Advancing Systematic Review Methods and Tools

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Board of Scientific Counselors (BOSC) Subcommittee
Chemical Safety for Sustainability (CSS) and
Health and Environmental Risk Assessment (HERA) National Research Programs
Virtual Meeting on February 2-5, 2021

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Office of Research and Development
Center for Public Health and Environmental Assessment

Assessment Methods in the IRIS Program

- **Described in the ORD Staff Handbook for Developing IRIS Assessments ("IRIS Handbook"), released November 2020 for public comment (ends March 1, 2021)**
- **Includes systematic review and dose-response methods**
- **Handbook will undergo peer-review by National Academy of Sciences (NAS) in Spring 2021 & expect report Summer 2021**
- **Core methods previously reviewed by NAS in 2018 and published in journal articles (Appendix B, Part 3)**

NAS (2018): Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation
https://www.nap.edu/catalog/25086/progress-toward-transforming-the-integrated-risk-information-system-iris-program

Systematic Review Method Development

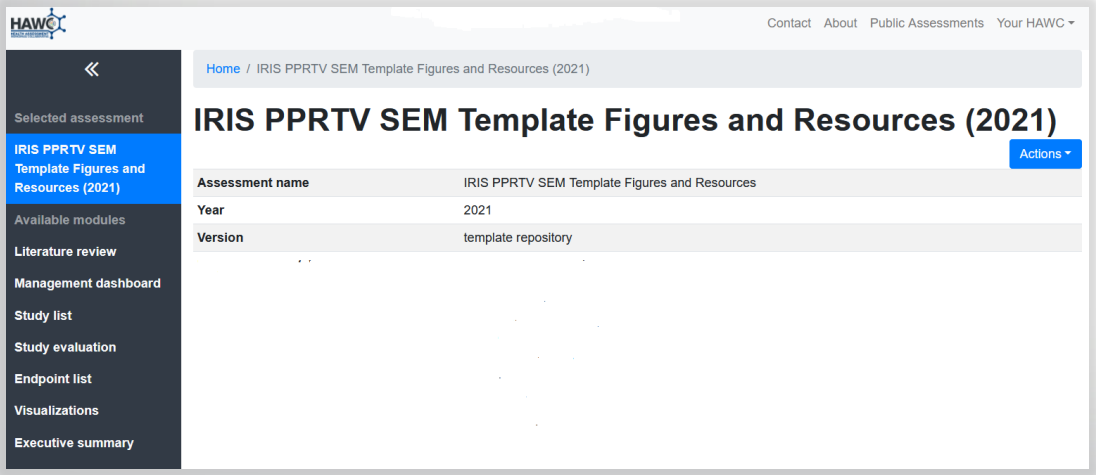
Systematic Review Activity	Status
Finding and screening studies for relevance	√ Methods stable and templates available. Specialized software used to manage process, including use of artificial intelligence (AI) which reduces level of effort and cost by 40-60%. Level of software intra-operability is functional.
Data extraction of study design and results from full-text	√ Stabilized on entities we extract for epidemiological and animal studies. √ Use of structured web-based forms for epidemiological and animal studies. In progress Extraction stabilizing on entities for *in vitro* and PBPK models.
Semi-automating process of data extraction ***Collaborative multi-year effort across ORD, OCSPP**	In progress (animal toxicology): Will begin to incorporate for fields where models perform well (e.g., species, strain, sex) and develop additional training sets to improve model performance for other entities (endpoints assessed, results). Will be approached using a "human-in-the loop" approach. "Automated/Machine Learning Approaches" (Michele Taylor presentation) Next up (epidemiological and exposure studies): Develop training sets for model development (2021-2022). Downstream: Develop training sets for full-text extraction of in vitro, ADME/toxicokinetic, PK/PBPK evidence.
Intra-operability across software platforms	Downstream: Ensure ability of HAWC to import extraction conducted elsewhere. Pertinent to "Semantic Ontology Mapping" (Michelle Angrish presentation)

Systematic Review Method Development

Systematic Review Activity	Status
Organizing and evaluating mechanistic evidence	In progress: "Organizing and Evaluating Mechanistic Evidence" (Catherine Gibbons presentation)
Study Evaluation	√ Methods stable for epidemiology and animal toxicology, with dissemination in many published articles. √ 2021 Dosimetry and Mechanism-Based Models Umbrella Quality Assurance Project Plan (QAPP) for PBPK models In progress (in vitro studies): "Organizing and Evaluating Mechanistic Evidence" (Catherine Gibbons presentation)
Evidence Synthesis/Integration	√ Structured frameworks for synthesis and integration of epidemiology, animal toxicology, and mechanistic evidence presented in IRIS Handbook. Will refine as needed based on external peer review. Developing examples and monitoring implementation to provide more information to staff on how to operationalize consistent application and decision documentation. In progress: Enhancements in HAWC to use forms for documenting evidence synthesis and integration decisions in evidence profile tables (web-based and interactive).

Sharing Systematic Review Resources

- **IRIS Handbook and assessment-material templates (assessment plan, protocol, draft assessment)**
- **Draft template for "fit for purpose" systematic evidence map (SEM) publication**
  - **SEM is a pre-decisional analysis, publishable in journals ("PFAS Systematic Evidence Maps" Laura Carlson presentation)**
- **Publicly accessible Health Assessment Workspace Collaborative (HAWC) project to share targeted resources, many of which are evergreen**



- **Commonly used data visualization templates**
- **Example answers for common study evaluation scenarios for animal toxicity studies**
- **Latest controlled vocabulary for data extraction**
- **Tips for using software**
- **Training slides on searching grey literature**

Specialized Software Tools

- Presentations in this session will mention a variety of specialized software used within HERA to manage the systematic review process
- Rapidly evolving field and requires extensive community engagement with developers and users to stay current
- Considerations for which software applications to use:
  - Performance, cost, ability of software developer to provide technical support to a large group, ability to make interoperable with HERO and other systematic review software, adaptability for environmental human health assessments
- Resourcing: HEEAD-HERO and CPAD staff, CCTE partnerships (e.g., ECOTOX, Chemicals Dashboard), OCSPP, and extramural contracts

Engagement

- Across EPA with other groups that conduct systematic reviews, e.g., CPHEA-HEEAD, OW, OPPT
- EPA Systematic Review Communities of Practice
- Working closely with CCTE (i.e., data curation workflows used for ECOTOX and Chemicals Dashboard, use of Chemicals Dashboard for chemical information presented in assessments)
- National and international collaborations (e.g., NTP, EFSA, International Collaboration for the Automation of Systematic Reviews, GRADE Working Group)
  - Includes discussions of approaches to maximize information retrieval and sharing of extracted data "Semantic Ontology Mapping" (Michelle Angrish presentation)

Engagement, continued

- NAS workshops
  - Upcoming workshops on (1) triangulation in evidence integration, and (2) artificial intelligence/open data practices. COVID has impacted scheduling.
  - Evidence Integration in Chemical Assessments Workshop (Jun 2019)
  - Strategies and Tools for Conducting Systematic Reviews of Mechanistic Data to Support Chemical Assessments (December 2018)
- Training
  - Training is typically hands on and includes within EPA, international and state engagements
  - Academic partnerships, e.g., ~25 student interns over past 2 years

Gauging Success

- Delivery of assessment products to partners and stakeholders
- Assess quality via feedback during review of IRIS Handbook and assessment products
- Semi-automation "Automated/Machine Learning Approaches" (Michele Taylor presentation)
  - Track time saved to complete task (and money saved)
  - Retain "human-in-the-loop" to assess performance of new machine-learning capabilities
- Publications
- Intra-operability (longer-term)
  - Ability to access extracted data from Chemicals Dashboard in ToxVal and utilize in read-across analyses
  - Moving data into HAWC, ability to conduct statistical analyses on stored data
- Monitor ability to meet Agency needs on high priority, emerging topics, or rapid risk assessment request, e.g., ("PFAS Systematic Evidence Maps" Laura Carlson presentation)
- Monitor uptake of methods by other groups (within and outside of EPA)

Agenda

HERA SESSION 2: Advancing Systematic Review Methods		
2:50 – 3:05	Advancing SR Methods and Tools Intro with Charge Question	Kris Thayer, CPHEA
3:05 – 3:25	Organizing and Evaluating Mechanistic Evidence	Catherine Gibbons, CPHEA
3:25 – 3:45	Automated Data Extraction	Michele Taylor, CPHEA
3:45 – 4:05	Semantic Ontology Mapping	Michelle Angrish, CPHEA
4:05 – 4:25	Application of Systematic Evidence Map Methods to Characterize Available Evidence for PFAS	Laura Carlson, CPHEA
4:25 – 5:00	BOSC Subcommittee discussion and Qs/As	Katrina Waters, Chair
5:00	ADJOURN	

Charge Question

Incorporating the principles of systematic review into the HERA portfolio of assessment products has been a goal of the HERA program for the last several years. In order to achieve this goal, the HERA program intends to advance the field of systematic review more broadly. Based on the progress to date and currently planned products, what suggestion(s) or recommendation(s) does the Subcommittee offer on HERA's research to advance methods for systematic review? [Research Area 3, Output 3.4]

Organizing and Evaluating Mechanistic Evidence: IRIS Systematic Review Methodology

U.S. EPA Office of Research and Development

Board of Scientific Counselors Subcommittee

Chemical Safety for Sustainability and Health and Environmental Risk Assessment National Research Programs

Catherine Gibbons

Center for Public Health & Environmental Assessment

Chemical & Pollutant Assessment Division

February 4, 2021

The views expressed in this presentation are solely those of the author(s) and do not necessarily reflect the views and policies of the U.S. Environmental Protection Agency (EPA)

Approach for systematically reviewing mechanistic studies

- **Goals:**
  - Transparent, operationalized method of systematically identifying mechanistic data
  - Fit-for-purpose methodology for evaluating mechanistic evidence—tailoring effort to assessment needs
- **Problem:** Difficult to know *a priori* how to tailor the effort
- **Solution:** Develop workflow for prioritization of studies to allow stepwise customization and refinement for responding to key questions and issues signaled by human and animal evidence
  - Release of interim products for public comment (IRIS Assessment Plan; Protocol) give opportunities for stakeholder engagement in this stepwise process

What is mechanistic evidence?

- Data from observational and experimental studies that inform biological or chemical events associated with toxic effects but are not generally considered to be adverse outcomes on their own
    - *In vivo* (cellular, biochemical, molecular)
    - *In vitro* or *ex vivo* (human or animal tissues or cells)
    - Non-animal or non-mammalian alternative animal models
    - Big data (‘omics or high-throughput assays) and in silico analyses
    - ADME, TK, physico-chemical properties

*tracked and evaluated by subject-matter experts, separately from other mechanistic studies

Importance in human health assessments

- Identify precursor events for apical toxicity endpoints
- Inform susceptibility (species, strain, or sex differences; at-risk populations or lifestages)
- Inform human relevance of animal data (note: the level of analysis will vary depending on the impact of the animal evidence)
- Provide biological plausibility (i.e., to human or animal health effect data when evidence is weak or critical uncertainties are identified)
- Establish mechanistic relationships (or lack thereof) across sets of potentially related endpoints/outcomes to inform the consideration of coherence during evidence integration
- Aid extrapolation (high-to-low dose; short-to-long duration; route-to-route)
- Improve dose-response modeling and characterization of uncertainties

Mechanistic study identification

- Initial broad chemical-specific literature search designed to identify primary studies (i.e., original data sources of health effects)
  - PECO provides screening criteria for human epidemiological and animal toxicology studies that provide apical health effect evidence
  - These studies are evaluated for reporting quality, risk of bias and sensitivity and often undergo full data extraction of study design and results
- "Potentially relevant supplemental information," including mechanistic, is more difficult to define for efficient screening
  - Toxicological significance is not always clear at outset
  - Importantly, being tagged as supplemental information does not indicate exclusion from consideration

Mechanistic study inventories

- Organizational categories based on characteristics of the available evidence that are grouped based on biological understanding and anticipated assessment uncertainties, e.g., key characteristics, key events, health effects

- Multi-purpose:
  - Produce high-level database snapshot for IRIS Assessment Plan/Protocol, aka Evidence Mapping
  - Facilitate efficient reviews and analyses by subject-matter experts
  - Create inventory for extracting study information and increasing transparency of decision-making

Organizational Frameworks for Mechanistic Data

Development and support by HERA scientists

- Developmental neurotoxicity (Carlson et al., 2020)
- EBTC-GRADE Workshop Report on evidence-based methods to construct mechanistic frameworks (ALTEX, accepted manuscript)
- Key Characteristics, with UC Berkeley and CalEPA: Organizational concept based on shared characteristics of chemicals that lead to toxic effects
  - Carcinogens (Smith et al., 2016; 2020)
  - Male reproductive toxicants (Arzuaga et al., 2019)
  - Female reproductive toxicants (Luderer et al., 2019)
  - Endocrine disrupting chemicals (La Merrill et al., 2020)
  - Under development: hepatotoxicants, neurotoxicants, cardiovascular toxicants

ELSEVIER

Neurotoxicology and Teratology

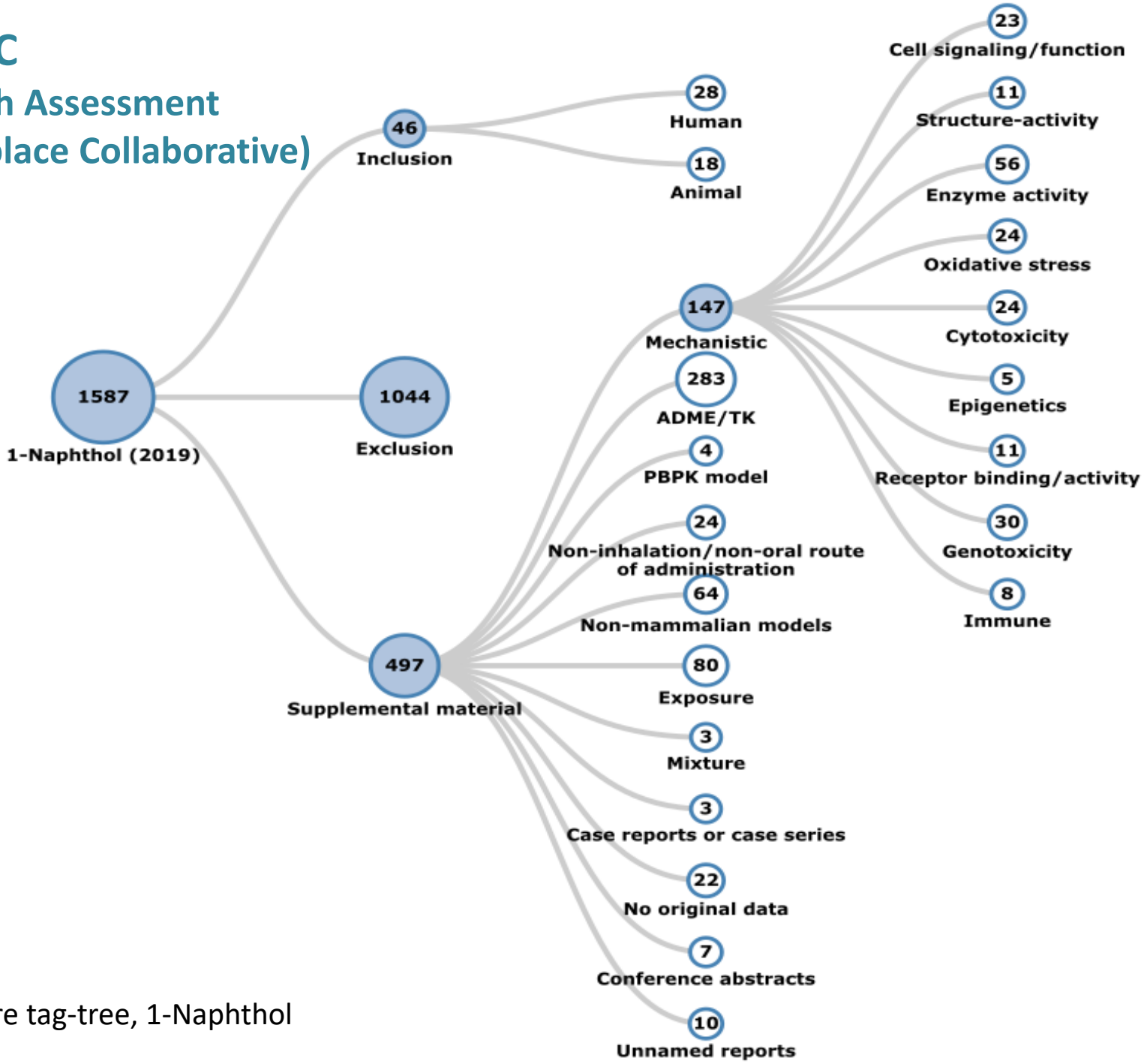
Volume 78, March–April 2020, 106865

Potential frameworks to support evaluation of mechanistic data for developmental neurotoxicity outcomes: A symposium report

Laura M. Carlson [a], Frances A. Champagne [b], Deborah A. Cory-Slechta [c], Laura Dishaw [a], Elaine Faustman [d], William Mundy [e, 1], Deborah Segal [f], Christina Sobin [g], Carol Starkey [h, 2], Michele Taylor [a], Susan L. Makris [f], Andrew Kraft [f, a]

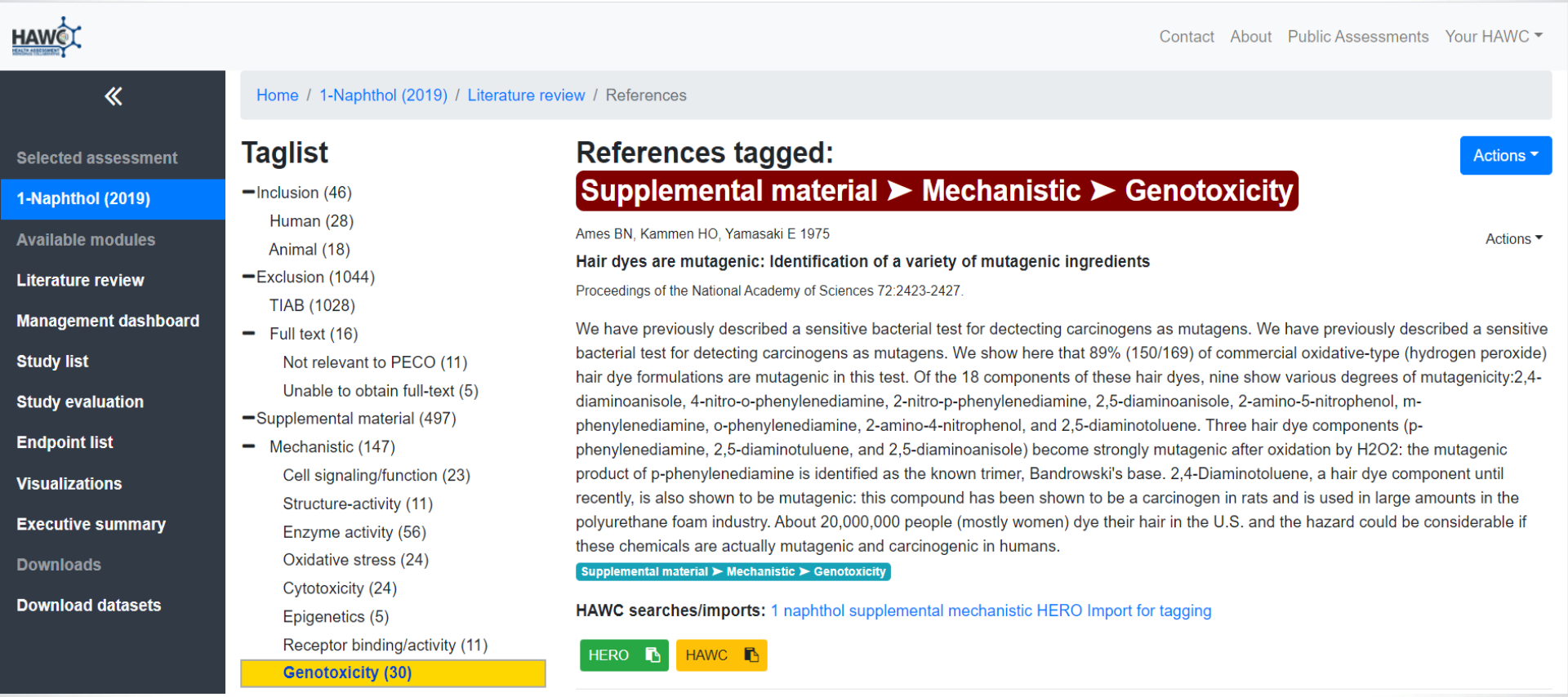
https://keycharacteristics.org/

HAWC
(Health Assessment Workplace Collaborative)



Literature tag-tree, 1-Naphthol

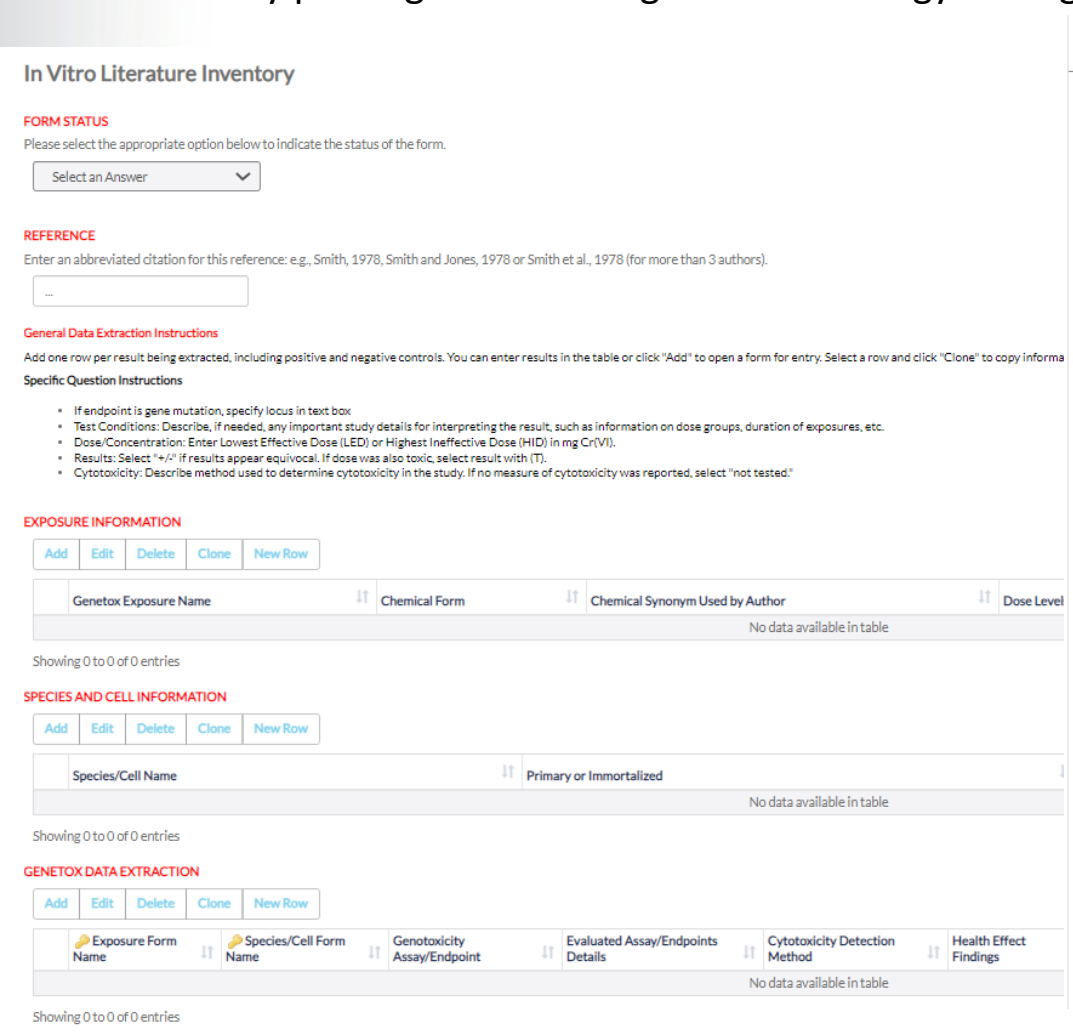
HAWC



Literature tag-tree, 1-Naphthol

Distiller

- Forms for initial screening as well as study detail extraction for building inventories
- Currently piloting in vitro and genetic toxicology testing-specific extraction forms



In Vitro Literature Inventory

FORM STATUS

Please select the appropriate option below to indicate the status of the form.

