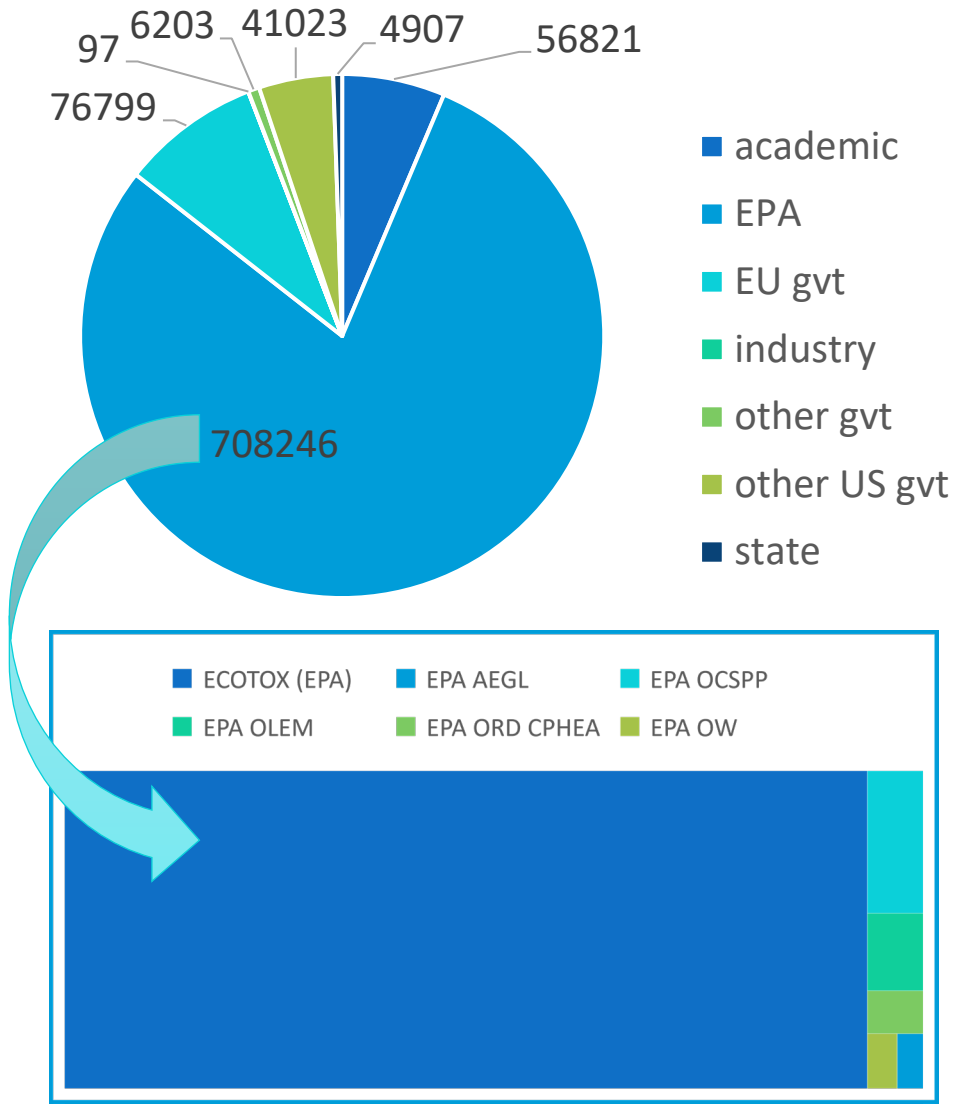
Toxicity Values Database (ToxValDB)