Select an Answer

REFERENCE

Enter an abbreviated citation for this reference: e.g., Smith, 1978, Smith and Jones, 1978 or Smith et al., 1978 (for more than 3 authors).

...

General Data Extraction Instructions

Add one row per result being extracted, including positive and negative controls. You can enter results in the table or click "Add" to open a form for entry. Select a row and click "Clone" to copy informa

Specific Question Instructions

- If endpoint is gene mutation, specify locus in text box
- Test Conditions: Describe, if needed, any important study details for interpreting the result, such as information on dose groups, duration of exposures, etc.
- Dose/Concentration: Enter Lowest Effective Dose (LED) or Highest Ineffective Dose (HID) in mg Cr(VI).
- Results: Select "+/-" if results appear equivocal. If dose was also toxic, select result with (T).
- Cytotoxicity: Describe method used to determine cytotoxicity in the study. If no measure of cytotoxicity was reported, select "not tested."

EXPOSURE INFORMATION

Add | Edit | Delete | Clone | New Row

Genetox Exposure Name	Chemical Form	Chemical Synonym Used by Author	Dose Level
No data available in table			

Showing 0 to 0 of 0 entries

SPECIES AND CELL INFORMATION

Add | Edit | Delete | Clone | New Row

Species/Cell Name	Primary or Immortalized
No data available in table	

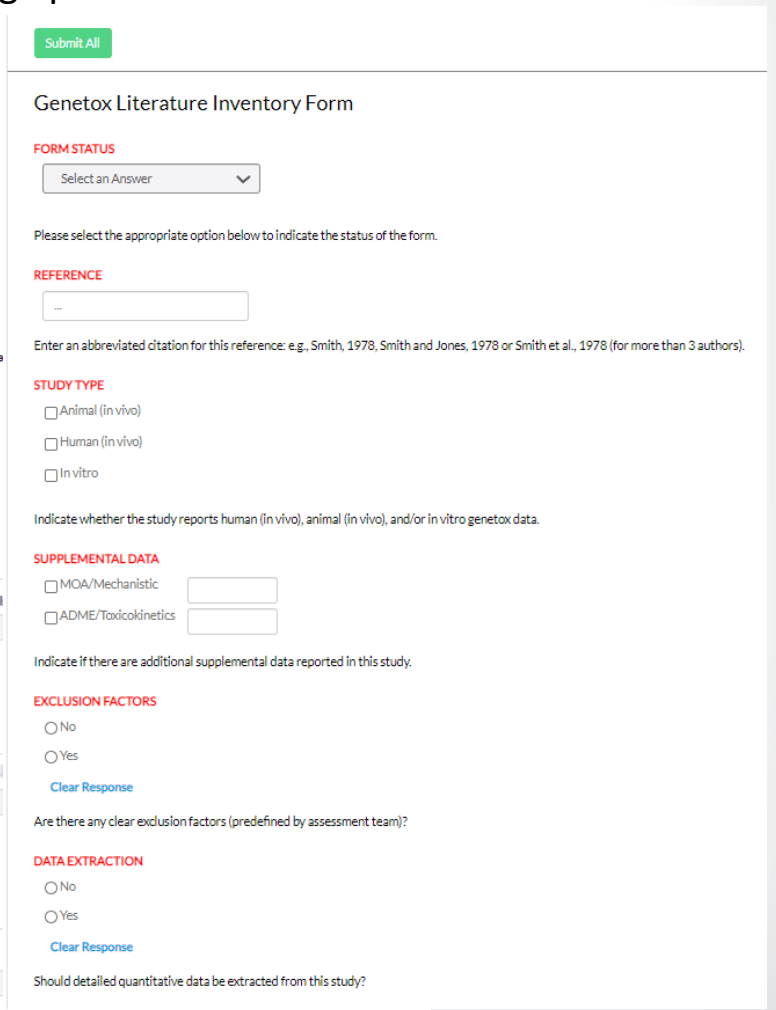
Showing 0 to 0 of 0 entries

GENETOX DATA EXTRACTION

Add | Edit | Delete | Clone | New Row

Exposure Form Name	Species/Cell Form Name	Genotoxicity Assay/Endpoint	Evaluated Assay/Endpoints Details	Cytotoxicity Detection Method	Health Effect Findings
No data available in table					

Showing 0 to 0 of 0 entries



Submit All

Genetox Literature Inventory Form

FORM STATUS

Select an Answer

Please select the appropriate option below to indicate the status of the form.

REFERENCE

...

Enter an abbreviated citation for this reference: e.g., Smith, 1978, Smith and Jones, 1978 or Smith et al., 1978 (for more than 3 authors).

STUDY TYPE

- Animal (in vivo)
- Human (in vivo)
- In vitro

Indicate whether the study reports human (in vivo), animal (in vivo), and/or in vitro genetox data.

SUPPLEMENTAL DATA

- MOA/Mechanistic
- ADME/Toxicokinetics

Indicate if there are additional supplemental data reported in this study.

EXCLUSION FACTORS

- No
- Yes

Clear Response

Are there any clear exclusion factors (predefined by assessment team)?

DATA EXTRACTION

- No
- Yes

Clear Response

Should detailed quantitative data be extracted from this study?

Narrow the focus for mechanistic syntheses

- Focused approach primarily driven by whether uncertainties exist in the human and animal evidence base
- Areas of focus for mechanistic analyses determined by:
  - Key science issues identified during problem formulation
  - Health effects indicated by human and animal evidence
  - The level of potential influence for making hazard ID and dose-response decisions
  - Known MOAs and pathways of toxicity
- Flexible approach
  - Syntheses can range from a high-level summary to a detailed MOA analysis with mechanistic study evaluations
  - Determined by availability of adequate chemical-specific data

Examples of Focused Key Science Issues for Evaluation

Hexavalent chromium systematic review protocol

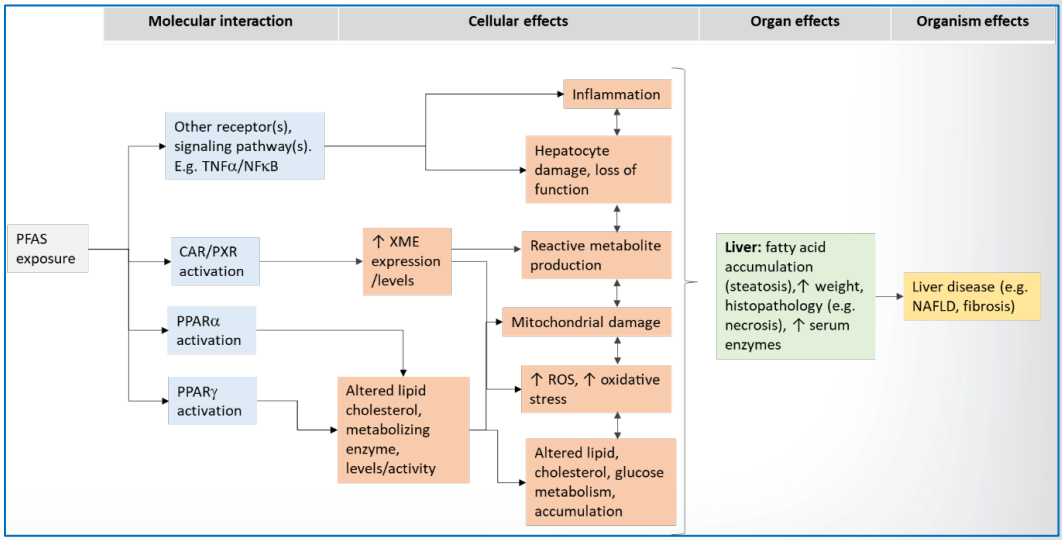
- Mutagenic MOA evaluation after oral or inhalation exposure
- Differences in detoxification of Cr(VI) to Cr(III) via oral exposures across species

Methylmercury assessment plan

- Accuracy of different biomarkers of human exposure (e.g., hair; cord or maternal blood)

PFAS systematic review protocol

- Toxicokinetic differences across species and sexes
- Human relevance of hepatic effects (e.g., PPARα receptor activation)



Rationale for prioritizing mechanistic outcomes for more in-depth analysis

- All studies informing mechanistic analyses of focused key science issues are considered
- A subset of these may be "prioritized" for further evaluation of a mechanistic event or for study-level evaluations (reporting quality, risk of bias, sensitivity)
  - If the assessment requires a more intensive evaluation to support human and/or animal evidence conclusions (or even a single key event) or
  - If event/MOA/AOP is controversial and/or has conflicting evidence
- Prioritization factors based on overall informativeness to the mechanistic pathway/MOA, for example:
  - Influence on biological plausibility of causal association
  - Exposure design and relevancy to susceptible risk group
  - Sensitivity and specificity of selected model test system
  - Informativeness to key event in a proposed MOA and/or AOP
  - Assays providing evidence for causal linkages between key events

Rationale for prioritizing mechanistic outcomes for more in-depth analysis

- Factors influencing prioritization strategy are clearly described
  - Example: Prioritization decisions for the focused evaluation of a key mechanistic event can be summarized in a table:

	Prioritized	Deprioritized
Population	• Humans • Experimental animals • In vitro studies in human primary or immortalized cells derived from liver	• Non-mammalian species • Non-human cells in vitro

Exposure	• Humans: Quantified (e.g., levels; duration) oral or inhalation exposure to chemical X
	• Animals:
	  ○ Quantified oral (drinking water, gavage, diet), inhalation
	  ○ Repeat-dose studies ≥28 days
	• In vitro: all
		• Injection, dermal exposures
		• No specific exposure to chemical X (e.g., mixtures)

Comparison	• Human and animal studies: Inclusion of a comparison group (e.g., pre- or post-exposure; no exposure; lower exposure level) • In vitro studies: untreated controls	• No comparator
Outcome	• Examining mechanistic endpoints relevant to interpretations of hepatic health effects in humans	• Endpoints not relevant to noncancer hepatic toxicity, including genotoxicity tests

Prioritization of mechanistic studies relevant to hepatic toxicity

Example: Targeted PECO for mutagenic MOA analysis

- Depending on the question and evidence available, some assessments may develop a targeted mechanistic PECO that clearly defines studies prioritized for study-level evaluation of specific mechanistic outcomes that will be highly impactful to assessment decisions

Populations	Studies in humans and mammals in vivo (including transgenic rodent models); primary human cells in vitro.
Exposures	Exposure to chemical X by inhalation or oral (drinking water, diet, or gavage) routes.
Comparators	Occupational studies: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of chemical X, or exposure to chemical X for shorter periods of time, Animal studies: a concurrent control group exposed to vehicle-only treatment or an untreated control,
Outcomes	Gene mutation (prior to tumorigenesis), micronuclei, and chromosomal aberrations.

Mechanistic PECO for studies measuring gene and chromosomal mutations useful for analyzing a mutagenic MOA using a database rich in genotoxicity studies

Pilot in vitro study evaluation domains

Animal study evaluation domains	Pilot in vitro study evaluation domains
Reporting quality	
Risk of Bias	
Allocation	N/A
Observational bias/blinding	Observational bias/blinding
Confounding/variable control	Variable control
N/A	Specificity
Selective reporting	Selective reporting
Attrition	N/A
Sensitivity	
Chemical characterization and administration	Chemical characterization and administration
Exposure timing, frequency, and duration	Exposure timing, frequency, and duration
Endpoint sensitivity and specificity	Endpoint sensitivity
Results presentation	Results presentation and analysis

Status and next steps for in vitro study evaluation

- Internal pilot testing to refine domains and descriptions
- In vitro evaluation domains are now in HAWC (first use with chloroform studies)
  - Determine whether in vitro domains need modification before application to other major study types, e.g., ex vivo and 3D tissue model systems, 'omics methods, and other NAMs, as needed
- **Developing outcome-specific criteria will be critical**
  - Key for enabling evaluation assistance from non-experts
  - Key for adapting existing domain-based study evaluation criteria from human and animal studies to mechanistic outcomes
  - Shareable
- Continuing external engagement (within and outside of EPA)
  - Discussions and collaborations with other groups developing in vitro criteria (e.g., OCSPP; NTP's Report on Carcinogens)
  - EBTC-GRADE Workshop on the development of mechanistic frameworks (June 2019)
  - NASEM Workshops on the systematic review of mechanistic data (2018, 2013)

Thank you

IRIS Program Planning

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Automating Data Extraction

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HERA BOSC
February 4, 2021

The views and opinions expressed here do not reflect official US Environmental Protection Agency policy.

Automating Data Extraction

GOALS

To develop a systematic method that allows for semi-automated extraction of data to increase efficiency and more easily integrate with other data management platforms

WHY?

To increase efficiency and interoperability for more streamlined, usable data.

PROGRESS

- Algorithms have been developed that extract common entities (chemical, dose, species) from animal toxicology studies

- PDFs can now be converted to machine-readable text so that algorithms can mine/extract data

PATH FORWARD

Support automated data extraction for various disciplines including:

- **Epidemiology**
- **Ecotoxicology**
- **Environmental Fate/Exposure**

Interoperable Software Tools

Study Screening

SWIFT REVIEW

SEARCH REFINEMENT
Discover important terms and phrases.

TOPIC MODELING
Uncover hidden structure in your literature corpus.

PROBLEM FORMULATION
Identify interesting, high impact research questions.

LITERATURE PRIORITIZATION
Use machine learning to triage your reading list.

USER FEEDBACK
User screening decisions are used to continuously refine the machine learning model.

SWIFT-ACTIVESCREENER

IMPROVED RANKING MODEL
The computer suggests the next articles to screen based on previously included articles.

Literature Tagging and Inventory

DistillerSR

tableau

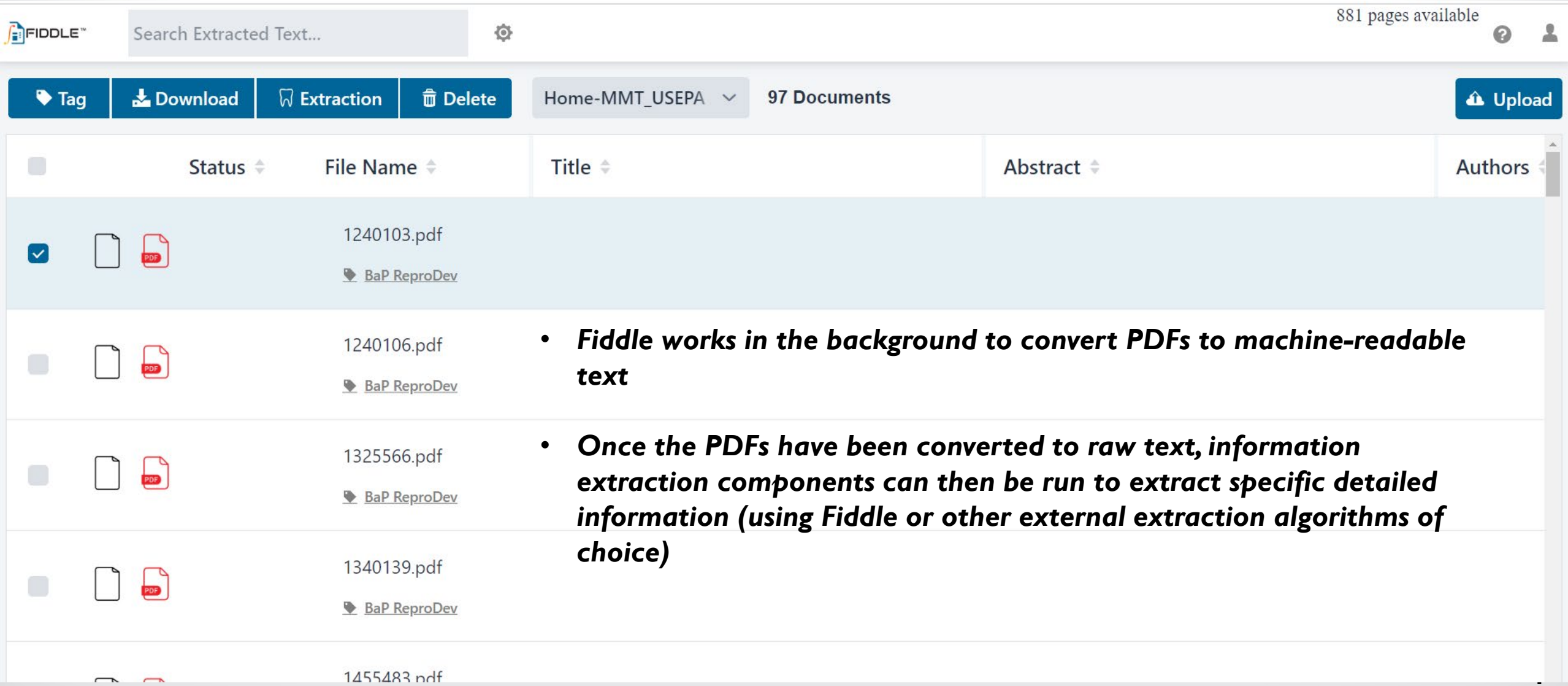
EPA
Health & Environmental Research Online (HERO)

Data Extraction

HAWC
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

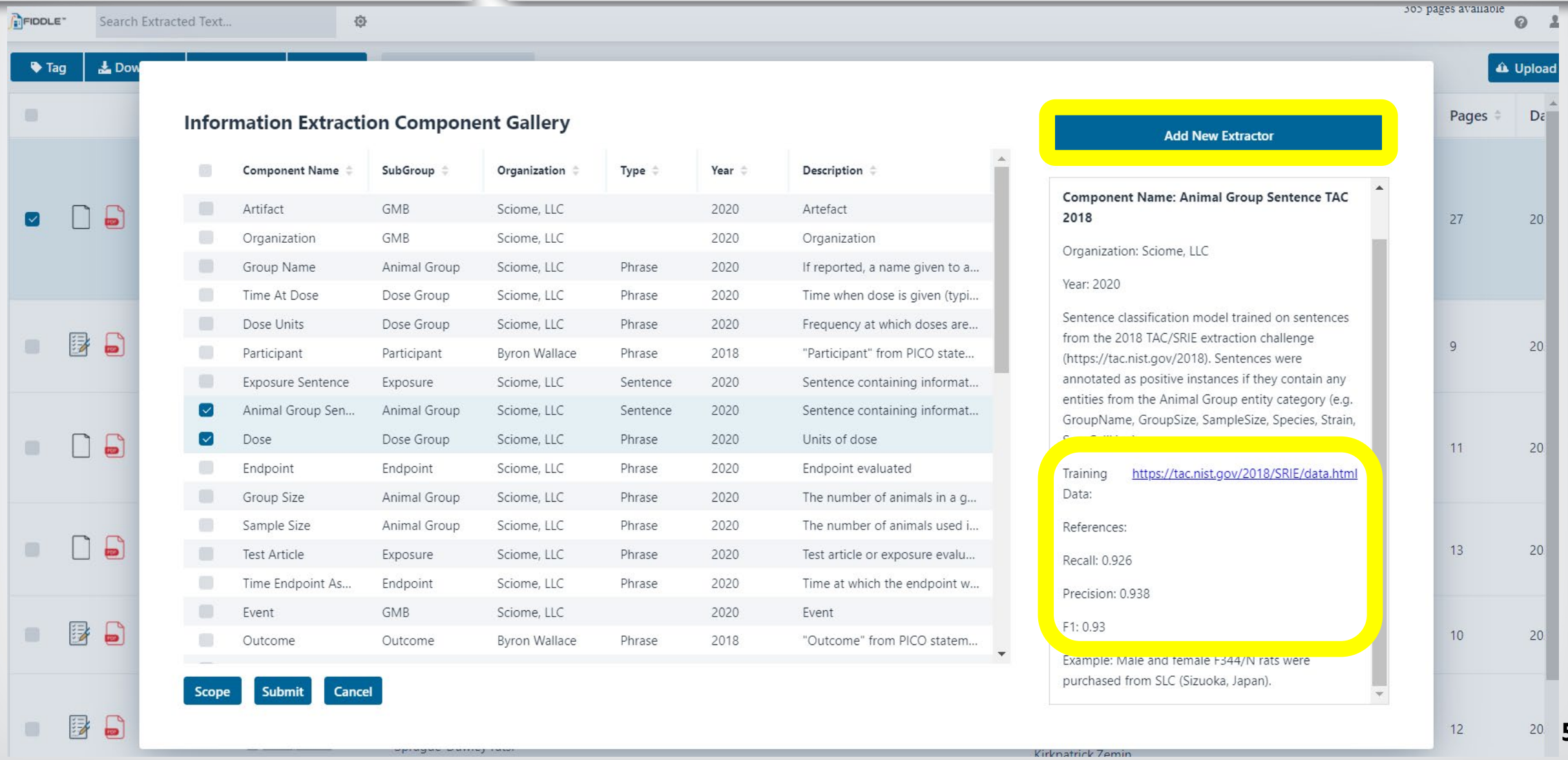
Data Visualization

Creating Machine Readable Text

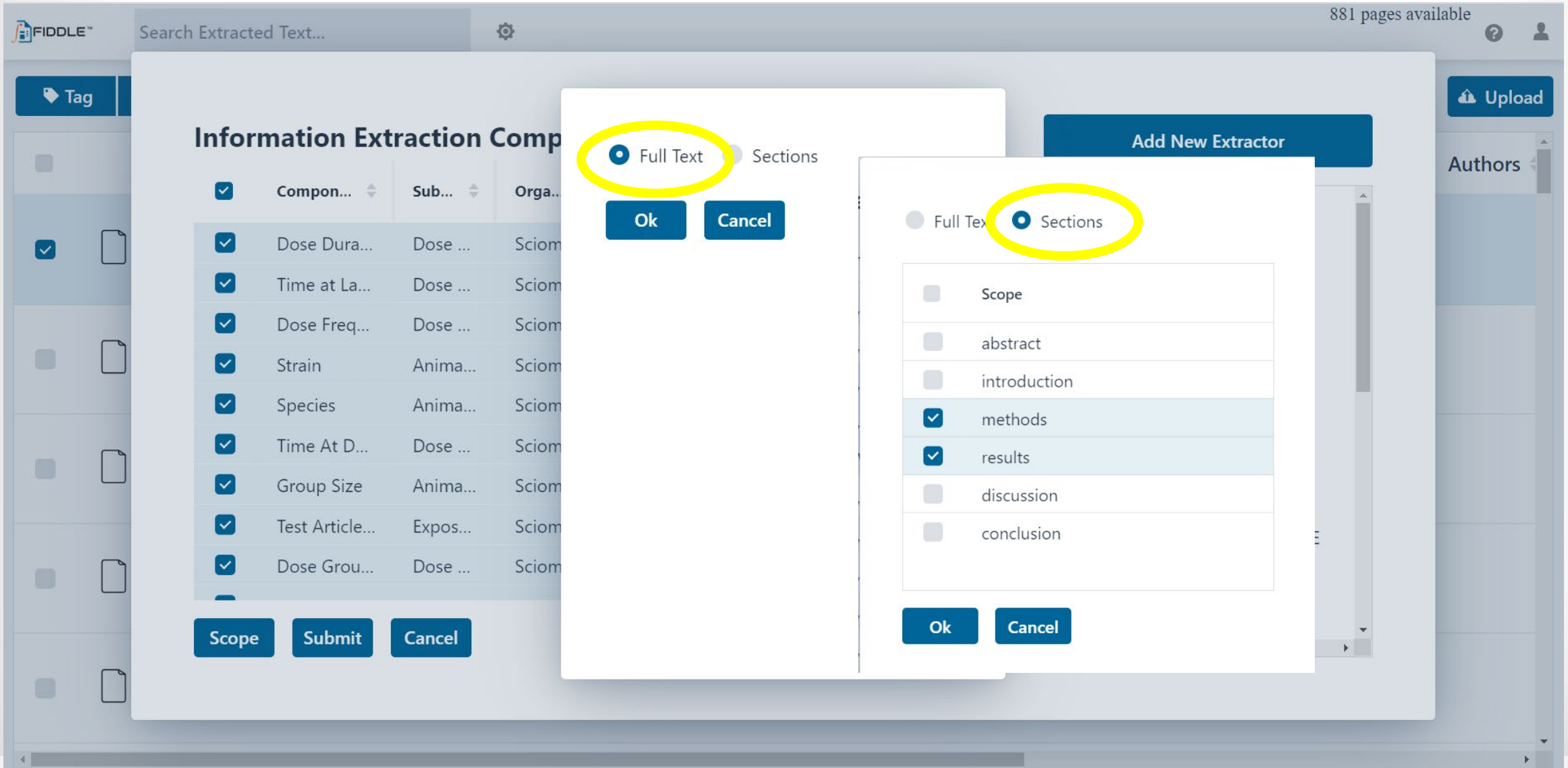


- ***Fiddle works in the background to convert PDFs to machine-readable text***
- ***Once the PDFs have been converted to raw text, information extraction components can then be run to extract specific detailed information (using Fiddle or other external extraction algorithms of choice)***

Algorithm Repositories



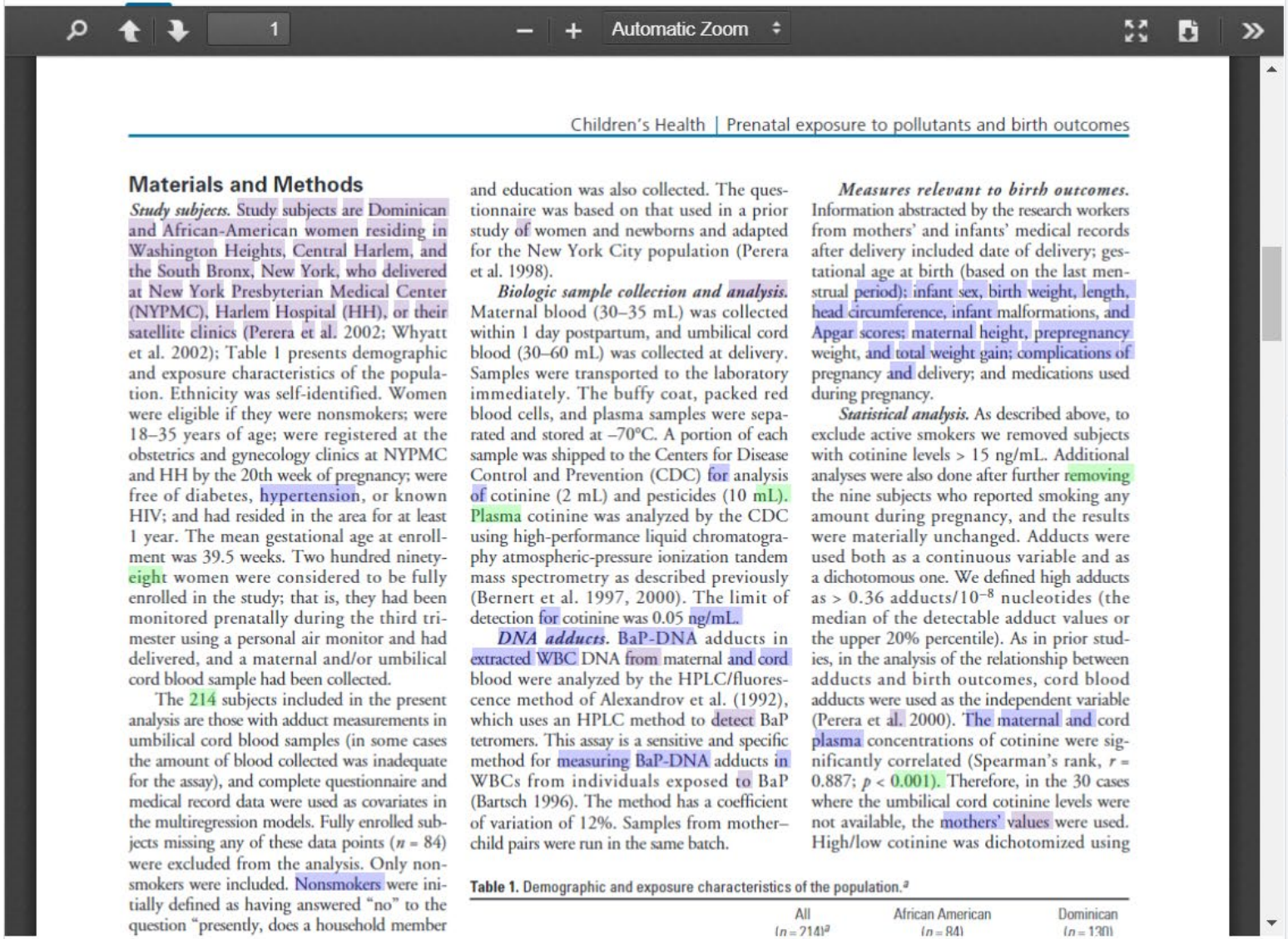
Extraction Components within Sectionalized Text



Extracted Text Highlighted and Contextual Information Provided

Text PDF

Facilitating Quality Checking



Children's Health | Prenatal exposure to pollutants and birth outcomes

Materials and Methods

Study subjects. Study subjects are Dominican and African-American women residing in Washington Heights, Central Harlem, and the South Bronx, New York, who delivered at New York Presbyterian Medical Center (NYPMC), Harlem Hospital (HH), or their satellite clinics (Perera et al. 2002; Whyatt et al. 2002); Table 1 presents demographic and exposure characteristics of the population. Ethnicity was self-identified. Women were eligible if they were nonsmokers; were 18–35 years of age; were registered at the obstetrics and gynecology clinics at NYPMC and HH by the 20th week of pregnancy; were free of diabetes, hypertension, or known HIV; and had resided in the area for at least 1 year. The mean gestational age at enrollment was 39.5 weeks. Two hundred ninety-eight women were considered to be fully enrolled in the study; that is, they had been monitored prenatally during the third trimester using a personal air monitor and had delivered, and a maternal and/or umbilical cord blood sample had been collected.

The 214 subjects included in the present analysis are those with adduct measurements in umbilical cord blood samples (in some cases the amount of blood collected was inadequate for the assay), and complete questionnaire and medical record data were used as covariates in the multiregression models. Fully enrolled subjects missing any of these data points ($n = 84$) were excluded from the analysis. Only nonsmokers were included. Nonsmokers were initially defined as having answered "no" to the question "presently, does a household member and education was also collected. The questionnaire was based on that used in a prior study of women and newborns and adapted for the New York City population (Perera et al. 1998).

Biologic sample collection and analysis. Maternal blood (30–35 mL) was collected within 1 day postpartum, and umbilical cord blood (30–60 mL) was collected at delivery. Samples were transported to the laboratory immediately. The buffy coat, packed red blood cells, and plasma samples were separated and stored at –70°C. A portion of each sample was shipped to the Centers for Disease Control and Prevention (CDC) for analysis of cotinine (2 mL) and pesticides (10 mL). Plasma cotinine was analyzed by the CDC using high-performance liquid chromatography atmospheric-pressure ionization tandem mass spectrometry as described previously (Bernert et al. 1997, 2000). The limit of detection for cotinine was 0.05 ng/mL.

DNA adducts. BaP-DNA adducts in extracted WBC DNA from maternal and cord blood were analyzed by the HPLC/fluorescence method of Alexandrov et al. (1992), which uses an HPLC method to detect BaP tetromers. This assay is a sensitive and specific method for measuring BaP-DNA adducts in WBCs from individuals exposed to BaP (Bartsch 1996). The method has a coefficient of variation of 12%. Samples from mother–child pairs were run in the same batch.

Measures relevant to birth outcomes. Information abstracted by the research workers from mothers' and infants' medical records after delivery included date of delivery; gestational age at birth (based on the last menstrual period); infant sex, birth weight, length, head circumference, infant malformations, and Apgar scores; maternal height, prepregnancy weight, and total weight gain; complications of pregnancy and delivery; and medications used during pregnancy.

Statistical analysis. As described above, to exclude active smokers we removed subjects with cotinine levels > 15 ng/mL. Additional analyses were also done after further removing the nine subjects who reported smoking any amount during pregnancy, and the results were materially unchanged. Adducts were used both as a continuous variable and as a dichotomous one. We defined high adducts as > 0.36 adducts/10^{-8} nucleotides (the median of the detectable adduct values or the upper 20% percentile). As in prior studies, in the analysis of the relationship between adducts and birth outcomes, cord blood adducts were used as the independent variable (Perera et al. 2000). The maternal and cord plasma concentrations of cotinine were significantly correlated (Spearman's rank, $r = 0.887$; $p < 0.001$). Therefore, in the 30 cases where the umbilical cord cotinine levels were not available, the mothers' values were used. High/low cotinine was dichotomized using

Table 1. Demographic and exposure characteristics of the population.[a]

	All ($n = 214$)[a]	African American ($n = 84$)	Dominican ($n = 130$)

Plasma cotinine	using high- performance liquid chromatogra- phy atmospheric- pressure ionization tandem mass spectrometry as described previously (Bernert et al .

Participant

S	Extracted Text	Context Text
	and African-American women residing in Washington Heights Central Harlem and the South Bronx New York who	Study subjects are Dominican and African-American women residing in Washington Heights , Central Harlem , and the South Bronx , New York , who

Data Downloadable in Several Formats for Increased Interoperability

Text PDF

Toxicology and Applied Pharmacology 208 (2005) 127 - 136
www.elsevier.com/locate/ytaap

Impact of maternal dietary exposure to endocrine-acting chemicals on

progesterone receptor expression in microdissected hypothalamic

medial preoptic areas of rat offspring

Hironori Takagia,b, Makoto Shibutania,b,T, Kyoung-Youl Leea, Naoya Masutomia,

Haruka Fujitaa, Kaoru Inouea, Kunitoshi Mitsumorib,c, Masao Hirosea

aDivision of Pathology, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan bUnited Graduate School of Veterinary Sciences, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan cLaboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology, 3-5-8 Saiwai-cho, Fuchu, Tokyo 183-8509, Japan

Received 18 December 2004; accepted 2 February 2005 Available online 17 March 2005

Download: plain text | json | yaml | sectionalized text | xml | full text | pdf

Text PDF

1 Automatic Zoom

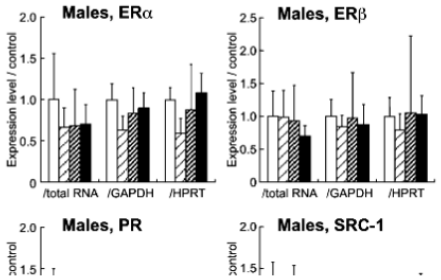
GAPDH or HPRT, and a similar tendency was also noted for PR expression, normalized for the input amount of total RNA. With ERα, SRC-2, GnRH, and CALB, no obvious change in expression was apparent.

Gene expression changes due to MXC

Based on the sexually dimorphism or alteration in the gene expression by EE, ERα, ERβ, PR, and SRC-1 were selected for gene expression analysis in the MPOA of animals exposed to other EACs.

In males, MXC at 1200 ppm decreased the PR level when normalized for GAPDH expression, and a tendency for decrease was also noted from 24 ppm with this normalization (Fig. 3). A similar tendency for decrease in PR expression (non-significant) was also observed with the other normalization procedures. No apparent expression change in ERα, ERβ, or SRC-1 was observed after MXC-exposure.

In females, MXC at 1200 ppm increased the PR expression on normalization for the HPRT value and a similar tendency was also noted with normalization for GAPDH (Fig. 4). With ERβ and SRC-1, a dose-unrelated decrease in expression was observed at 240 ppm, on



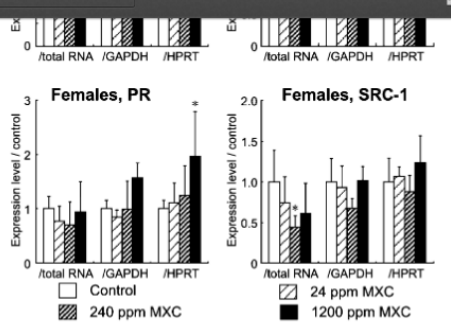


Fig. 4. Gene expression data for the MPOA at PND 10 of female pups exposed maternally to MXC. Data are ratios to control values, expressed as mean ± SD, and normalized for the input amount of total RNA, or GAPDH or HPRT expression. *Significantly different from the controls ($*P < 0.05$ by Dunnett's test).

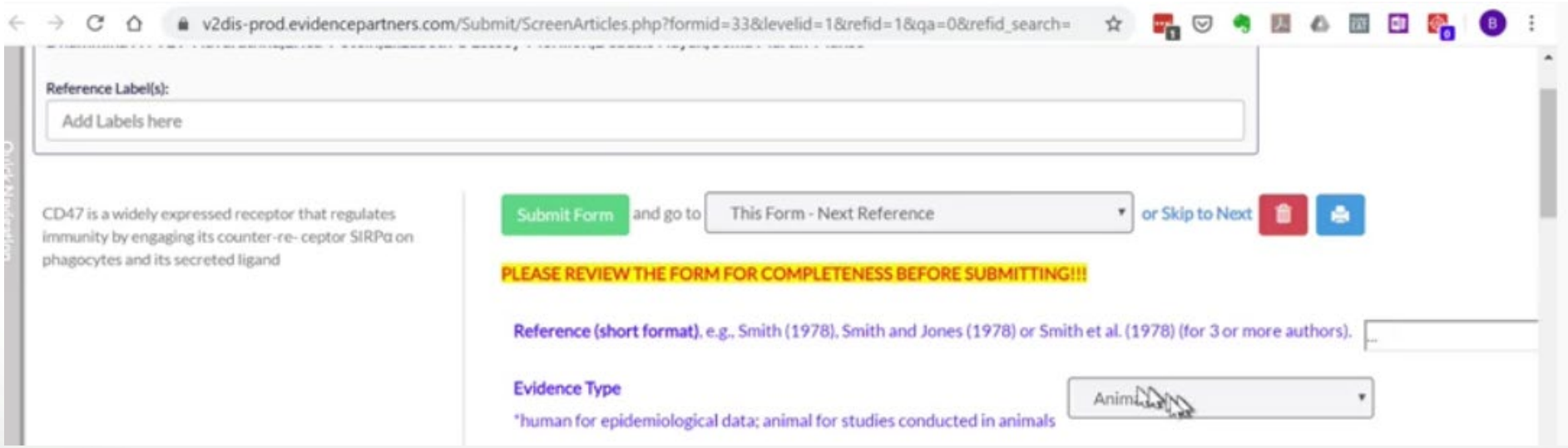
normalization for the input amount of total RNA, and a decreasing tendency at this dose was also noted with normalization for GAPDH expression. ERα did not show any apparent expression change with MXC treatment in females.

Gene expression changes with DINP or GEN

In males, neither DINP nor GEN changed the expression levels of ERα, ERβ, PR, or SRC-1 (Fig. 5). In females, expression levels of PR with DINP at 20,000 ppm were decreased when normalized for GAPDH expression and a similar tendency for decrease (non-significant) was also observed on normalization for the HPRT value, no such change/tendency being detected when correction was for the input amount of total RNA (Fig. 6). GEN at 1000 ppm did not cause any apparent expression change in the genes

Import Extracted Data into Data Extraction Software

- Export the machine-extracted data into other software applications where extraction is currently done (now 100% manual), aka "pre-populated" forms
- Our standard process includes a primary extractor and another person to QC. Thus, humans can fill in the blanks and QC the machine-extracted data.
- This creates a workflow where we can onboard and evaluate machine-extracted data as the models are developed



NIST-TAC Challenge Reboot

DRAFT Annotation Guidelines

ANNOTATION INSTRUCTIONS

Each document has 24 types of entities (defined in Table 1) to annotate (see figure 1). Annotation of a document includes assigning entity types to mentions and assigning mentions to groups (defined in Table 2).

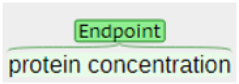


Figure 1: a sample annotation in which 'protein concentration' is a mention of entity type 'Endpoint'.

Steps to annotating a PDF document include:

Preparing Article for Annotation:

1. Copy the text from the articles' PDF file into a text file using the article id as the name of the text file (e.g., pubmed id).
2. Clean the text file by ...TBD
3. Ensure the Abstract, Methods, and Results section of the file are clear. If not, add a label to the document indicating the section type.
4. Import the text file into your assigned annotation folder (e.g., sysreview/vwalker for Vickie Walker).