Risa Sayre

Overview

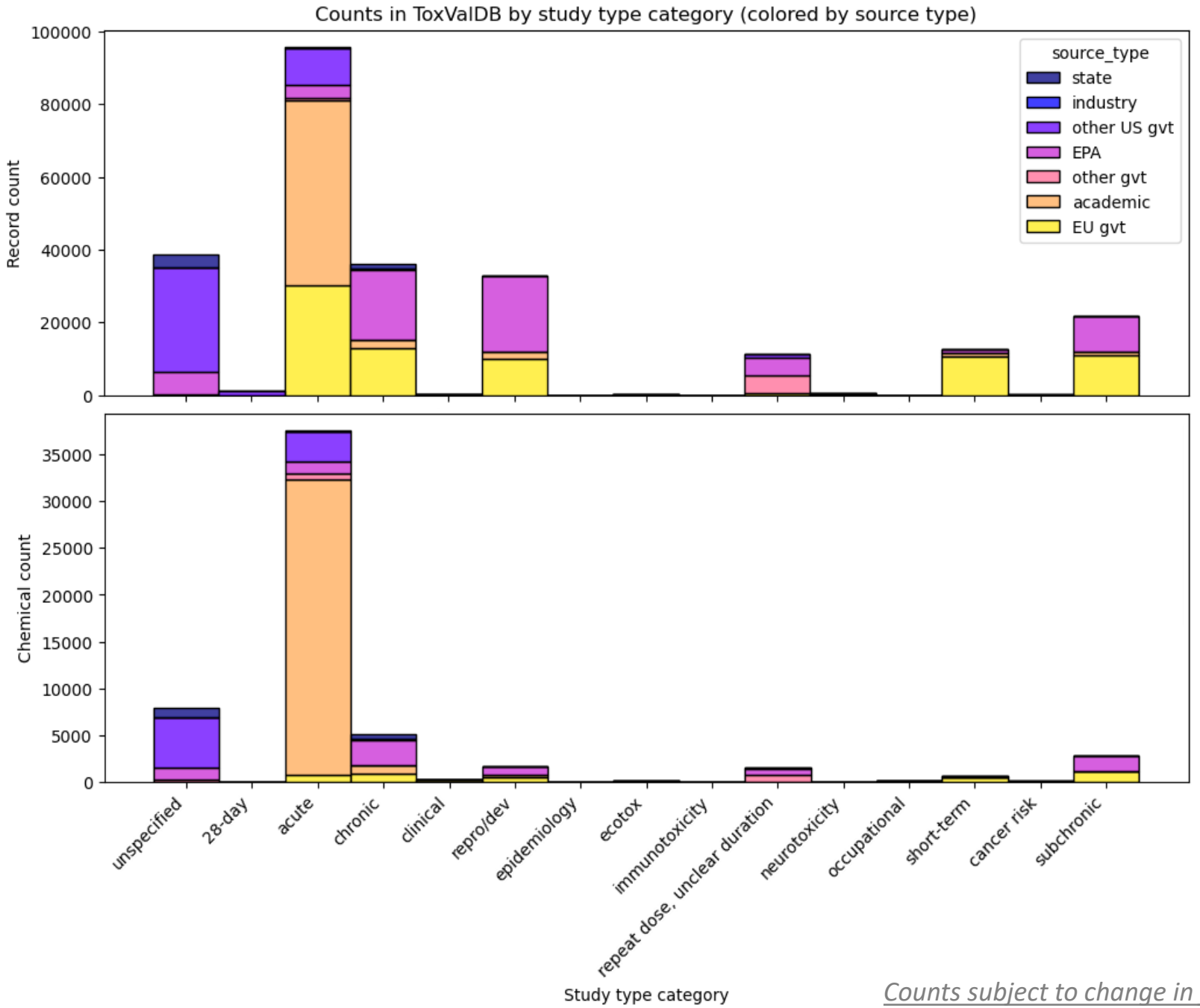
- **Toxicity Values Database** contains high-level overview values from *in vivo* studies and safety assessments
- Data is accepted as provided
- Useful for identification of data gaps, identifications of data providers, or analyses where some noise is tolerable, and a great deal of detail is not needed
- Version released on the CCD in 2024 receiving a massive overhaul

Count of ToxValDB records by data provider type



Counts subject to change in final v9.5

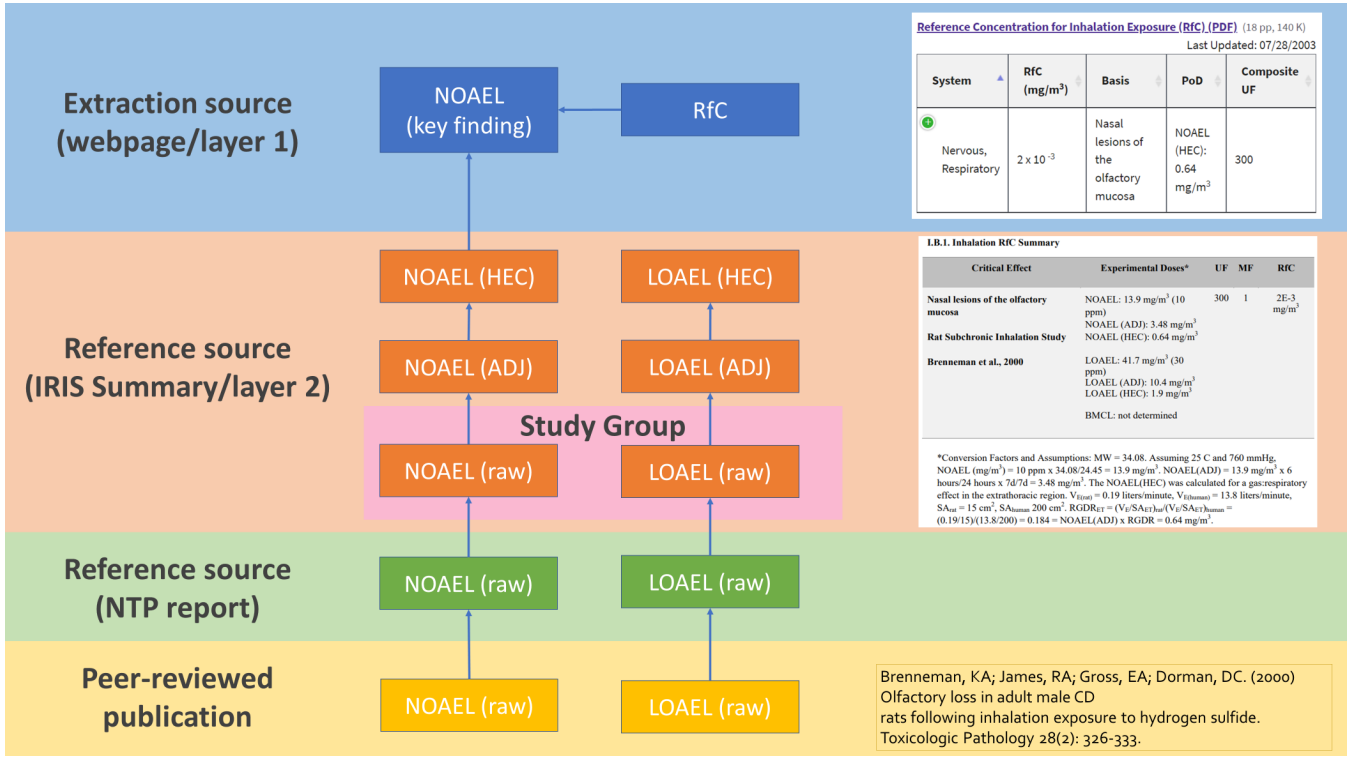
Coverage



Counts subject to change in final v9.5

Updates to version 9.5

- New sources & retired sources
- Enhanced document cataloging
- Tagging of experimental records
- Between-version audit logging
- Linkage of study groups
- QC categories