Conducting Annotation:

1. Annotate all mentions with their respective entity types, see Section Annotating Mentions
2. Annotate groups, in the following order, See Section Annotating Groupings
   - 2.1. TreatmentGroups
   - 2.2. DoseGroups
   - 2.3. DoseDurationGroups
   - 2.4. EndpointGroups
   - 2.5. AnimalGroups

ANNOTATING MENTIONS

Table 1. Entity Types

Category	Annotation Tag	Description
ARTICLE	Funding	Text indicating source of funding
	COI	Text indicating conflict of interest; declarations or none to report
EXPOSURE	TestArticle	Test article or exposure evaluated
	Vehicle	The solution the test article is in
	TestArticlePurity	Purity of test article
	TestArticleVerification	Text indicating that the test article was confirmed
ANIMAL GROUP	GroupName	If reported, an indicator of a treatment group or positive/negative control group (ie DES-10 or control or treated).
	GroupSize	The number of animals in a group
	Species	The species names
	Strain	The strain names
	Sex	Gender of the animal group(s)
DOSE GROUP	Dose	Dose
	DoseUnits	Units of dose
	DoseDuration	Duration of treatment (dose)
	DoseDurationUnits	Units of dose duration
	DoseRoute	Route of administration
	AgeAtDose	Age when dose is given
	AgeUnits	Units used for animal ages
	AgeAtFirstDose	Age at which first dose is given
	AgeAtLastDose	Age at which last dose is given
ENDPOINT	Endpoint	Endpoint evaluated
	EndpointUnitOfMeasure	Units of measured endpoint
	EndpointMethod	Text describing the method used to assess the outcome
	AgeAtEndpoint	Age at assessment

General Guidelines for Annotating Mentions:

- Extract Exposure, Animal Group, and Dose Group information from the Abstract & Methods section.

Training Sets for Algorithm Building

Quick Match | match whole word | ignore case | ignore punctuation | auto quick match | 5 occurrences found | 788325

(250mg/kg),

is known about the combined toxicity of DBP and BaP. In the current study, male Sprague Dawley rats were subchronically exposed to single doses of DBP

chemical

(250mg/kg), single doses of BaP (5mg/kg) and combined doses of DBP and

chemical

BaP. Significant adverse effects were observed on the reproductive system, including decreased sperm count, increased production of abnormal sperm, changes in serum testosterone levels and irregular arrangements of the seminiferous epithelium. Biochemical analyses showed that the activities of superoxide dismutase and glutathione peroxidase decreased after exposure to these EDs. Therefore, our

chemical

data suggest that exposure to DBP and BaP, in either separate or combined doses, can affect the reproductive system of male rats adversely via oxidative stress-related mechanisms. No significant additive effect was observed after

these results indicate that exposure to mixtures of EDs have

Entities | Groups | Relations

exposure (0)

chemical → dose

Name of new relation type...

Start Entity: chemical

End Entity: dose

Create New Relation Type

Manual Annotation Leveraging Ontologies

Collapse All | Expand All

Toggle Spans

Save and Proceed

Validate Annotations

Automating Data Extraction

NEXT STEPS:

- **Develop and disseminate guidance on data extraction which ties into ontology (Michelle Angrish will discuss next)**
- **Collaborate Across Disciplines (Exposure/Ecotox/Epi) to Develop Fit for Purpose Algorithms**
- **Develop Training Sets (Manually Annotating)**
- **Put Quality Controls Checks in Place**

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- Brian Howard

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- Elisa Aiassa

Health Canada
- Ben Ling

- **This work will be expanded into other disciplines (ECOTOX) and includes extensive collaboration across CSS and HERA as well as other agencies/offices conducting assessments**

Semantic Ontology Mapping

Michelle Angrish

US EPA/ORD/CPHEA/CPAD

HERA BOSC

February 4, 2021

The views and opinions expressed here do not reflect official US Environmental Protection Agency policy.

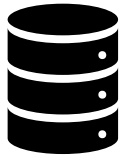
Approach for Semantic Ontology Mapping

- **Problem:**
  - Information retrieval and knowledge organization is a semantic and conceptual challenge because the formal record of scientific research is almost exclusively a written study report
- **Solution:**
  - Apply ontologies to increase the efficiency of information retrieval and prioritization
  - Expand controlled vocabulary to normalize information extracted using systematic review methodology
  - Standardized data extraction formats for enhanced interoperability between systematic review tools and databases
  - Develop knowledge organization systems to enhance data curation and evidence integration frameworks

Information Retrieval Challenge

- **SR methods provide a mechanism for ensuring a chemical assessment fully and transparently uses all relevant evidence.**
- **The extent that this evidence can be retrieved is heavily constrained by current approaches to storing and cataloguing scientific knowledge.**

The formal record of scientific research is almost always a written study report



Reports stored in siloed databases that:
- Cover different portion of total literature
- Have unique data schemas and search interfaces

Searches return a large proportion of false positives that must be manually evaluated.

- **Information retrieval is a lengthy process that may still exclude relevant records**
  - **The content of a document is represented by a number of key words, plus the words in the titles and abstracts.**
  - **Only information known by researchers and coded as conceptually related in a database is retrieved.**

Semantic Factor

- **Semantic Factor**
  - **Semantic because meaning is a function of the relationship between words and the context in which they were presented so even if a person uses a word incorrectly the correct meaning is still interpreted.**
- **If an information retrieval strategy does not include all the words and their related concepts (in a database specific manner) then relevant documents will be overlooked.**

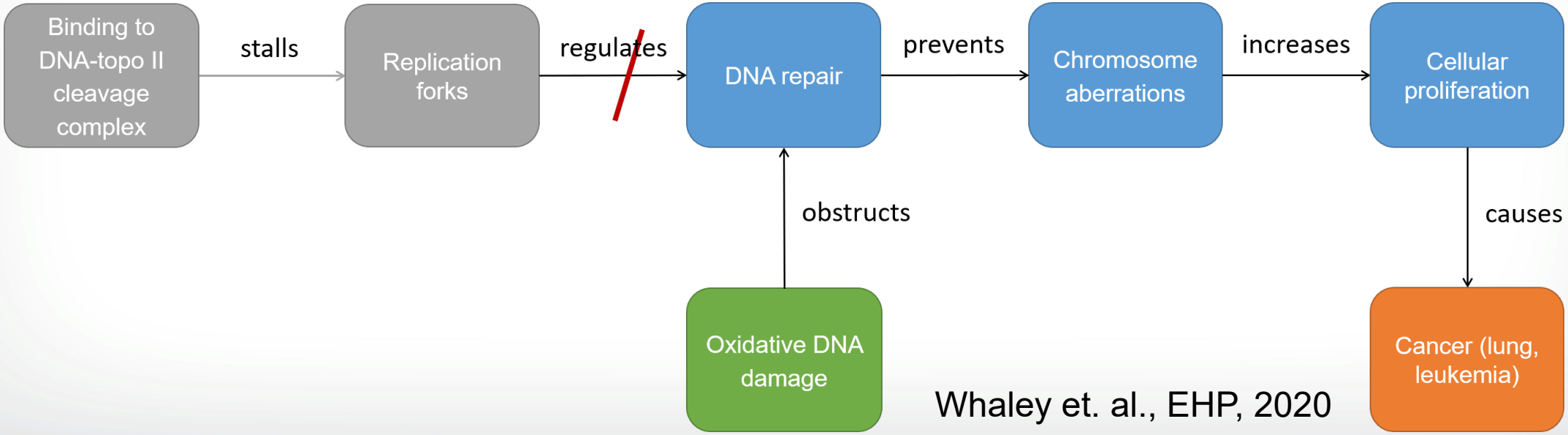
Table 1. Demonstration of how variation in language used by study authors in title, abstract, and author keywords fields affects search results in PubMed. Database syntax is used to ensure the phrase entered is the exact one being searched for. Date of searches: 15 July 2020.

PubMed Query	Results
"PAHs" [Title/Abstract] OR "PAHs" [Other Term]	15,912
"PAH" [Title/Abstract] OR "PAH" [Other Term]	22,605
"polycyclic aromatic hydrocarbon" [Title/Abstract] OR "polycyclic aromatic hydrocarbon" [Other Term]	4,545
"aromatic polycyclic hydrocarbons" [Title/Abstract] OR "aromatic polycyclic hydrocarbons" [Other Term]	59
"polycyclic aromatic hydrocarbons" [Title/Abstract] OR "polycyclic aromatic hydrocarbons" [Other Term]	19,311

Whaley et. al., EHP, 2020

Conceptual Factor

- **Conceptual Factor**
  - **For any topic or domain of interest there is an expansive network of related concepts and sub-concepts that may also be relevant to a SR or SEM.**
  - **Having a complete map of the relationships among these concepts is necessary if the full body of assessment relevant literature is to be retrieved.**



Whaley et. al., EHP, 2020

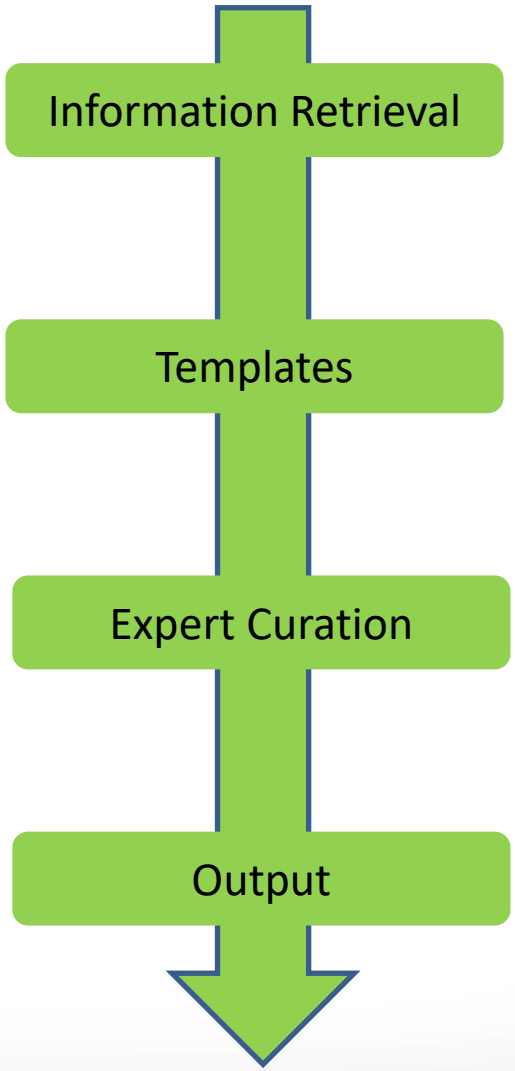
The Solution: Knowledge Organization Systems

- Knowledge organization system (KOS) for environmental health science information.
- Controlled Vocabulary (CV) – list of words and phrases (concepts) used to tag content in a database to make that content retrievable via navigation or search (Pomerantz, 2015)
- Ontologies – representation of the properties of relations between concepts
- Useful for:
  - Information retrieval
  - Normalizing extracted data from written text
  - Developing standardized data extraction formats
  - Facilitating software application interoperability
  - Data integration

Efficiency in the Chemical Assessment Workflow

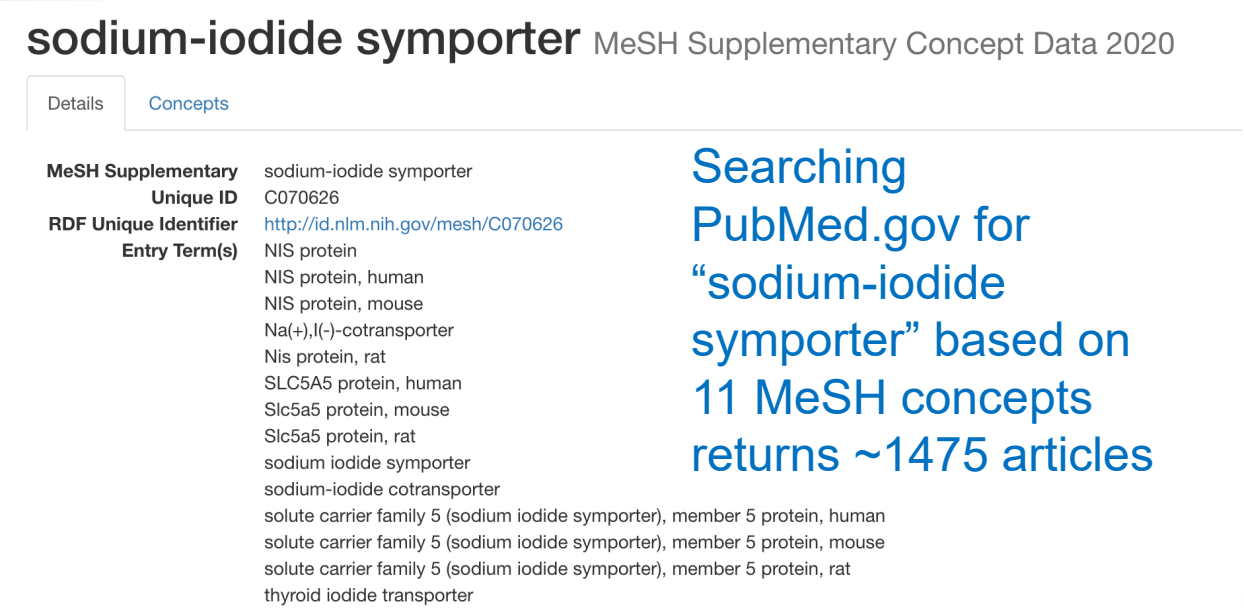
Assessment Method

- Problem Formulation & Scoping
- Literature Searches
- Literature Screening & Tagging
- Literature Inventory
- **Summary Level Data Extraction (e.g., Chemical & Evidence Type)**
- Key Questions
- Evaluation of Study Methods
- **Dose Response Data Extraction**
- Synthesis of Results
- Evidence Integration (includes WoE)
- Dose-response Analysis
- Toxicity Value

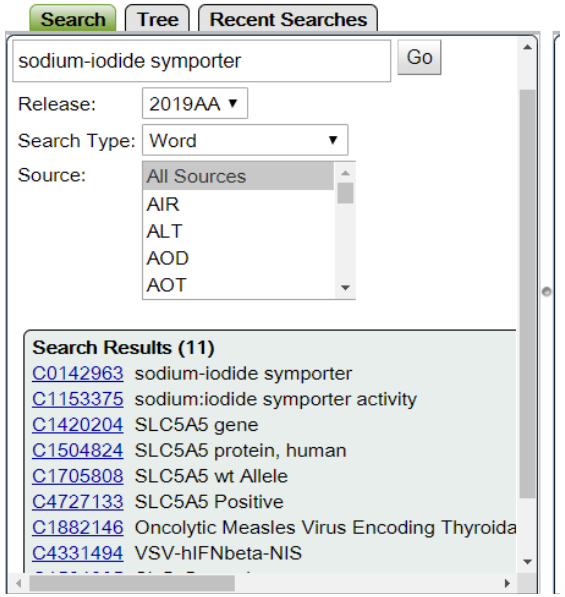


Ontologies for Information Retrieval*

- **Query Expansion**
  - **Litsearches may only capture 50-80% of relevant studies**
  - **Ontology tools can expand the search concepts**



Searching PubMed.gov for "sodium-iodide symporter" based on 11 MeSH concepts returns ~1475 articles

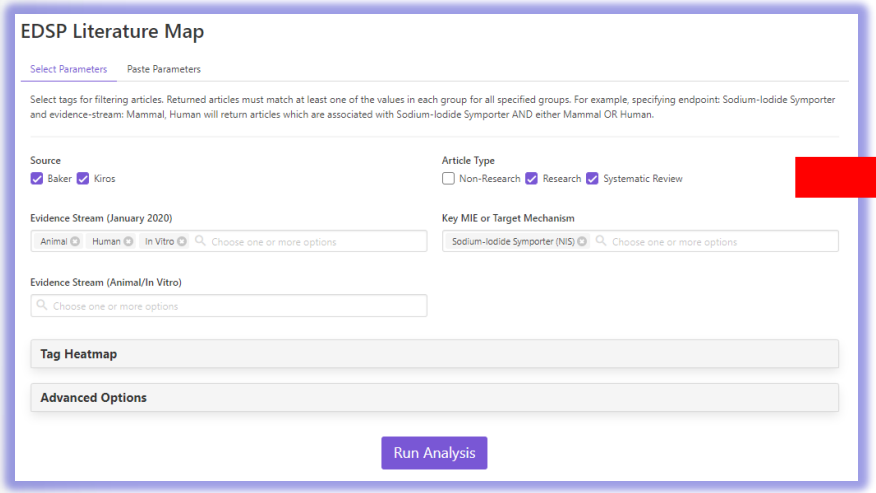


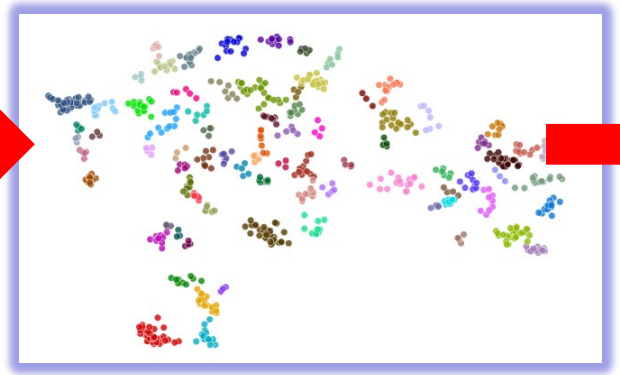
Searching PubMed.gov for "sodium-iodide symporter" using UMLS

*Work done in collaboration with Endocrine Disruptor Screening program in EPA/OCSPP

Ontologies for Information Retrieval and Prioritization*

- **Query Expansion***
  - **Can return very large number of studies (1000K to >>22K studies for the NIS example)**
- **Topic Modeling and Clustering via semantic concepts**





*Work done in collaboration with Endocrine Disruptor Screening program in EPA/OCSPP

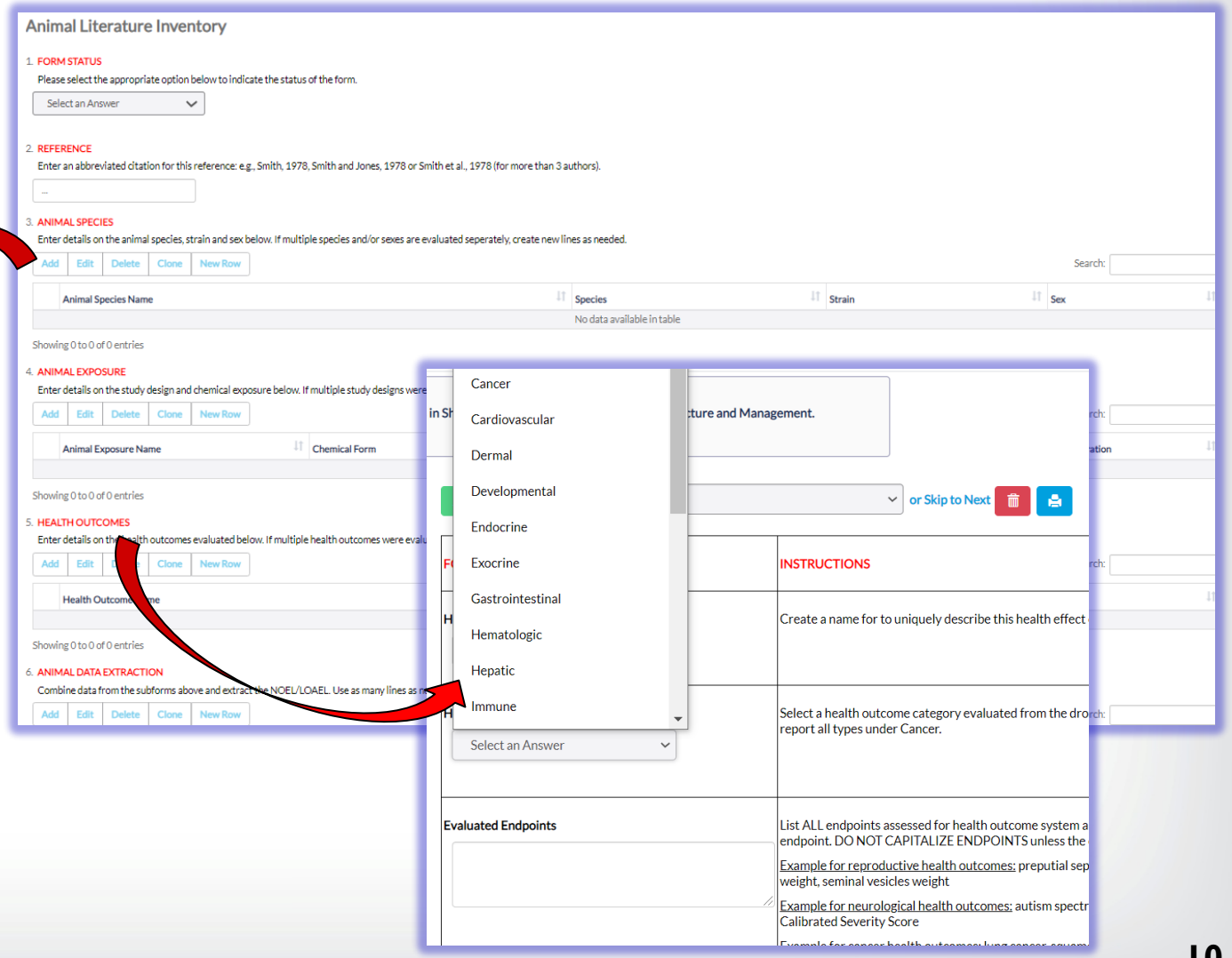
- Graphical view of **cluster concepts**
- Papers clustered via **semantic concepts** and annotated with **MeSH Terms** or **named entities**

- Built & filtered from **cluster concepts**
- Interactive component allows **user to select concepts** to further filter the clusters

Controlled Vocabularies for Templates

Outline for the NIEHS & EPA Retrospective and Prospective Coordination on Annotation Guidelines for Toxicology

FORM	INSTRUCTIONS
Animal Species Name	Create a name for to uniquely describe this animal group (used to identify
Species	Select the species from the dropdown menu. If a non-mammalian species
Strain	Enter the strain used. Use "not reported" if appropriate.
Sex	Enter the sex evaluated for this subform. If the sexes will be extracted sep males and females are presented the option "both" is used and sex-specifi the studies most informative for hazard would be fully extracted in HAW



Controlled Vocabularies for Data Interoperability

Environmental Health Vocabulary (EHV) - a recommended terminology for outcomes/endpoints - October 2020

Updated on October 5, 2020, this version contains the list of **Preferred Terms** for the key fields Endpoint, System, Organ, Effect and Effect Subtype in HAWC. Start with the **ReadMe** tab for additional instructions.