From SOT 2024 poster: https://doi.org/10.23645/epacomptox.25472164
"Developing data provenance approaches in ToxValDB: An IRIS Case Study"

Our team

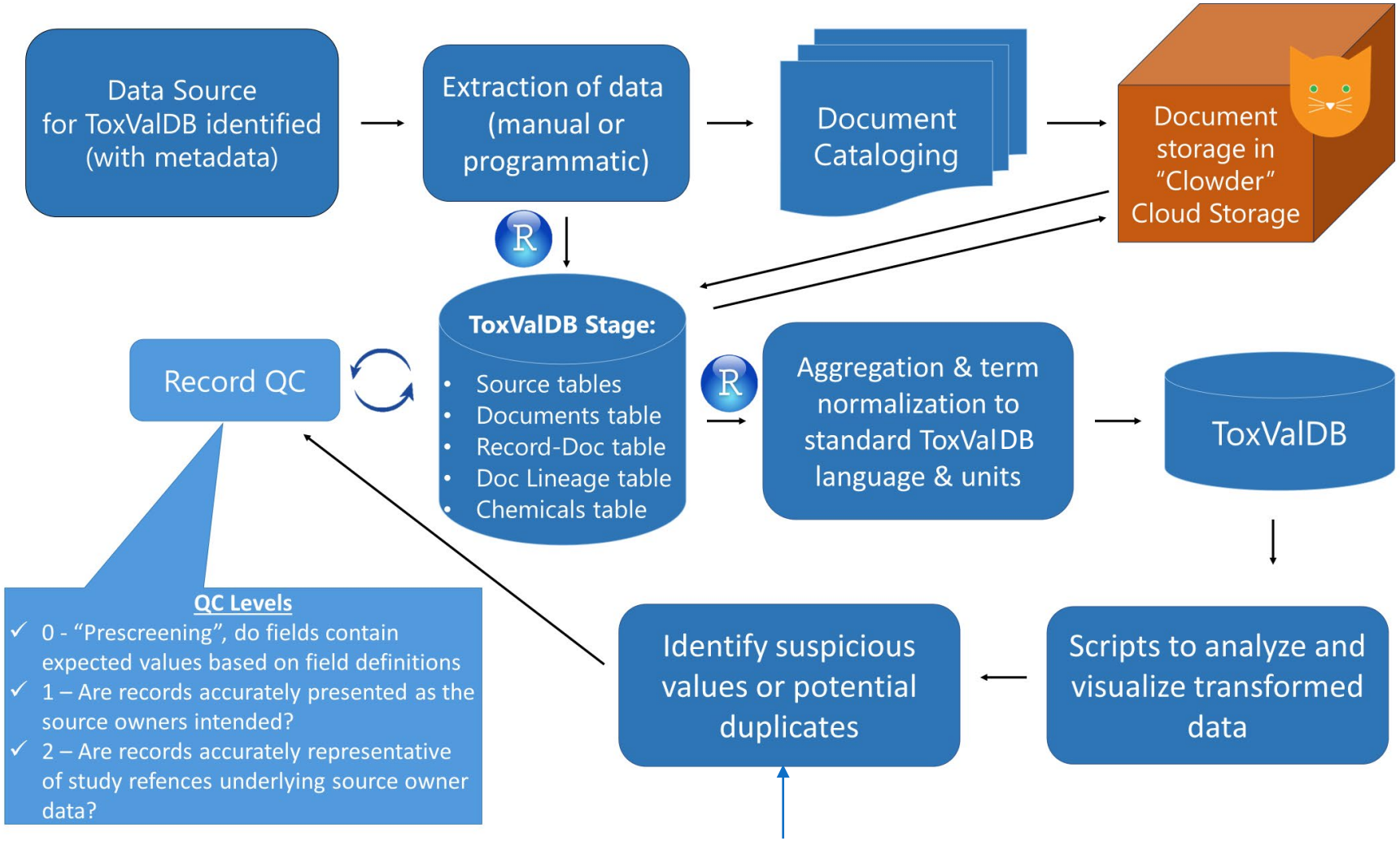
- Started by Richard Judson (retiring, BCTD)
- Continued by Taylor Wall (SCDCD), Chelsea Weitekamp (IO), and myself
- Substantial curation by SEE Doris Smith
- Current SSC team:

Jennat Aboabdo
Will Casey
Max Groover
Jasmine Hope
Branislav Kesic
Evelyn Rowan
Adrianna Webb
Samuel Winter

In addition to download through the CCD, access ToxValDB via:

- Complete download: https://www.epa.gov/comptox-tools/downloadable-computational-toxicology-data#AT
- API: https://api-ccte.epa.gov/docs/hazard.html

How data gets into ToxValDB



SOT 2023 poster: https://doi.org/10.23645/epacomptox.22280572.v1

Demo

Risa Sayre

Toxicity Reference Database (ToxRefDB)