Edit | Delete

Endpoint/Adverse outcome*

940 | Load ID

Total Bilirubin (TBILI)

Selected term: 940 | Total Bilirubin (TBILI) ×

☑ Use controlled vocabulary

System	Organ/Tissue/Region	Effect	Effect subtype
Hepatic	Liver	Hepatobiliary Component	Clinical Chemistry
Selected term: 888 | Hepatic ×	**Selected term:** 889 | Liver ×	**Selected term:** 934 | Hepatobiliary Component ×	**Selected term:** 935 | Clinical Chemistry ×
☑ Use controlled vocabulary	☑ Use controlled vocabulary	☑ Use controlled vocabulary	☑ Use controlled vocabulary

Demonstrating using the controlled vocabulary digitized by mapping to Unified Medical Language Syntax (UMLS)

- *Critical for interfacing with other databases and tools!*

Here we want to define custom text, but it auto populates with existing text

Endpoint/Adverse outcome*

Total Bilirubin (TBILI) custom text

☐ Use controlled vocabulary

Total Biliru

Total Bilirubin

Total Bilirubin (TBILI)

Total Bilirubin (TBILI) (48d)

Total Bilirubin (TBILI), Blood

Total Bilirubin (TBILI), Recovery

Total Bilirubin (TBILI), Recovery, Serum

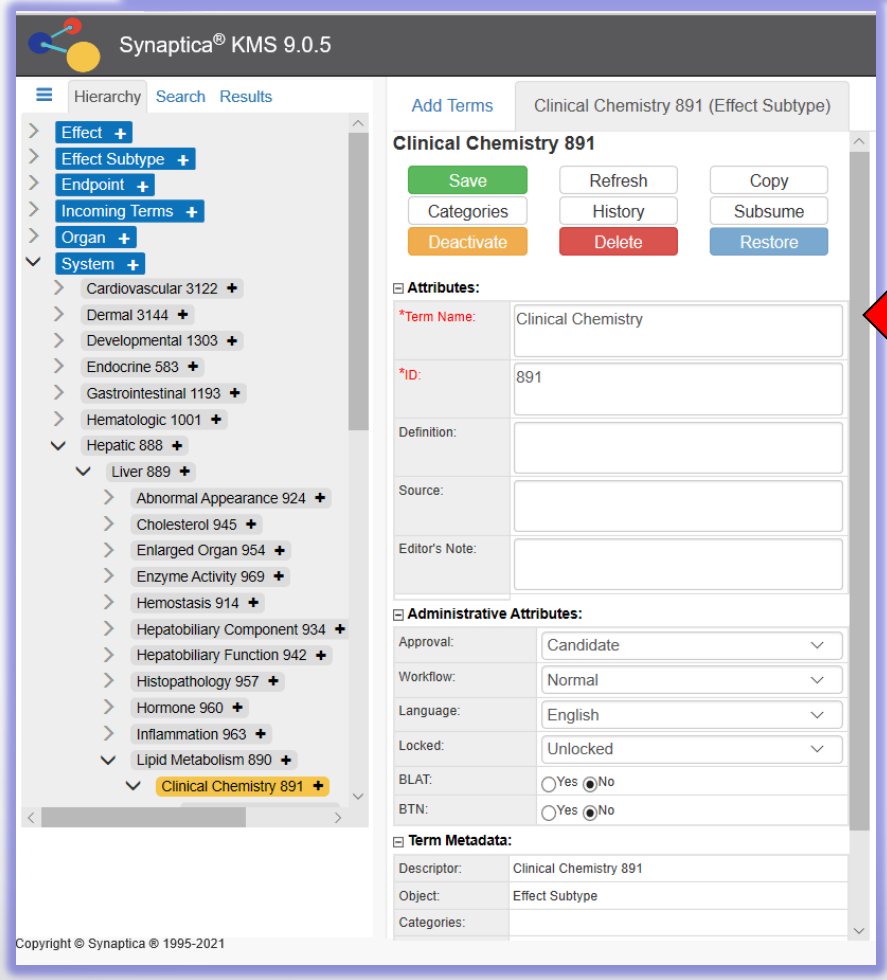
Or we can select to use the EHV.

Expert Curation of Controlled Vocabularies

Environmental Health Vocabulary (EHV) - a recommended terminology for outcomes/endpoints - October 2020

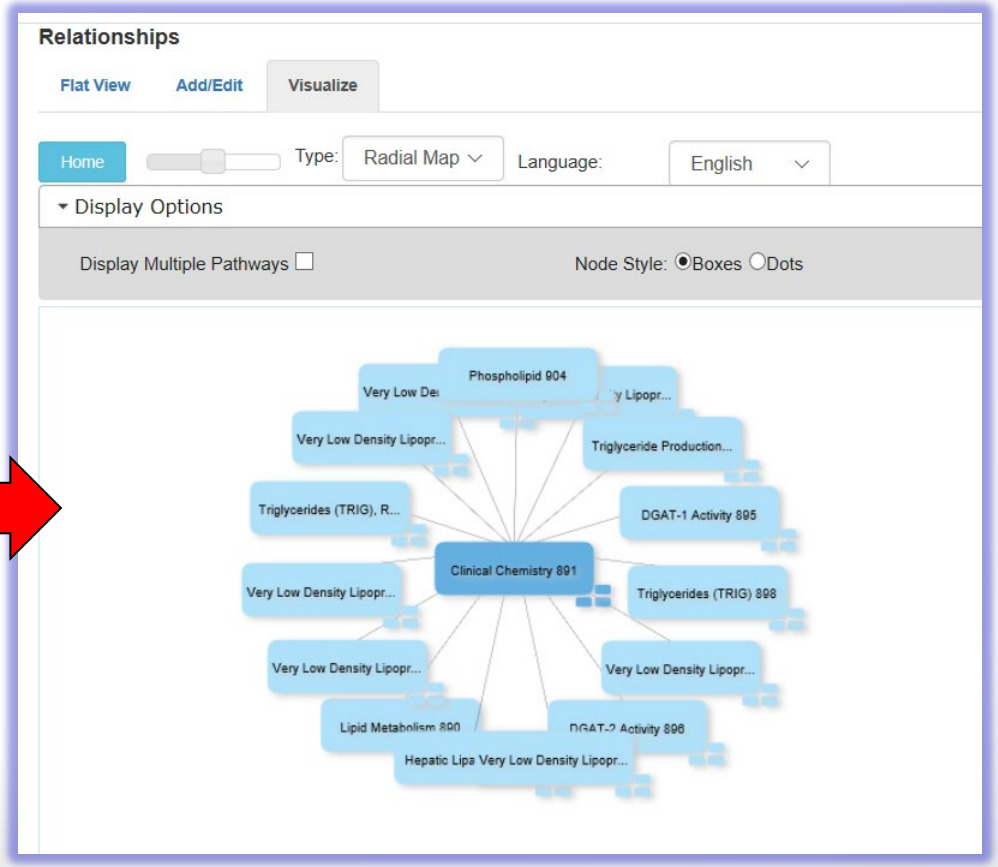
Updated on October 5, 2020, this version contains the list of **Preferred Terms** for the key fields Endpoint, System, Organ, Effect and Effect Subtype in HAWC. Start with the **ReadMe** tab for additional instructions.

Edit | Delete



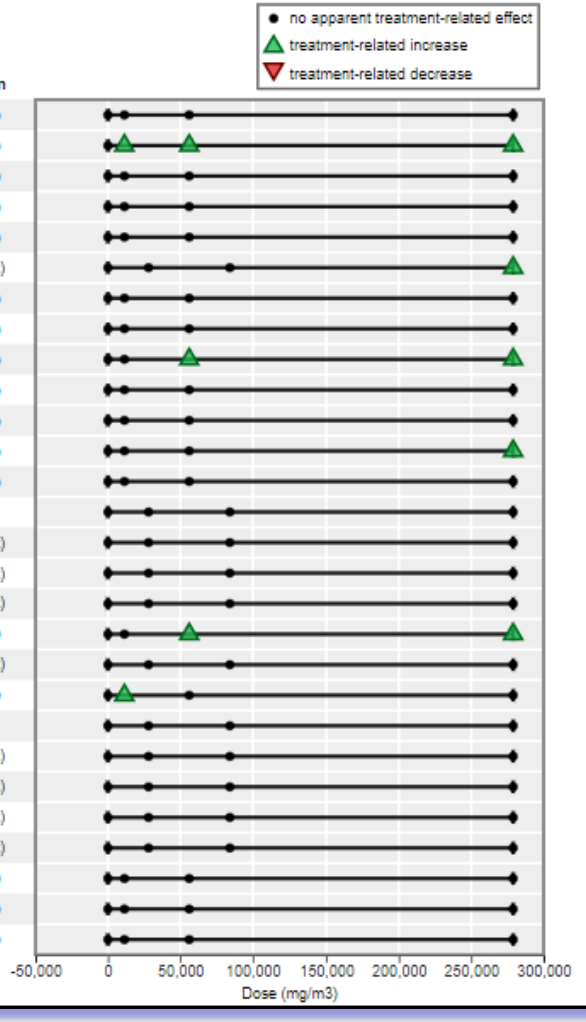
Synaptica KOS for expert curation of EHV

And exploration of relationships



Controlled Vocabularies for Data Management

Endpoint	Study	Animal Description	Route	Exposure Duration
Alanine Aminotransferase (ALT), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Albumin (A), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Alkaline Phosphatase (ALP), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
	Malley et al. 1996	Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
	Haskell Laboratory 1995	Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Aspartate Aminotransferase (AST), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Cholesterol (CHOL), Total, Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Focal Liver Necrosis	Malley et al. 1998	Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Liver Histopathology	Malley et al. 1998	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Liver Weight, Absolute	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Mouse, Crl:CD-1(ICR)BR (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
	Malley et al. 1998	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
	Malley et al. 1996	Rat, Crl:Cd Br (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
	Malley et al. 1998	Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Liver Weight, Relative	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Mouse, Crl:CD-1(ICR)BR (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
Total Bilirubin (TBILI), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Triglycerides (TRIG), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)



Demonstrating use of the Environmental Health Vocabulary (EHV) in the EPA Health Assessment Workplace Collaborative (HAWC) for data management and integration.

- e.g., data grouped by endpoint
- HAWC facilitates transparency and data accessibility

Controlled Vocabularies for Data Interoperability

Home / PFAS 150 (2020) / Endpoints / Bioassay endpoint heatmap summary

Visual | Data | Customize

Dashboard selection: system vs. test subject

system vs. test subject

System	Mouse			Rabbit		Rat			Grand Total
	Combined	Female	Male	Combined	Female	Combined	Female	Male	
Cardiovascular									
Dermal									
Developmental									
Endocrine									
Gastrointestinal									
Hematologic									
Hematopoietic									
Hepatic		4	5		1	2	18	15	45
Immune									
Multi-System									
Multi-system									
Musculoskeletal									
Nervous									
Ocular									
Repiratory									
Reproductive									
Respiratory									
Urinary									
Whole Body									
[System]									
Grand Total		**4**	**5**		**1**	**2**	**18**	**15**	**45**

Species & Sex

Study Citation

- 1 BioDynamics 1991
- 2 Covance 2000
- 2 Dupont, 1991, 5380491
- 2 ECHA, 1995, 6299219
- 2 ECHA, 2001, 6299228
- 2 ECHA, 2007, 5701160
- 2 ECHA, 2007, 6299223
- 2 ECHA, 2011, 5701148

Experiment Type

- 5 Developmental
- 6 Reproductive
- 18 Short-term (1-30 days)
- 16 Subchronic (30-90 days)

Generation

- 1 First-generation (F1)
- 34 N/A (not generational-study)
- 10 Parent-generation (P0)

Endpoint Name

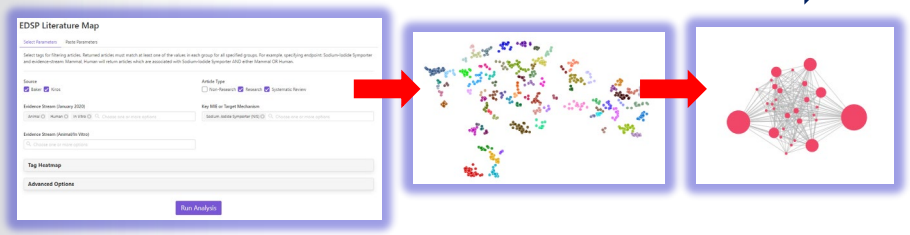
- 0 Liver Histopathology, Recovery
- 0 Liver Weight, Absolute
- 45 Liver Weight, Relative
- 0 Liver Weight, Relative to Brain, Recovery
- 0 Liver Weight, Relative, Recovery

Study Citation	Experiment Name	Animal Group Name	System	Organ	Effect	Endpoint Name
Ladics et al. 2008	gavage rats 8:2 Fluorotelomer alcohol	Male Sprague-Dawley Rat	Hepatic	Liver	Organ Weight	Liver Weight, Relative
Ladics et al. 2008	gavage rats 8:2 Fluorotelomer alcohol	Female Sprague-Dawley Rat	Hepatic	Liver	Organ Weight	Liver Weight, Relative
Saillenfait et al. 1997	Developmental Oral Rat	P0 Female Sprague Dawley Rat	Hepatic	Liver	Organ Weight	Liver Weight, Relative
Saillenfait et al. 1997	Developmental Oral Rat	F1 Male/Female Sprague Dawley Rat	Hepatic	Liver	Organ Weight	Liver Weight, Relative

Explore by endpoint name

Semantic Ontology Mapping for Automated Workflows

Information Retrieval and Prioritization



Study Screening and Tagging

DistillerSR

EPA United States Environmental Protection Agency
Health & Environmental Research Online (HERO)

Data Extraction

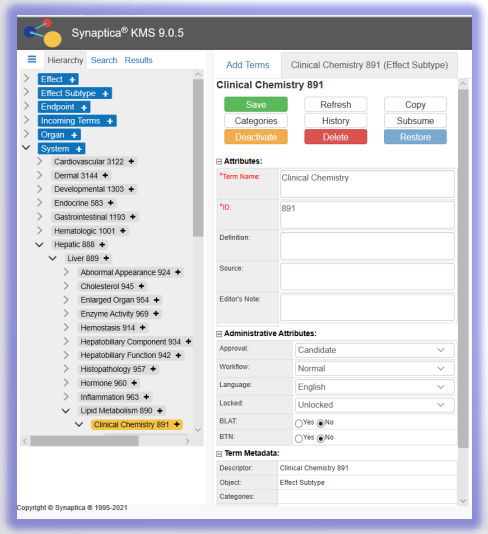
Publication Information

Refid	469756
Title	Alterations of Cytokines and MAPK Signaling Pathways are Related to the Immunotoxic Effect of Perfluorononanoic Acid
Abstract	The developmental toxicity of perfluorohexane sulfonate (PFHxS) is largely unknown despite widespread environmental contamination and presence in human serum, tissues and milk.To thoroughly investigate PFHxS toxicity in developing rats and to mimic a realistic human exposure situation, we examined a low dose close to human relevant PFHxS exposure, and combined the dose-response studies of PFHxS with a fixed dose of twelve environmentally relevant endocrine disrupting chemicals (EDmix).Two reproductive toxicity studies in time-mated Wistar rats exposed throughout gestation and lactation were performed. Study 1 included control, two doses of PFHxS and two doses of PFHxS+EDmix (n = 5-7). Study 2 included control, 0.05, 5 or 25 mg/kg body weight/day PFHxS, EDmix-only, 0.05, 5 or 25 mg PFHxS/kg plus EDmix (n = 13-20).PFHxS caused no overt toxicity in dams and offspring but decreased male pup birth weight and slightly increased liver weights at high doses and in combination with the EDmix. A marked effect on T4 levels was seen in both dams and offspring, with significant reductions from 5 mg/kg/day. The EDmix caused anti-androgenic effects in male offspring, manifested as slight decreases in anogenital distance, increased nipple retention and reductions of the weight of epididymides, ventral prostrate and vesicular seminalis.PFHxS can induce developmental toxicity and in addition results of the co-exposure studies indicated that PFHxS and the EDmix potentiate the effect of each other on various endpoints, despite their different modes of action. Hence, risk assessment may underestimate toxicity when mixture toxicity and background exposures are not taken into account.

Ontologies for query expansion, study retrieval, and clustering using semantic concepts

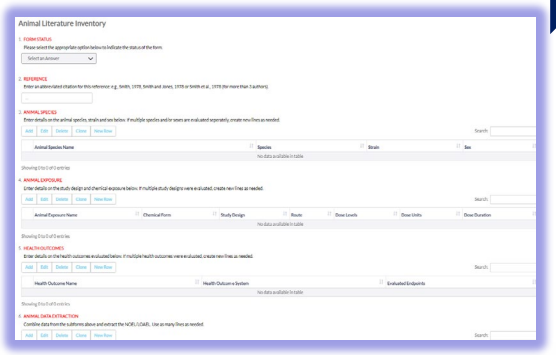
Annotation tools for data extraction from study pdfs

Term Mapping and Curation



Semantic concept matching for data normalization

Standard Data Extraction Formats



Structured formats for data interoperability

Data Integration, Display, and Download

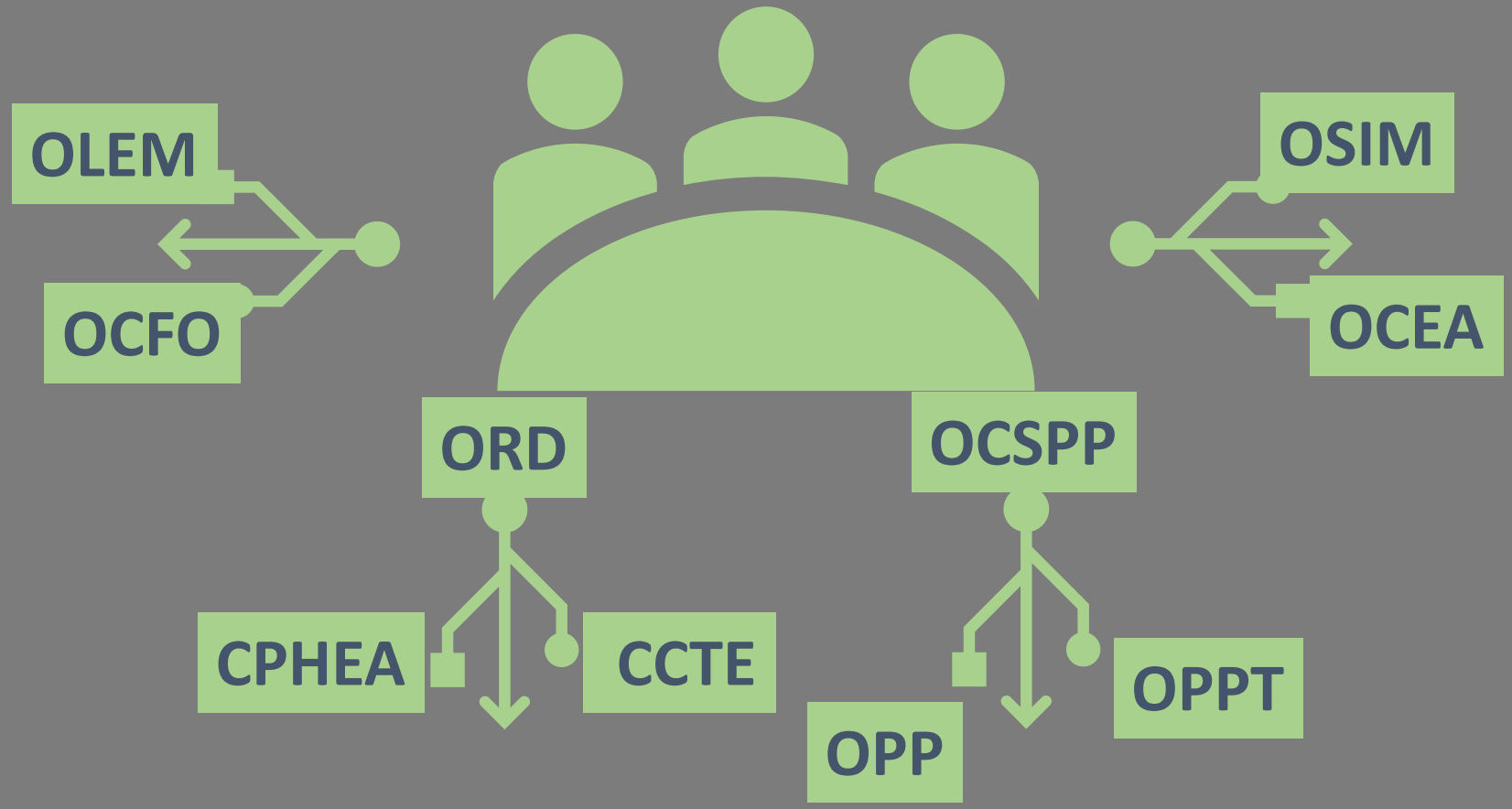
HAWC HEALTH ASSESSMENT WORKSPACE COLLAB

+ableau

Semantic Ontology Mapping Moving Forward

- Expand ontology query expansion and topic clustering tool capability
- Standardize data extraction formats and normalize content within those fields across EPA
- Expand EHV to other domains
  - exposure
  - mechanistic
  - methods
  - others
- Map EHV to other ontologies
  - Using KOS for
    - advanced queries
    - better understanding of the data
    - integration with other databases (i.e. EPA Comptox Chemicals Dashboard)

Internal EPA Collaborators to Achieve this Vision



External Collaborations and Partnerships

Communities of Practice

- Systematic Review CoP
  EPA, NTP, DOD, USGS, FDA
- EHS Vocabulary Initiative
  EPA & NTP
- Data Science CoP
  EPA only

Federal Agencies & Int. Partners

National Toxicology Program
U.S. Department of Health and Human Services

NIH U.S. National Library of Medicine

NIST National Institute of Standards and Technology
U.S. Department of Commerce

ATSDR
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

OAK RIDGE National Laboratory

United States Environmental Protection Agency

efsa
European Food Safety Authority

OECD
BETTER POLICIES FOR BETTER LIVES

ECHA
EUROPEAN CHEMICALS AGENCY

International Agency for Research on Cancer
World Health Organization

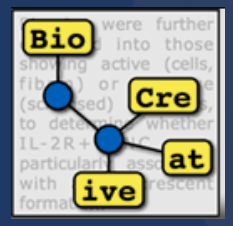
Government of Canada / Gouvernement du Canada

Software Tools & Contractors

ToxStrategies
Innovative Solutions / Sound Science

BATTELLE

BioPortal



CGI

SciOme

Evidence Partners

Evidence Prime

ICF

ILS
Advancing Science, Improving Lives

IIA
Information International Associates

RTI INTERNATIONAL

Johns Hopkins University

Lancaster University

Application of Systematic Evidence Map Methods to Characterize Available Evidence for PFAS

Laura Carlson

US EPA/ORD/CPHEA/HEEAD

HERA BOSC

February 4, 2021

The views and opinions expressed here do not reflect official US Environmental Protection Agency policy.

Acknowledgements

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[1]Center for Public Health and Environmental Assessment, Chemical & Pollutant Assessment Division (CPAD)

[2]Center for Public Health and Environmental Assessment, Health & Environmental Effects Assessment Division (HEEAD)

[3]Center for Computational Toxicology and Exposure (CCTE)

[4]ICF, VA, USA

Systematic Evidence Maps (SEM)

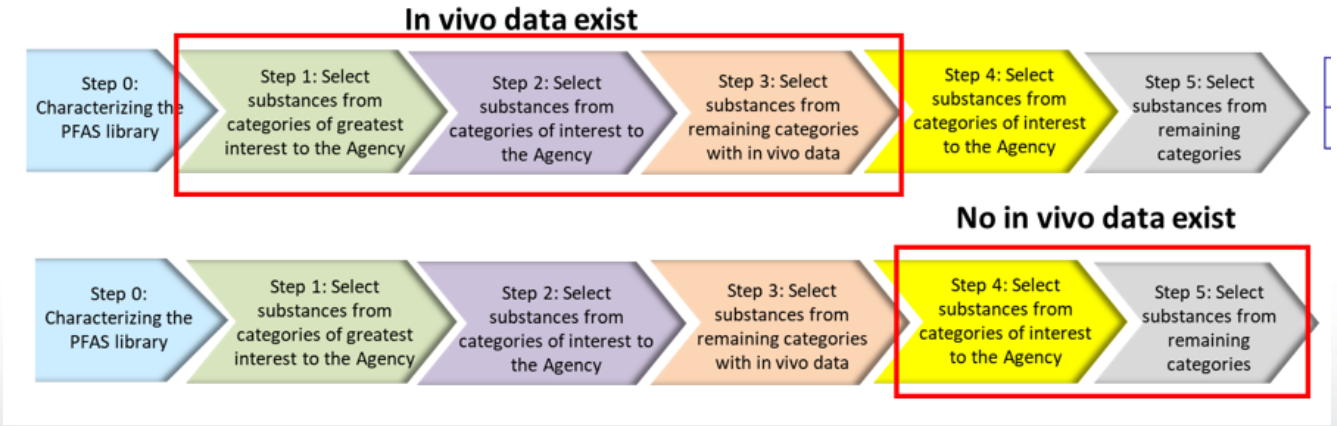
- Pre-decisional analysis that uses systematic review methods to compile and summarize evidence but does not reach assessment hazard or toxicity value conclusions
  - Front end compilation of evidence
  - Publishable in journals
- Used for:
  - Prioritization
  - Problem formulation and scoping
  - Identifying data gaps
  - Need for assessment update?
- EPA IRIS Program began creating SEMs in 2019, now becoming a routine analysis for HERA products such as IRIS, PPRTV, and other fit for purpose assessment products

Systematic Evidence Maps (SEM)

- Rapid preparation – weeks to a few months in most cases with experienced teams and use of specialized software
- Tailored to meet decision making needs
  - Include summarization of study designs and results, can also include study evaluation, identification of studies to possibly consider for dose response analysis
- Use of standardized template format reduces time to prepare and review
- Highly visual with interactive displays
- Structured data entry that is made available to the public
  - Enhances transparency and re-use across assessment groups, including by other Federal and State programs
- Results can be disseminated in reports, interactive data interfaces, and EPA Comp Tox Chemicals Dashboard (https://comptox.epa.gov/dashboard)

Per- and Polyfluoroalkyl Substances (PFAS) 150 SEM

- One component of the EPA PFAS Action Plan involves the use of new approach methods to help fill information gaps. This ongoing work involves tiered toxicity testing of a structurally diverse landscape of PFAS using a suite of in vitro toxicity and toxicokinetic assays
- One goal is to use existing in vivo toxicity data to infer (read-across) missing information for a similar PFAS target (similarity starting point is "structural similarity")
- PFAS "150" SEM conducted to help identify in vivo data



Status

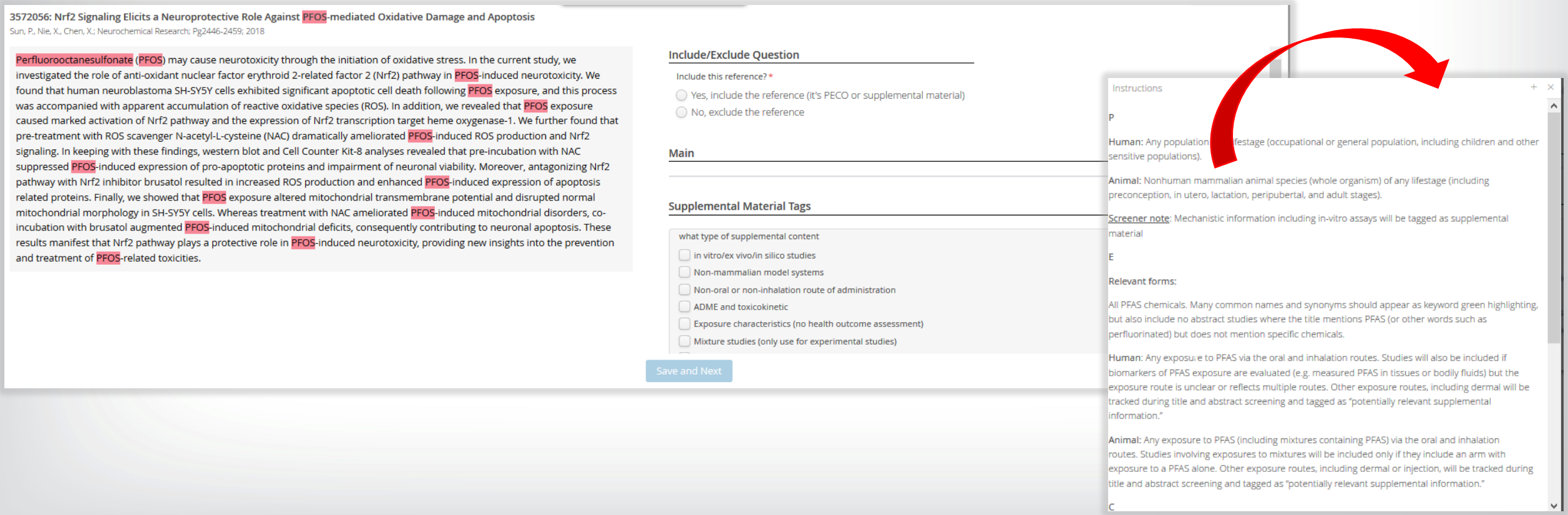
- PFAS 150 Systematic Evidence Map (SEM)
  - Started September 2019; Public report in FY2021
- Experience with 150 PFAS was encouraging, so we are expanding the work to include:
  - Characterization of an additional 430 PFAS (2021)
  - Expanded list of ~9,000 PFAS substances and structures (2022)
- Not included are PFAS under assessment by EPA
  - PFBS, GenX chemicals, PFOS, PFOA, PFBA, PFHxA, PFHxS, PFNA, PFDA

Methods

- Use information from the EPA CompTox Chemicals Dashboard to create higher throughput methods to search for hundreds of chemicals at a time (new semi-automated processes)
- Search journal databases (PubMed, WoS, Toxline (pre-2019)) and grey literature from Chemicals Dashboard ToxVal database and manual searches of ECHA for additional studies
- Create interactive literature inventories to show landscape of studies
- Conduct full data extraction and study evaluation on animal toxicology studies of repeat dose, developmental or reproductive design
- Publish report and make animal toxicity information accessible via EPA PFAS Dashboard
- A related analysis is focusing on the epidemiological data (journal article)

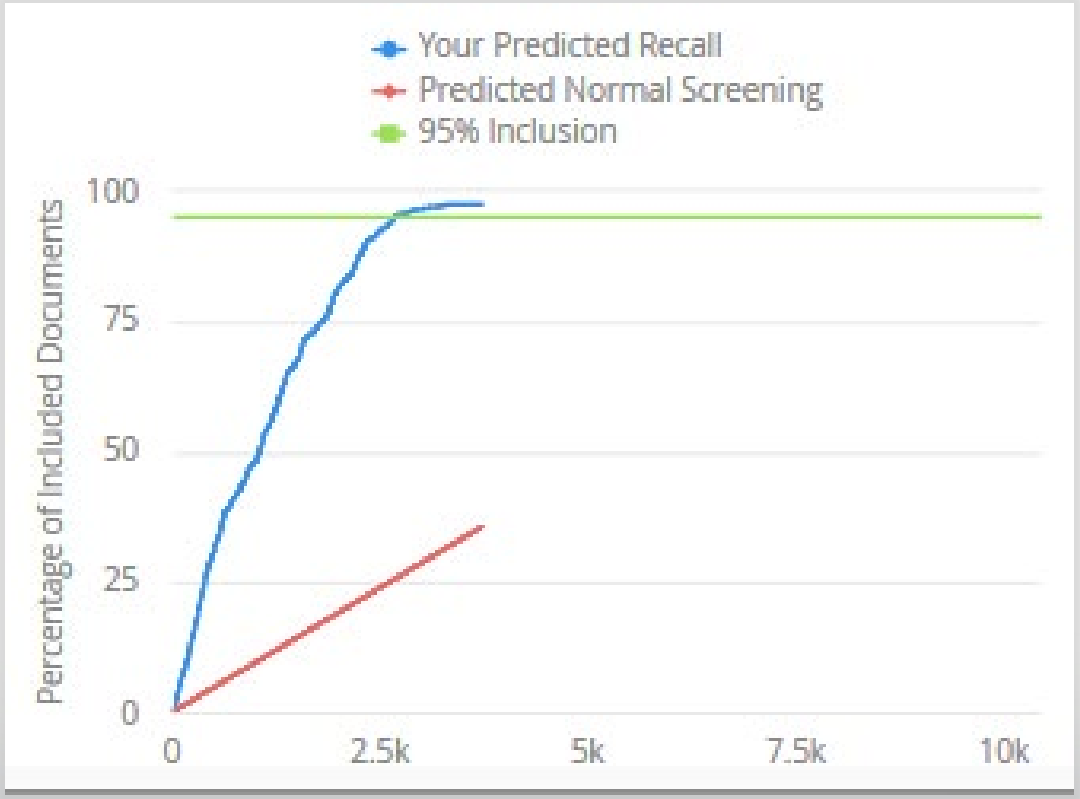
Use of Machine-Learning to Screen at Title and Abstract Level

- **Used SWIFT Active (about 5-10 seconds per title/abstract)**
- **Machine-learning can decrease the screening burden by 40-60%**



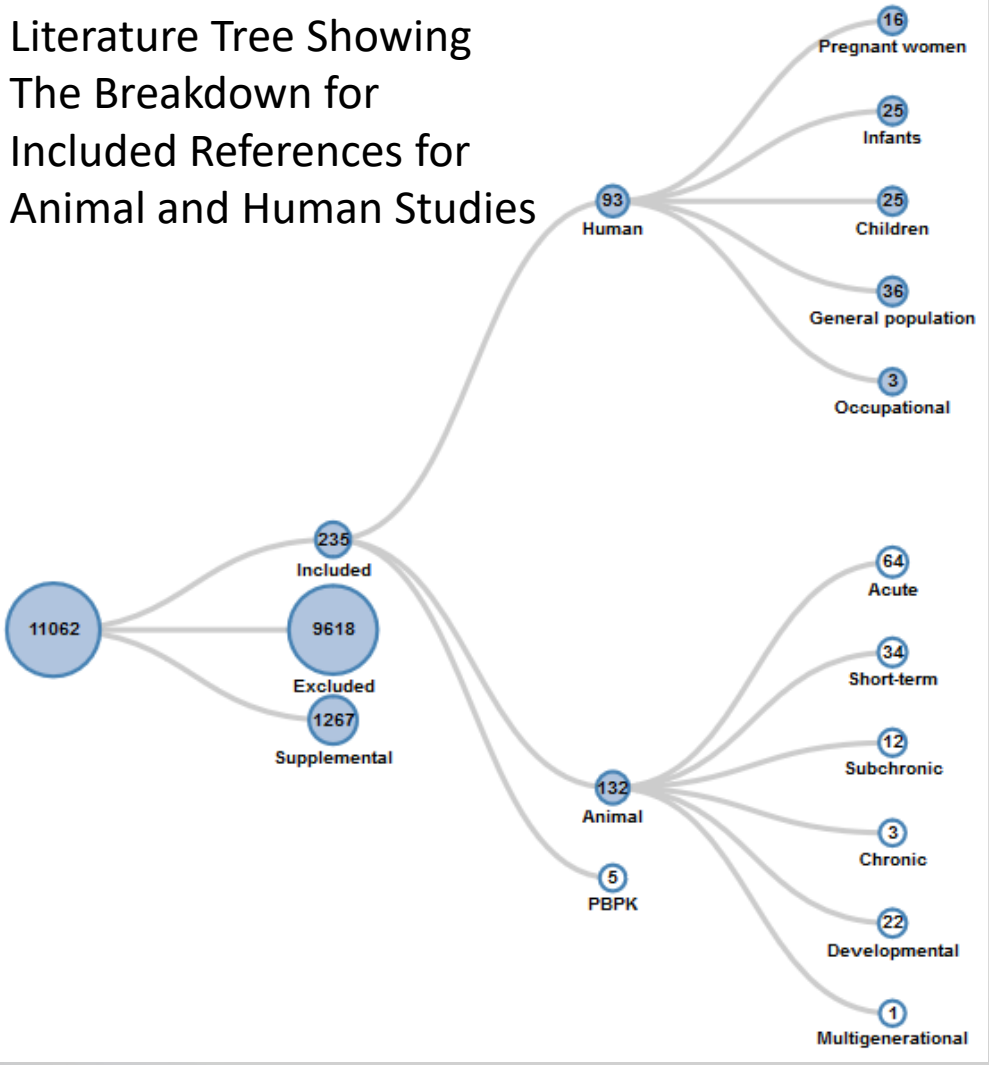
Use of Machine-Learning to Screen

	Successfully Screened					
Level	Included	Excluded	Partially Screened	Conflicted	Not Screened	Total
Level 1 - Title & Abstract	1088	2637	0	0	6733	10458

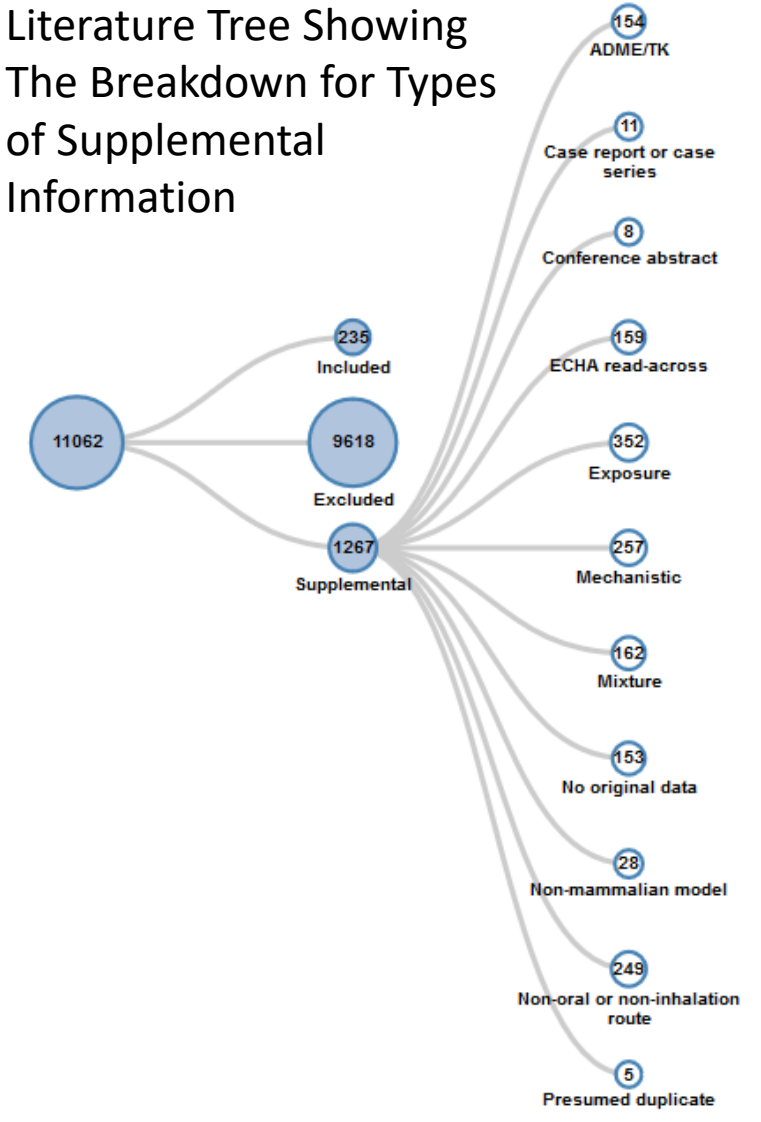


PFAS 150 SEM Screening Results

Literature Tree Showing The Breakdown for Included References for Animal and Human Studies