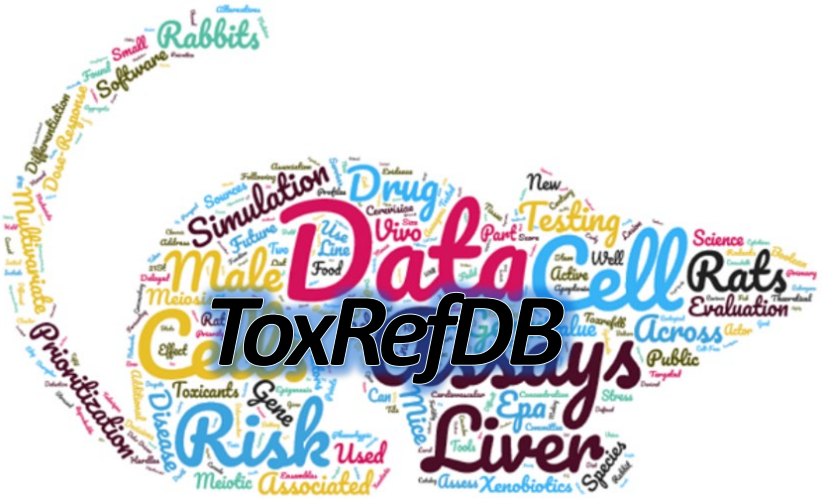
Madison Feshuk

(with contributions from Katie Paul Friedman)

Overview

- **Toxicity Reference Database** contains highly-curated legacy information from guideline and guideline-like *in vivo* studies

- Important for many retrospective and predictive toxicology applications, such as:
  - To set benchmarks to predict quantitative points-of-departures and build scientific confidence in the performance of new approach methodologies (NAMs)
  - To inform toxicity predictions as training data (ex. **GenRA** [Generalized Read-Across])
  - To evaluate reproducibility and variability of observed *in vivo* outcomes



ToxRefDB: Goals

- Aggregate complex and heterogeneous *in vivo* study data into an interoperable database
- Capture the quantitative dose-response data for each dose treatment group, including control groups, for all observed endpoints
  - Including treatment group size, incidence or effect values, and variance information (e.g., standard deviation, standard error) where provided
- Capture points of departures (PODs) from dose-response data including doses that are deemed ***treatment-related*** (statistically significant from control group) and/or ***critical*** (adverse) within a study
- Employ a controlled vocabulary for accurate data extraction, aggregation, and integration, enhancing data quality at the source
- Distinguish between missing (not tested) or negative (tested with no effect observed) endpoints

Coverage

- ToxRefDB contains summary information from 5986 studies for 1143 chemicals.
- As part of ToxRefDB v2.0 curation effort, complete dose-response data and observations were extracted for 3871 studies (as indicated with a 'processed' flag within the study table.)
- There are plans to extract and update the remaining studies in subsequent data releases

Figure 1: Study-Level Data Landscape

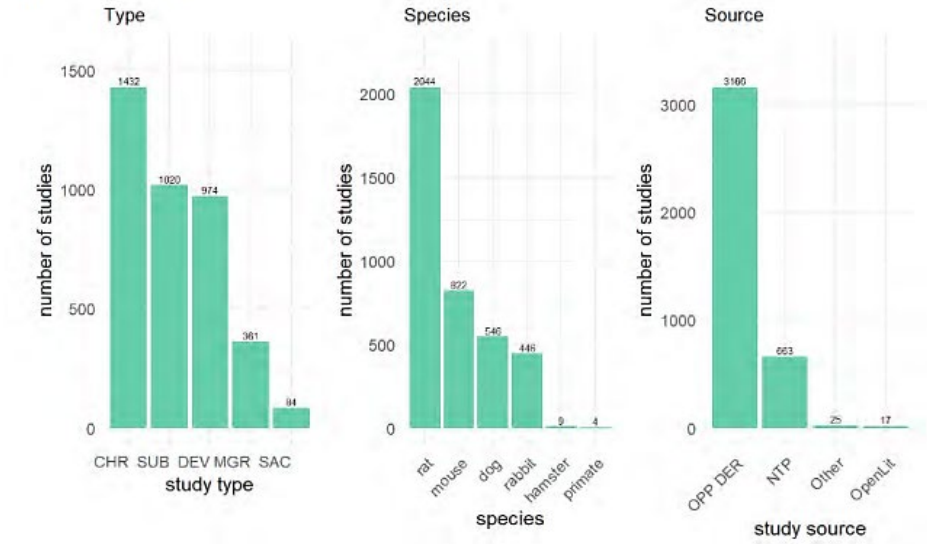
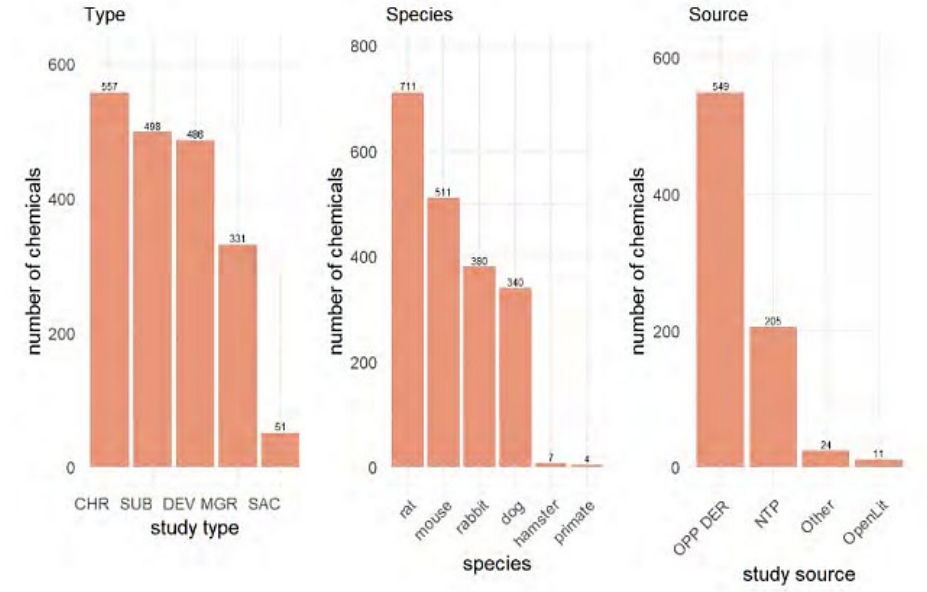


Figure 2: Chemical-Level Data Landscape



Coverage

- Many of the studies (over 3,000) come from registrant-submitted toxicity studies in data evaluation records (DERs) from the U.S. EPA's Office of Pesticide Programs (OPP).
  - 90% of the studies with completed curation correspond to pesticide actives and inerts
  - Other sources include NTP reports, Pharma, and OpenLit

Figure 1: Study-Level Data Landscape

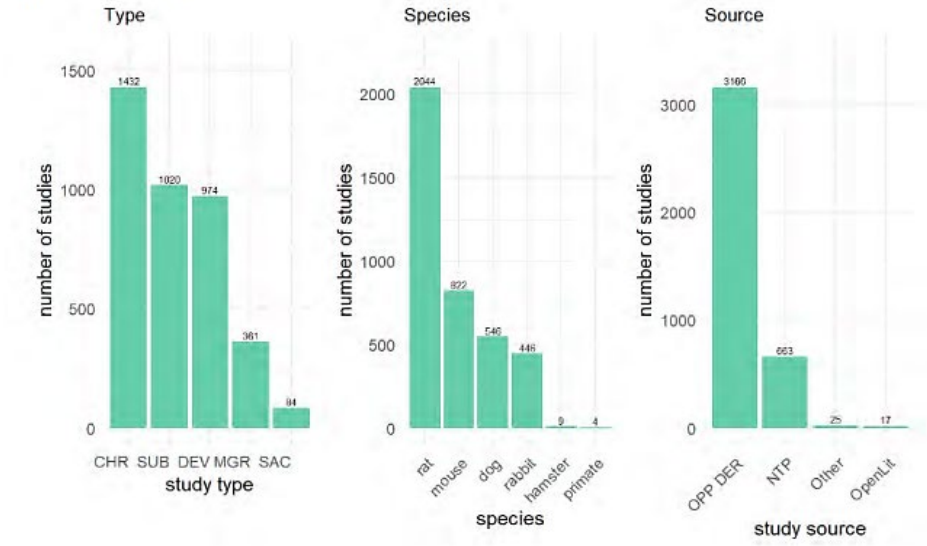
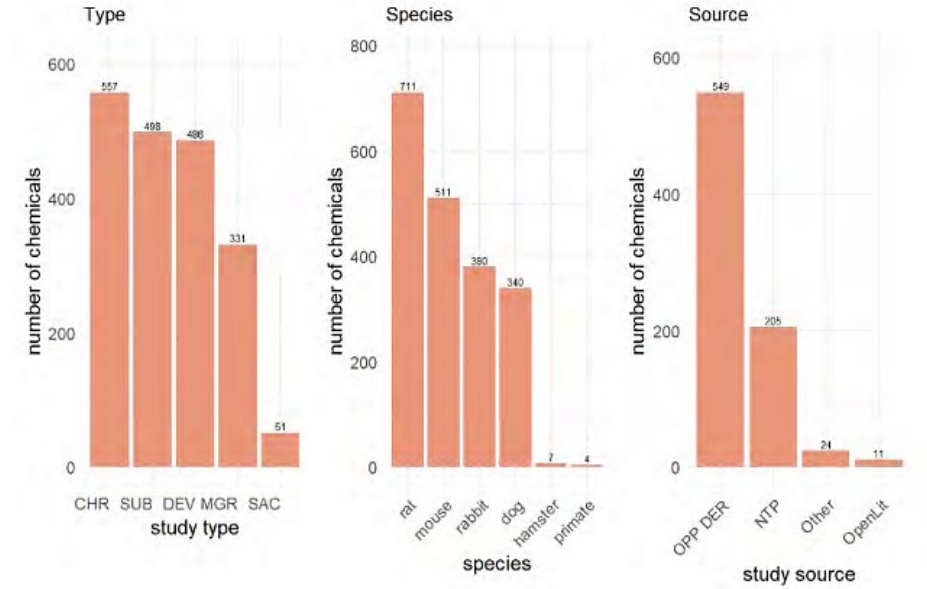


Figure 2: Chemical-Level Data Landscape



Coverage

The study types covered include the following repeat dose study designs utilizing various administration routes (predominantly oral):

- **Chronic** (CHR; 1-2 year exposures depending on species and study design) conducted in rats, mice, and dogs
- **Subchronic** (SUB; 90 day exposures) conducted in rats, mice, and dogs
- **Subacute** (SAC; 14-28 day exposures depending on the source and guideline) conducted in rats, mice, and dogs
- **Prenatal developmental** (DEV) conducted in rats and rabbits
- **Multigeneration reproductive** (MGR) conducted in rats
- Reproductive (REP) conducted in rats
- *Developmental neurotoxicity* (DNT) conducted in rats
- Small number of studies with designs characterized as acute (ACU), neurological (NEU), or "*other*"(OTH)
  - ToxRefDB includes this guideline profile **currently** or *planned for future release*