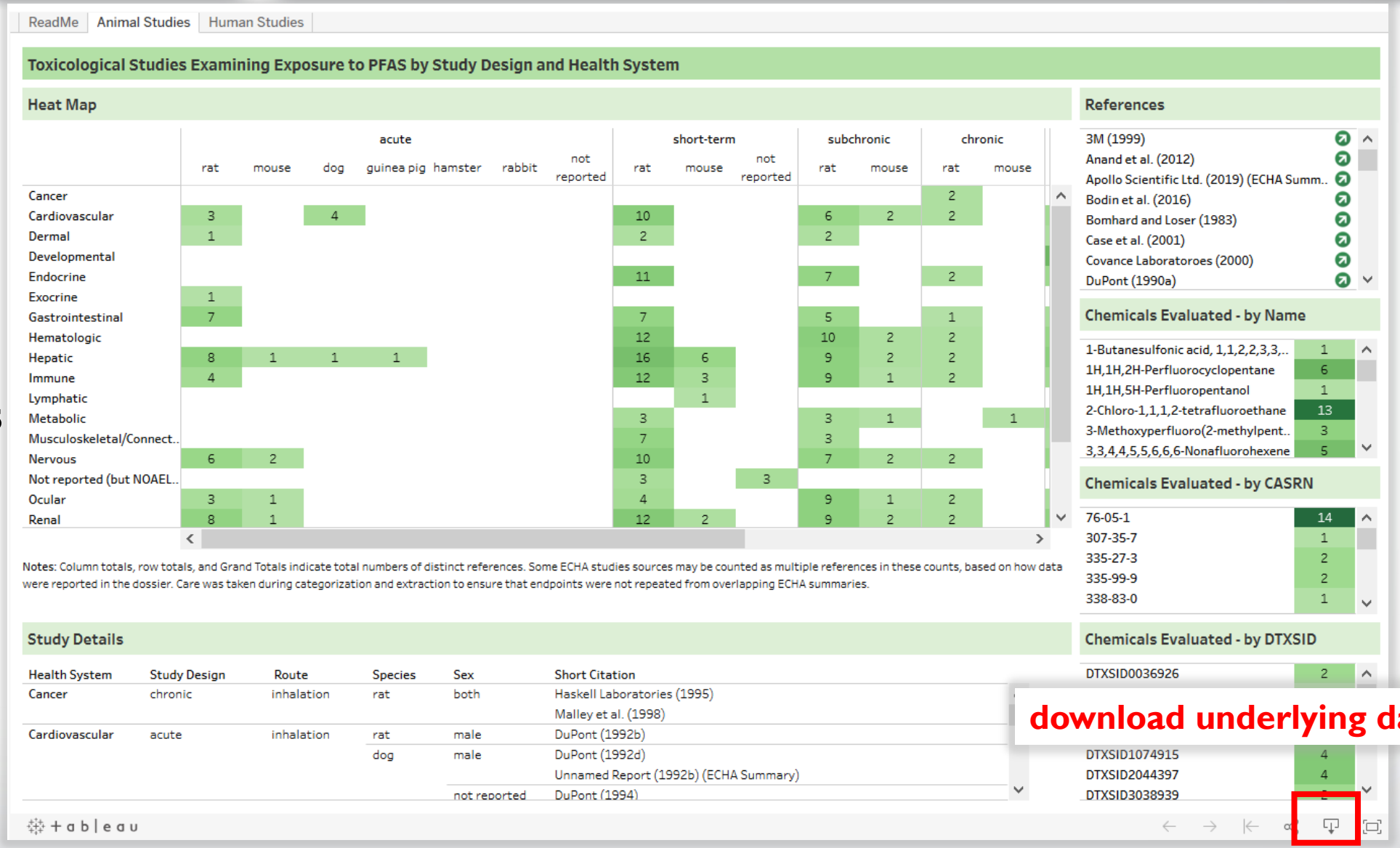


Literature Tree Showing The Breakdown for Types of Supplemental Information



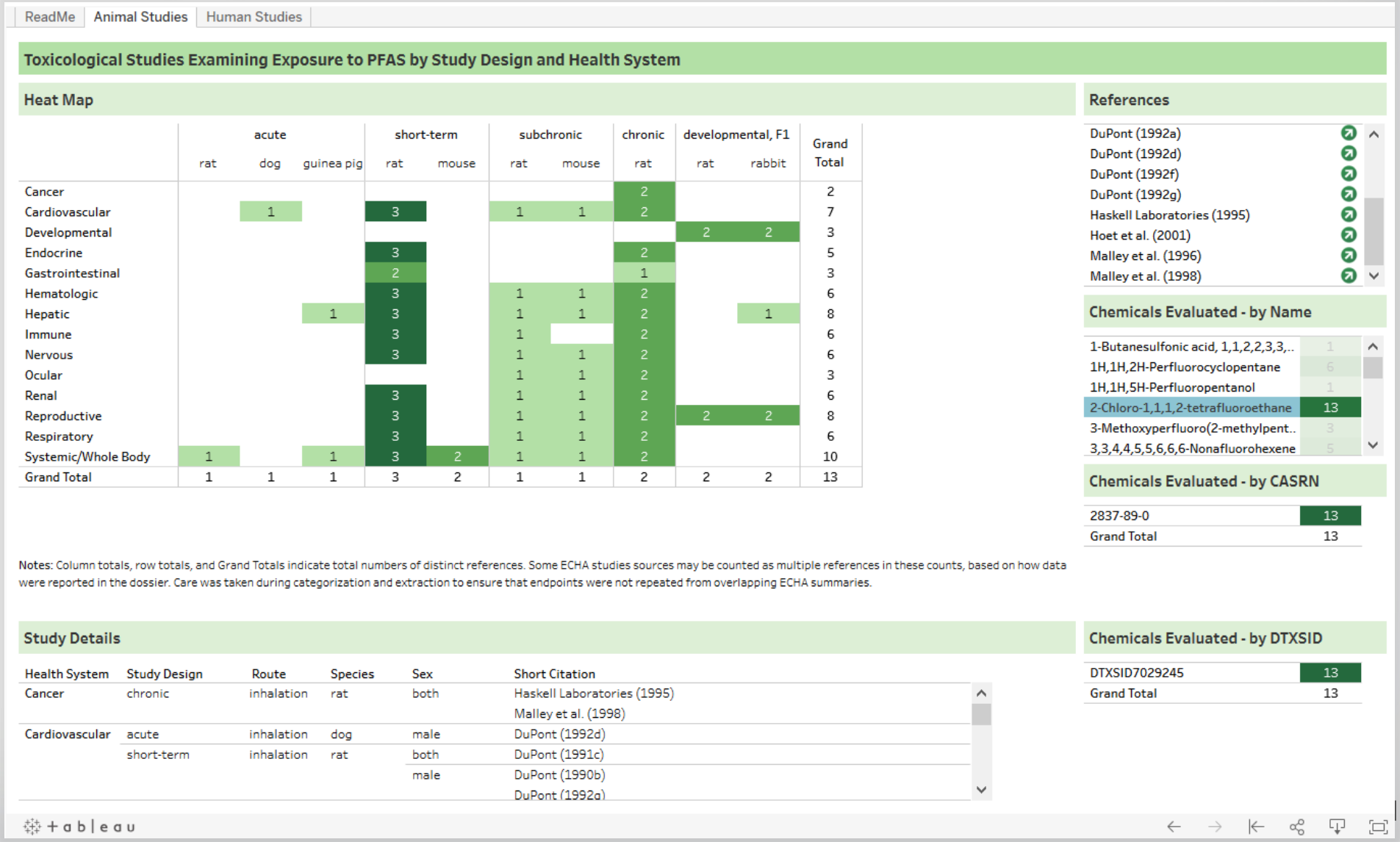
PFAS 150 SEM Literature Inventory: Animal Studies

- ~35 PFAS
- ~130 studies



PFAS 150 SEM Literature Inventory: Interactive Features

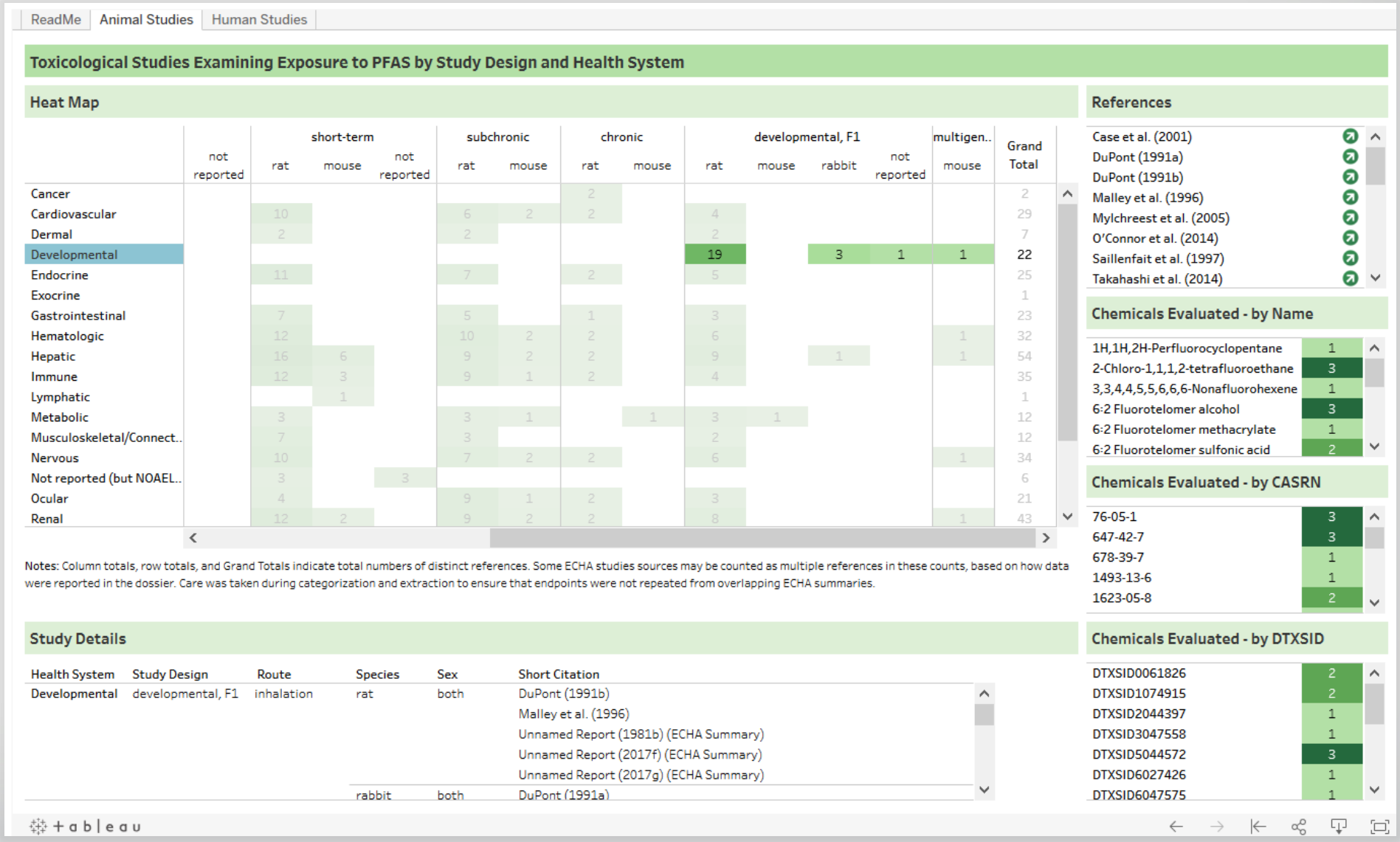
Explore by PFAS



	acute			short-term		subchronic		chronic	developmental, F1		Grand Total
	rat	dog	guinea pig	rat	mouse	rat	mouse	rat	rat	rabbit	
Cancer								2			2
Cardiovascular		1		3		1	1	2			7
Developmental									2	2	3
Endocrine				3				2			5
Gastrointestinal				2				1			3
Hematologic				3		1	1	2			6
Hepatic			1	3		1	1	2		1	8
Immune				3		1		2			6
Nervous				3		1	1	2			6
Ocular						1	1	2			3
Renal				3		1	1	2			6
Reproductive				3		1	1	2	2	2	8
Respiratory				3		1	1	2			6
Systemic/Whole Body	1		1	3	2	1	1	2			10
Grand Total	1	1	1	3	2	1	1	2	2	2	13

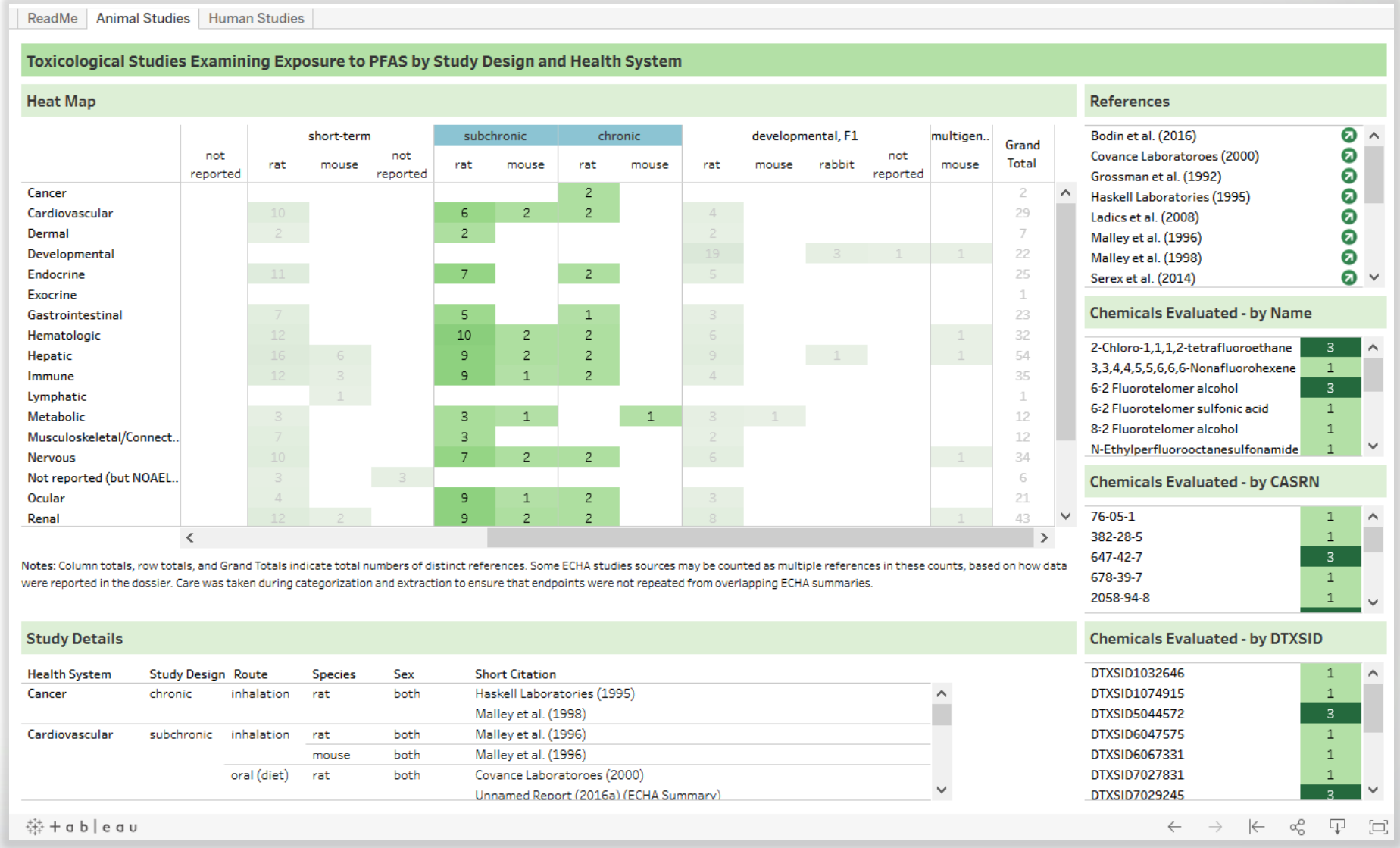
PFAS 150 SEM Literature Inventory: Interactive Features

Explore by health category



PFAS 150 SEM Literature Inventory: Interactive Features

Explore by study design

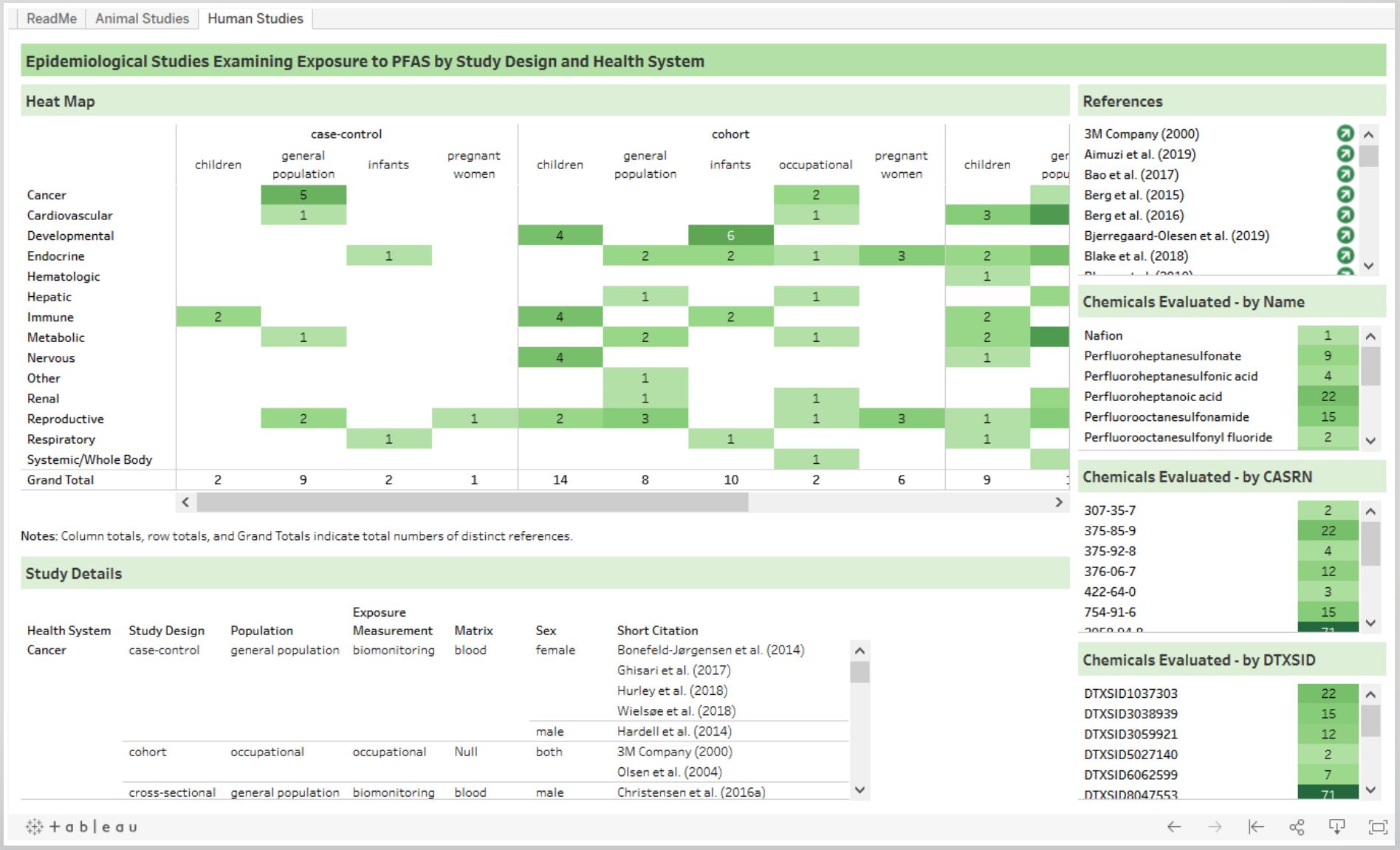


	not reported	short-term rat	short-term mouse	short-term not reported	subchronic rat	subchronic mouse	chronic rat	chronic mouse	developmental, F1 rat	developmental, F1 mouse	developmental, F1 rabbit	developmental, F1 not reported	multigen.. mouse	Grand Total
Cancer							2							2
Cardiovascular		10			6	2	2		4					29
Dermal		2			2				2					7
Developmental									19		3	1	1	22
Endocrine		11			7		2		5					25
Exocrine														1
Gastrointestinal		7			5		1		3					23
Hematologic		12			10	2	2		6				1	32
Hepatic		16	6		9	2	2		9		1		1	54
Immune		12	3		9	1	2		4					35
Lymphatic			1											1
Metabolic		3			3	1		1	3	1				12
Musculoskeletal/Connect..		7			3				2					12
Nervous		10			7	2	2		6				1	34
Not reported (but NOAEL..		3		3										6
Ocular		4			9	1	2		3					21
Renal		12	2		9	2	2		8				1	43

Health System	Study Design	Route	Species	Sex	Short Citation
Cancer	chronic	inhalation	rat	both	Haskell Laboratories (1995)
					Malley et al. (1998)
Cardiovascular	subchronic	inhalation	rat	both	Malley et al. (1996)
			mouse	both	Malley et al. (1996)
		oral (diet)	rat	both	Covance Laboratoroes (2000)
					Unnamed Report (2016a) (ECHA Summary)