Figure 1: Study-Level Data Landscape

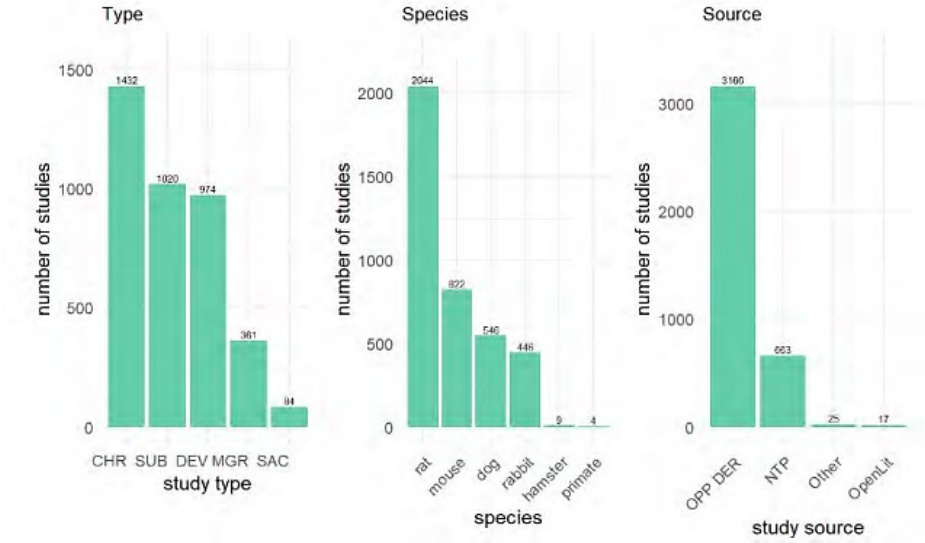
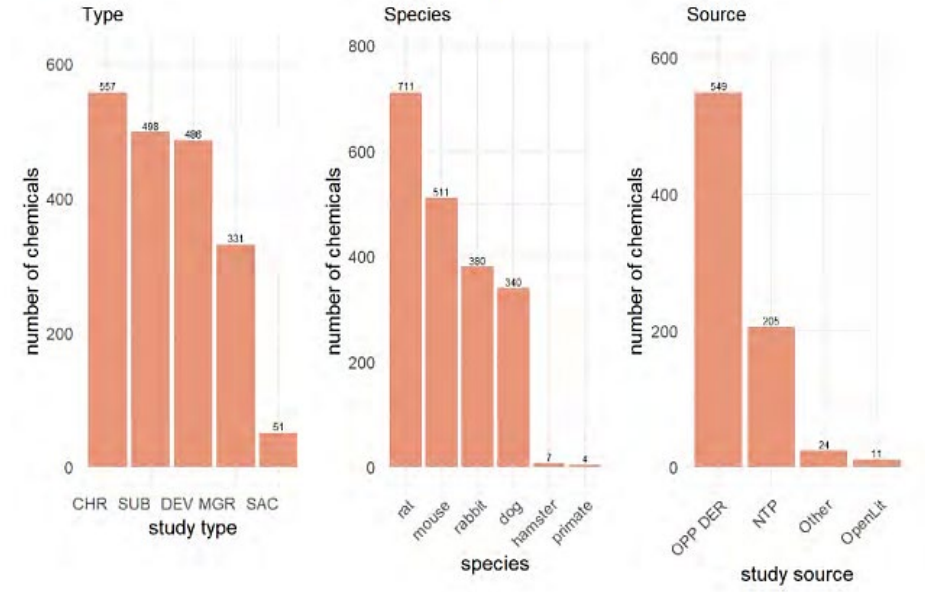
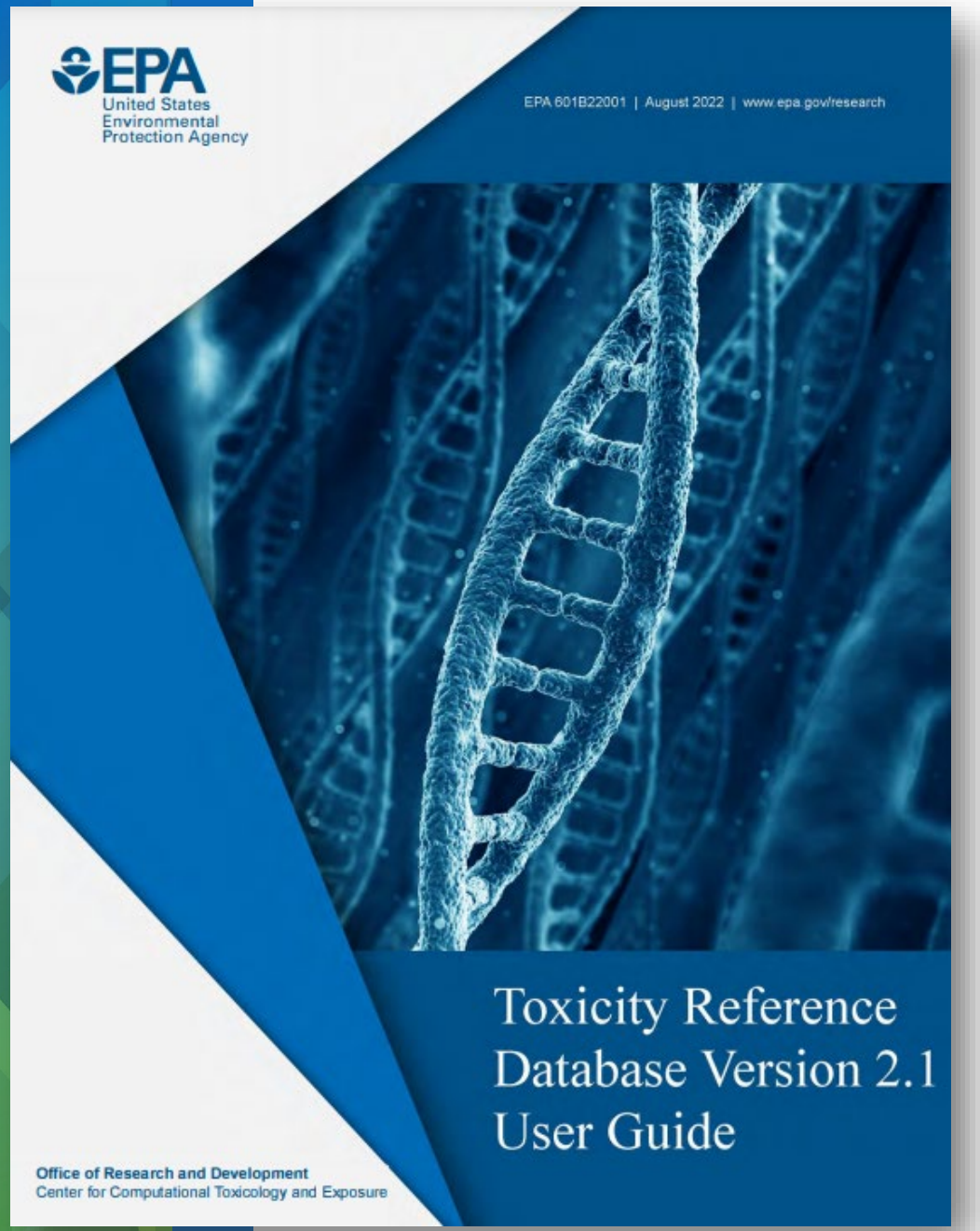


Figure 2: Chemical-Level Data Landscape





Accessibility

- Visit https://www.epa.gov/chemical-research/downloadable-computational-toxicology-data to download v2.1 database package and user guide.
- Check out some ToxRef-related publications
  - Feshuk, M., Kolaczkowski, L., Watford, S., & Paul Friedman, K. (2023). **ToxRefDB v2.1: update to curated *in vivo* study data in the Toxicity Reference Database.** *Frontiers in toxicology*, *5*, 1260305. https://doi.org/10.3389/ftox.2023.1260305
  - Watford, S., Ly Pham, L., Wignall, J., Shin, R., Martin, M. T., & Friedman, K. P. (2019). **ToxRefDB version 2.0: Improved utility for predictive and retrospective toxicology analyses.** *Reproductive toxicology (Elmsford, N.Y.)*, *89*, 145–158. https://doi.org/10.1016/j.reprotox.2019.07.012
  - Pham, L. L., Watford, S., Friedman, K. P., Wignall, J., & Shapiro, A. J. (2019). **Python BMDS: A Python interface library and web application for the canonical EPA dose-response modeling software.** *Reproductive toxicology (Elmsford, N.Y.)*, *90*, 102–108. https://doi.org/10.1016/j.reprotox.2019.07.013

- **If you have trouble getting access or find a curation error, please let us know by emailing** CCTE@epa.gov. We can help troubleshoot your connection or inspect the source documents.

Data Interoperability Example

Different approaches depending on needs

- Hazard NAMs ***like ToxCast*** are often compared to other data, such as hazard information from traditional animal models or exposure information
- Can prioritize chemical(s) *using all* bioactivity endpoints or *subsets* of bioactivity endpoints for a particular biological target based on Bioactivity:Exposure Ratio (BER) or Points of Departures (PODs) to assess NAM performance

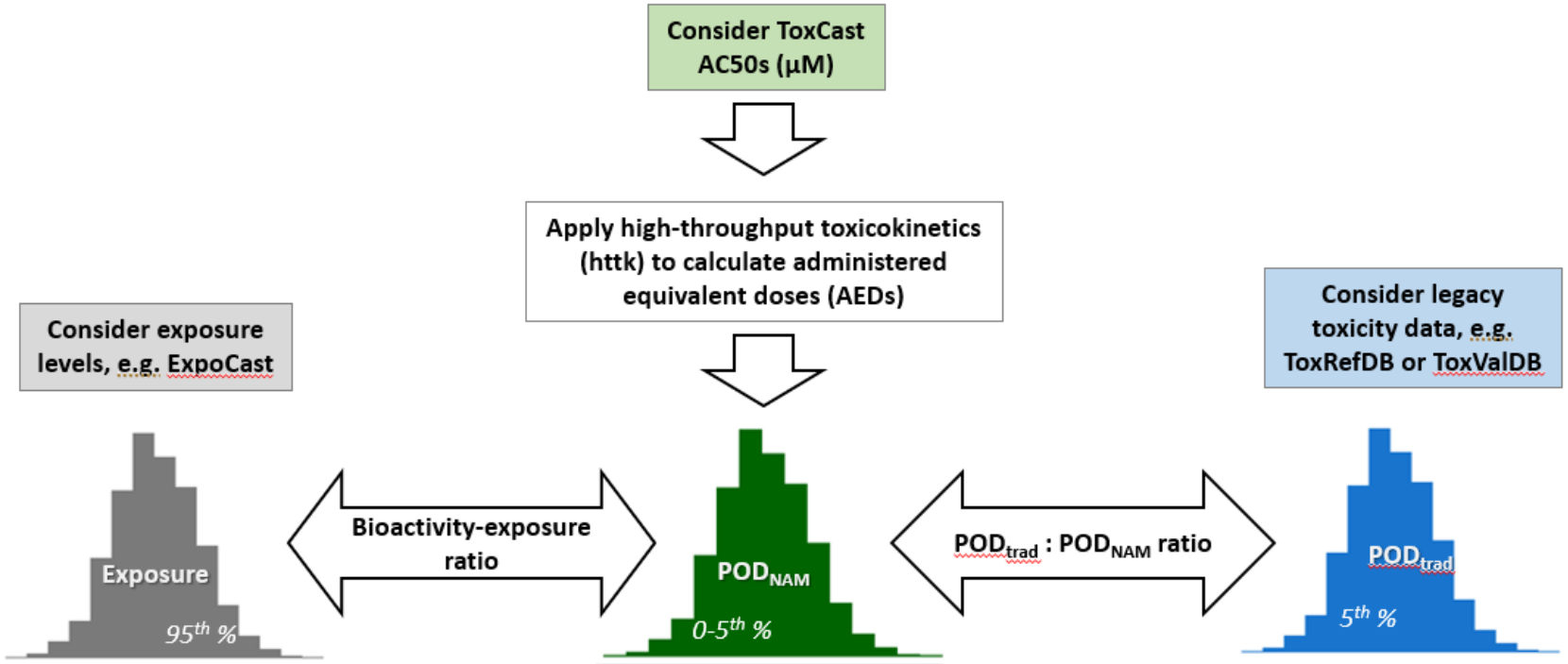
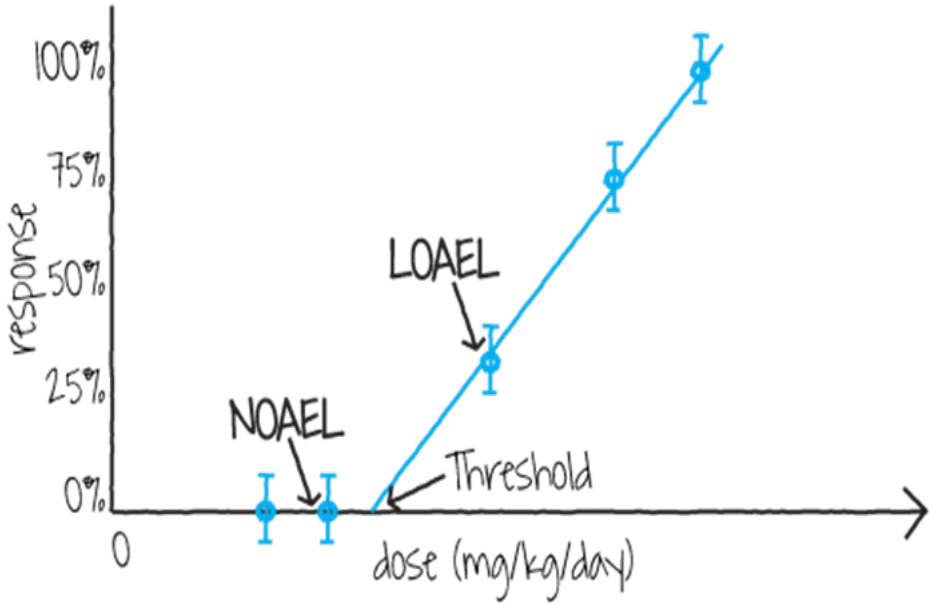


Figure adapted from: Paul Friedman et al. (2020) https://doi.org/10.1093/toxsci/kfz201

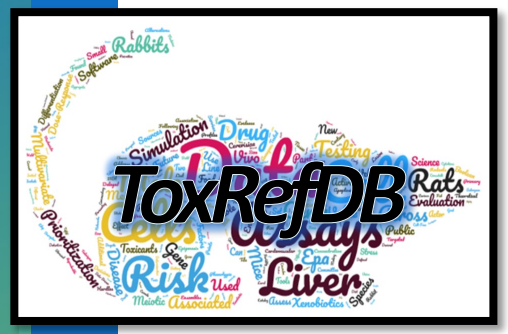
Points-of-Departure (PODs)

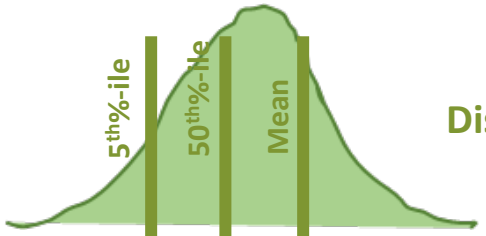
- For each animal toxicity study in ToxRefDB, data on multiple endpoint targets is collected at each dose level.
- PODs correspond with the lowest dose levels at which effects are observed, which are important for extrapolating to a reference dose (RfD) in risk assessments
- 4 Types:
  - **LEL:** Lowest Effect Level
  - **NEL:** No Effect Level
  - **LOAEL:** Lowest Observed Adverse Effect Level
  - **NOAEL:** No Observed Adverse Effect Level
- For ToxValDB, ToxRefDB PODs derived for lifestage-generation-sex endpoint category per study.



Examining $POD_{Traditional}$:POD_{NAM}

"Traditional"





Distribution of AC50 values

HTTK

NAMs

Distribution of PODs

Distribution of administered equivalent dose (AED) values

	Traditional POD (mg/kg/day)	ToxCast-based PODs (mg/kg/day)		
	LOAEL	AED95 (5%ile AC50)	AED95 (50%ile AC50)	AED95 (mean AC50)
Chemical X	???	???	???	???

- Full process reported in Paul Friedman et al (2023). https://doi.org/10.1016/j.comtox.2023.100287
- Full example coming to the ToxCast pipeline (tcpl) Data Retrieval vignette soon

Demo

Madison Feshuk

Demo

- Downloadable Computational Toxicology Data: https://www.epa.gov/comptox-tools/downloadable-computational-toxicology-data#AT
  - Database Package
  - User Guide
    - Database structure
    - Example queries
    - Data dictionary
- CCD: https://comptox.epa.gov/dashboard/
  - Batch Search Export of ToxRefDB Details
  - Examine BPA: ToxValDB vs ToxRefDB Details
- CCTE APIs home https://api-ccte.epa.gov/docs/ (Must request API key to access)
- Hazard APIs https://api-ccte.epa.gov/docs/hazard.html
  - Overview of different request types
  - ToxRefDB requests coming soon!
- ccdR for accessing APIs https://cran.r-project.org/web/packages/ccdR/index.html