PFAS 150 SEM Literature Inventory: Epidemiology Studies

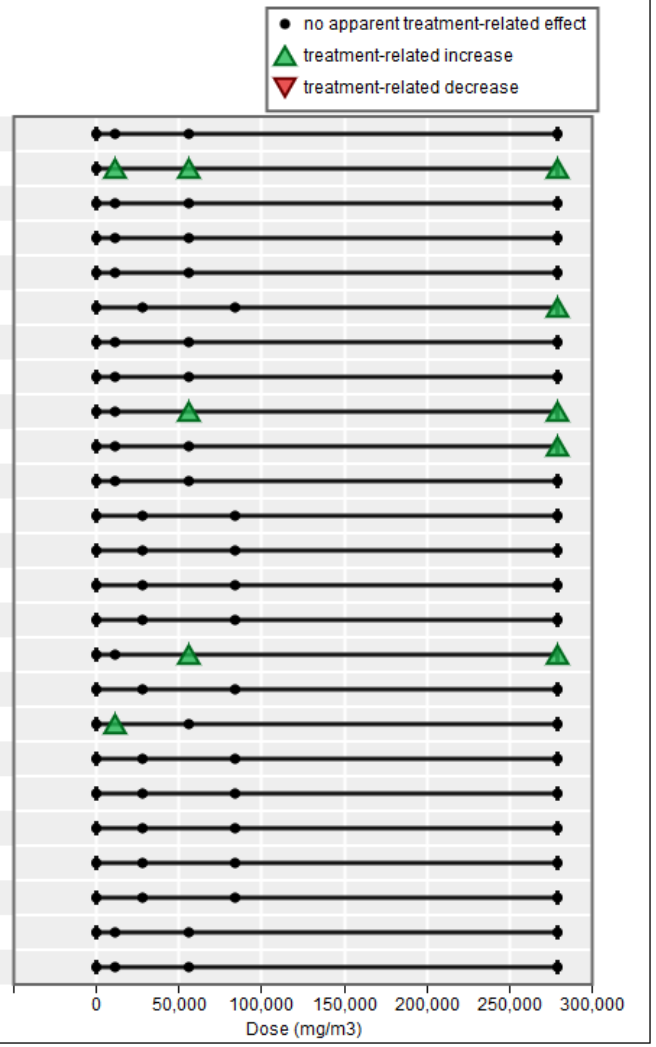
- ~10 PFAS
- ~95 studies



Example HAWC Data Extraction

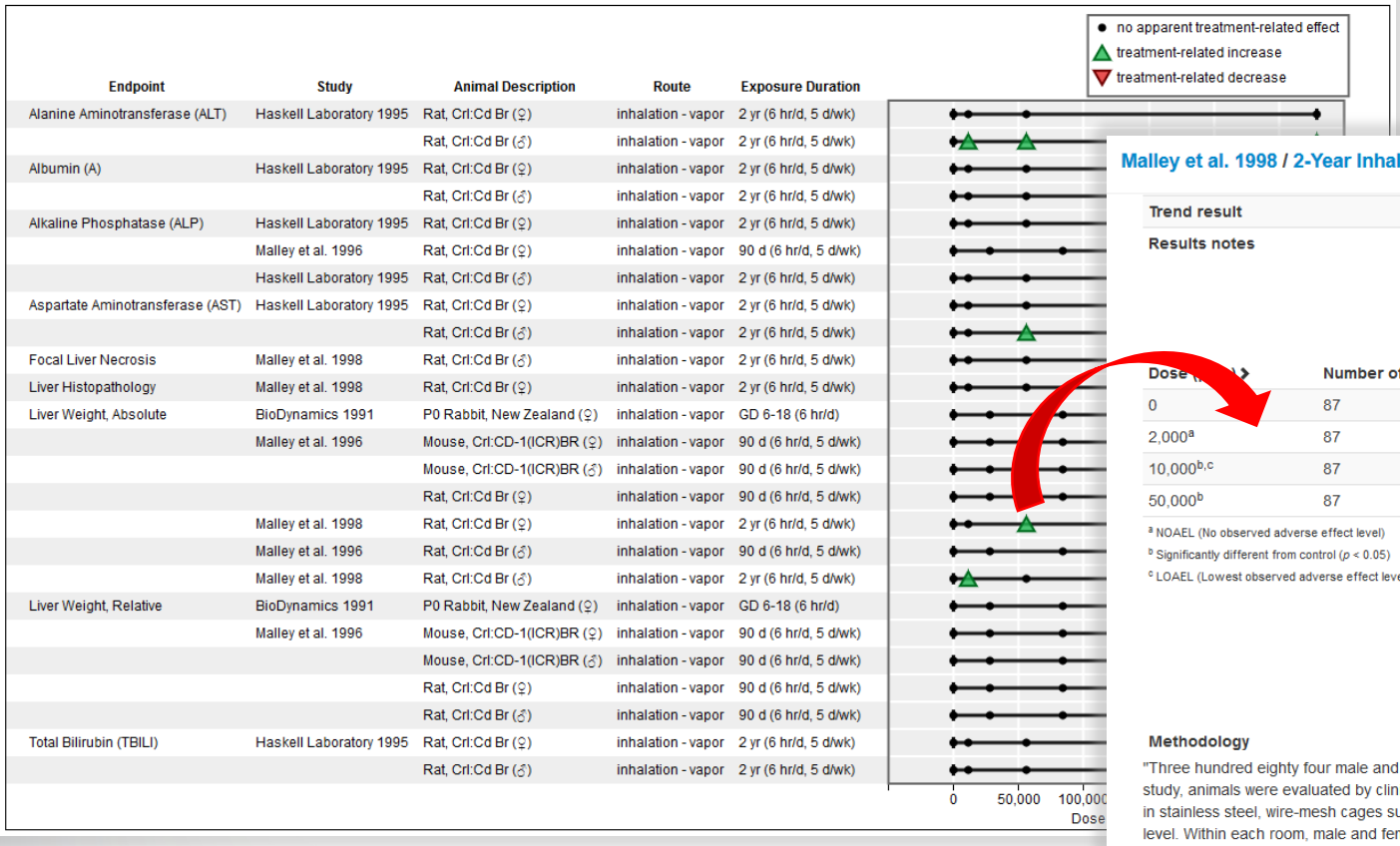
Figure 33. 2-Chloro-1,1,1,2-tetrafluoroethane and Hepatic Effects

Endpoint	Study	Animal Description	Route	Exposure Duration
Alanine Aminotransferase (ALT)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Albumin (A)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Alkaline Phosphatase (ALP)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
	Malley et al. 1996	Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
	Haskell Laboratory 1995	Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Aspartate Aminotransferase (AST)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Focal Liver Necrosis	Malley et al. 1998	Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Liver Histopathology	Malley et al. 1998	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Liver Weight, Absolute	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Mouse, Crl:CD-1(ICR)BR (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
	Malley et al. 1998	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
	Malley et al. 1996	Rat, Crl:Cd Br (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
	Malley et al. 1998	Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Liver Weight, Relative	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Mouse, Crl:CD-1(ICR)BR (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
Total Bilirubin (TBILI)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)



Example HAWC Data Extraction

Figure 33. 2-Chloro-1,1,1,2-tetrafluoroethane and Hepatic Effects



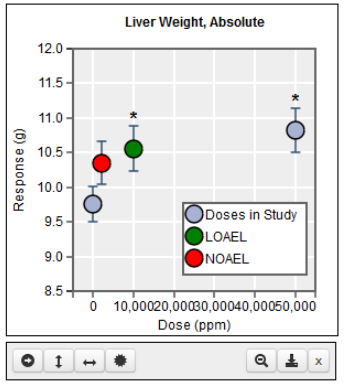
Endpoint	Study	Animal Description	Route	Exposure Duration
Alanine Aminotransferase (ALT)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Albumin (A)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Alkaline Phosphatase (ALP)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
	Malley et al. 1996	Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
	Haskell Laboratory 1995	Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Aspartate Aminotransferase (AST)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Focal Liver Necrosis	Malley et al. 1998	Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Liver Histopathology	Malley et al. 1998	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Liver Weight, Absolute	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Mouse, Crl:CD-1(ICR)BR (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
	Malley et al. 1998	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
	Malley et al. 1996	Rat, Crl:Cd Br (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
	Malley et al. 1998	Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
Liver Weight, Relative	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Mouse, Crl:CD-1(ICR)BR (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)
Total Bilirubin (TBILI)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)

Malley et al. 1998 / 2-Year Inhalation Study in Rats / Female Crl:CD BR Rat / Liver Weight, Absolute

Trend result	not reported
Results notes	"There were no compound-related effects on mean absolute or mean relative organ weight in males or females at the one-year interim sacrifice or at the 24-month terminal sacrifice for any exposure concentration (Table II). Some statistically significant organ weight changes were observed, but these are most likely attributable to higher mean final body weights in test rats. "

Dose ( )	Number of Animals	Response (g)	Standard Deviation
0	87	9.758	1.17
2,000[a]	87	10.35	1.46
10,000[b,c]	87	10.56	1.55
50,000[b]	87	10.82	1.47

[a] NOAEL (No observed adverse effect level)
[b] Significantly different from control ($p < 0.05$)
[c] LOAEL (Lowest observed adverse effect level)



Methodology

"Three hundred eighty four male and 384 female weanling Crl:CD BR rats were received from Charles River Laboratories, Inc., Portage, Michigan. Prior to being used in the study, animals were evaluated by clinical observations and body weight determinations during a 3-week quarantine period. Rats were housed three per cage, genders separate, in stainless steel, wire-mesh cages suspended above cage boards. Rats were housed in four laminar flow animal rooms with males and females housed together by exposure level. Within each room, male and female rats were housed on separate cage racks. A system of rotation was employed to relocate cage racks within the animal room each week and to reposition the cages on the rack every two weeks. Animal rooms were targeted at a temperature of 23+/- 2°C and a relative humidity of 55 +/-15%. Animal rooms were artificially illuminated (fluorescent light) on a 12-hour light/dark cycle. Throughout the test period, except during exposure, each cage of females and each cage of males were supplied with a feeder filled daily with approximately 50 or 70g of irradiated Purina Rodent Chow #5056 (chunk), respectively. In case of premature death or scheduled sacrifice, the amount of chow was adjusted according to the number of animals remaining in a cage. Rats were allowed free access to the food and to tap water except during

Close

Facilitate Dose-Response Analysis with BMDS Online

Malley et al. 1998 / 2-Year Inhalation Study in Rats / Female Crl:CD BR Rat / Liver Weight, Absolute

Trend result	not reported
Results notes	"There were no compound-related effects on mean absolute or mean relative organ weight in males or females at the one-year interim sacrifice or at the 24-month terminal sacrifice for an… significant organ weight changes were observed, but these are most… in test rats. "

Dose (ppm)	Number of Animals	Response (g)	Standard Deviation
0	87	9.758	1.17
2,000[a]	87	10.35	1.46
10,000[b,c]	87	10.56	1.55
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[a] NOAEL (No observed adverse effect level)
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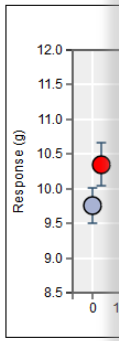

Methodology

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HAWC

Contact About Public Assessments Your HA…

Home / PFAS 150 (2020) / Malley et al. 1998 / 2-Year Inhalation Study in Rats / Female Crl:CD BR Rat / Liver Weight, Absolute /

SELECTED ASSESSMENT
PFAS 150 (2020)

AVAILABLE MODULES
- Literature review
- Management dashboard
- Study list
- Study evaluation
- Endpoint list
- Visualizations
- Executive summary

DOWNLOADS
- Download datasets

Liver Weight, Absolute

Actions

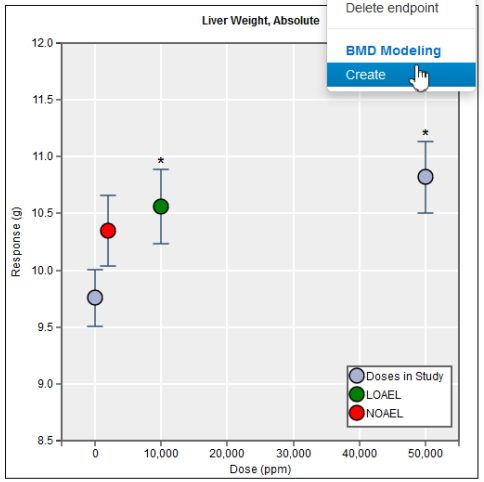
Endpoint Editing
Update endpoint
Delete endpoint

BMD Modeling
Create

Endpoint Details

Endpoint name	Liver Weight, Absolute
System	Hepatic
Organ	Liver
Effect	Organ Weight
Effect subtype	Absolute
Diagnostic description	Female absolute liver weight
Observation time	24 mo
Data reported?	✔
Data extracted?	✔
Values estimated?	–
Location in literature	Table 2
Expected response adversity direction	increase from reference/control group
NOAEL	2,000 ppm
LOAEL	10,000 ppm
Monotonicity	--
Statistical test description	Dunnett's test
Trend result	not reported
Results notes	"There were no compound-related effects on mean absolute or mean relative organ weight in males or females at the one-year interim sacrifice or at the 24-month terminal sacrifice for any exposure concentration (Table II). Some

Plot



Methodology

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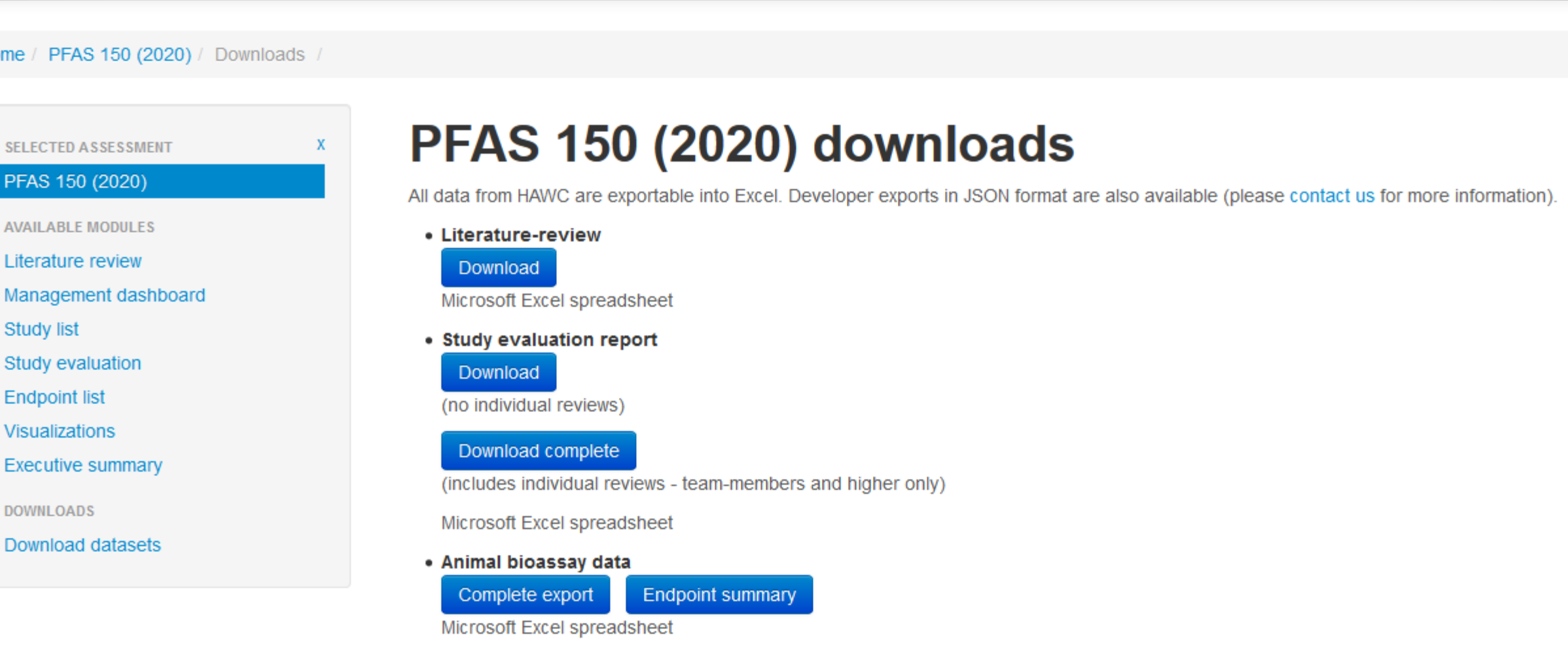
Download Data Sets



Preliminary Results: PFAS 430

Toxicological Studies Examining Exposure to PFAS by Study Design and Health System

Heat Map

	acute					short-term			subchro..	chronic	developmental, F1		multige..	not repo..	Grand Total
	rat	mouse	pig	dog	not reported	rat	mouse	not reported	rat	rat	rat	not reported	not reported	not reported	
Cardiovascular	5		1	6		22	1		4	2	6				46
Dermal	6	1				7			1						15
Developmental											19				19
Reproductive	5					22			6	2	19		1		52
Endocrine	2					18			5		7				31
Gastrointestinal	5	2				12			4		3				25
Hematologic						20			8		3				30
Hepatic	5					30	1		6	1	5				46
Immune	6	1				22	1		5		4				38
Lymphatic						9			2		1				12
Metabolic						7			3	1					10
Musculoskeletal/Connect..						9			4		1				13
Nervous	17			2	1	18		1	11		8				54
Ocular	6	1				8			6						21
Renal	5					25			8	2	7				44
Respiratory	17	3	1			17			3		8				49
Sensory	1	1													2
Systemic/Whole Body	42	4	1	4	7	37	1		9	2	16				116
Not reported (but NOAEL	18	2			3	13		3	3		8	1			49

Notes: Column totals, row totals, and Grand Totals indicate total numbers of distinct references. Some ECHA studies sources may be counted as multiple references in these counts, based on how data were reported in the dossier. Care was taken during categorization and extraction to ensure that endpoints were not repeated from overlapping ECHA summaries.

Study Details

Health System	Study Design	Route	Species	Sex	Short Citation
Cardiovascular	acute	inhalation	rat	both	Eastman Kodak (1992)
					Unnamed Report, 2019 (ECHA Summary)b
				male	E.I. duPont de Nemours and Co. (1992)
			pig	not reported	Steffey et al. (1998)
			dog	male	Dodd and Vinegar (1998)

References

- Blake et al. (1970)
- Brock et al. (1995)
- Chambers et al. (1950)
- Chen et al. (2018)b
- Ding et al. (2009)
- Dodd and Vinegar (1998)
- Dupont (1992)a
- Dupont (1992)b

Chemicals Evaluated - by Name

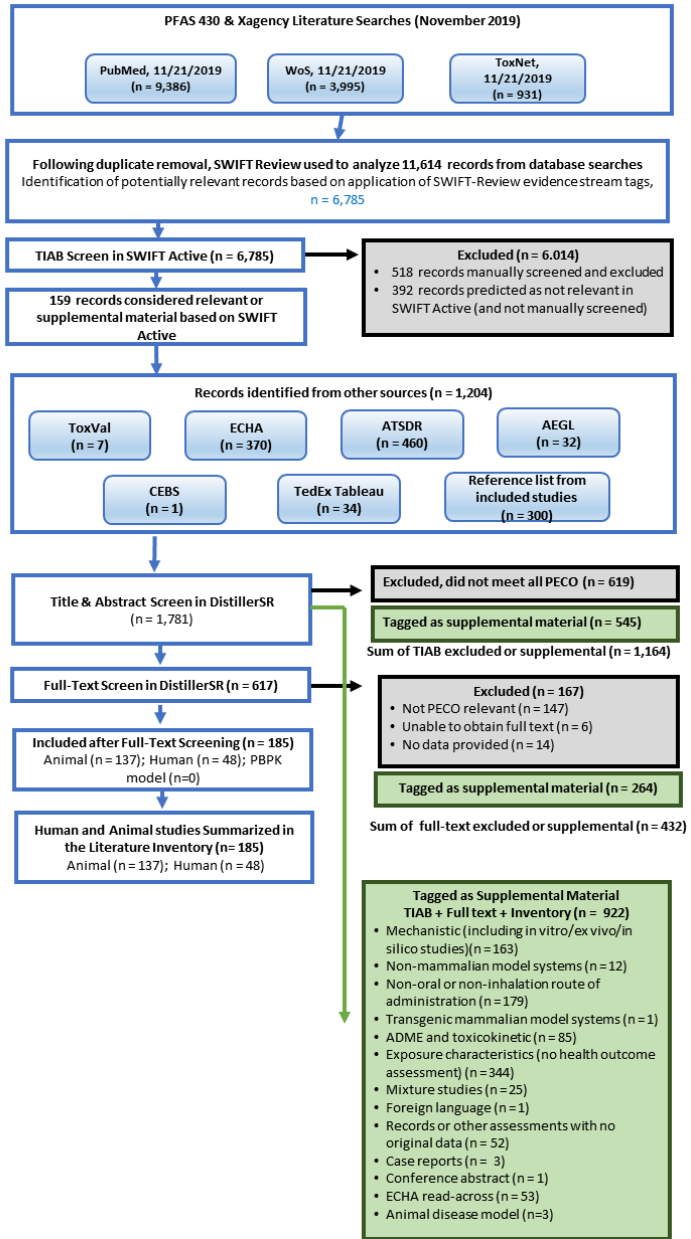
1-(Perfluorohexyl)ethane	3
1-(Perfluorohexyl)octane	1
1,6-Diiodoperfluorohexane	6
1,6-Divinylperfluorohexane	2
1H-Perfluorohexane	6
1H,1H,5H-Perfluoropentyl methacr..	4

Chemicals Evaluated - by CASRN

307-55-1	10
335-36-4	1
355-02-2	3
355-20-4	2
355-37-3	6
355-93-1	4

Chemicals Evaluated - by DTXSID

DTXSID1022134	11
DTXSID1061073	2
DTXSID1073365	3
DTXSID3032620	2
DTXSID4059966	6
DTXSID4066389	2



Preliminary Results: PFAS 430

Toxicological Studies Examining Exposure to PFAS by Study Design and Health System

Heat Map

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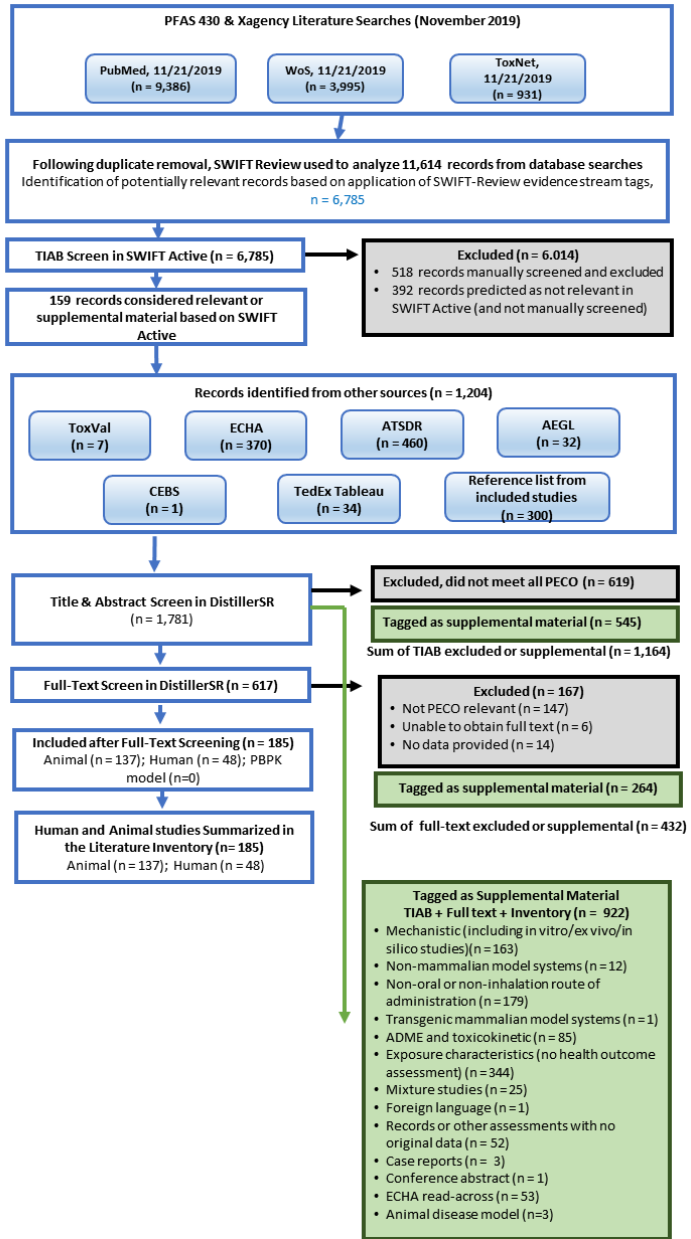
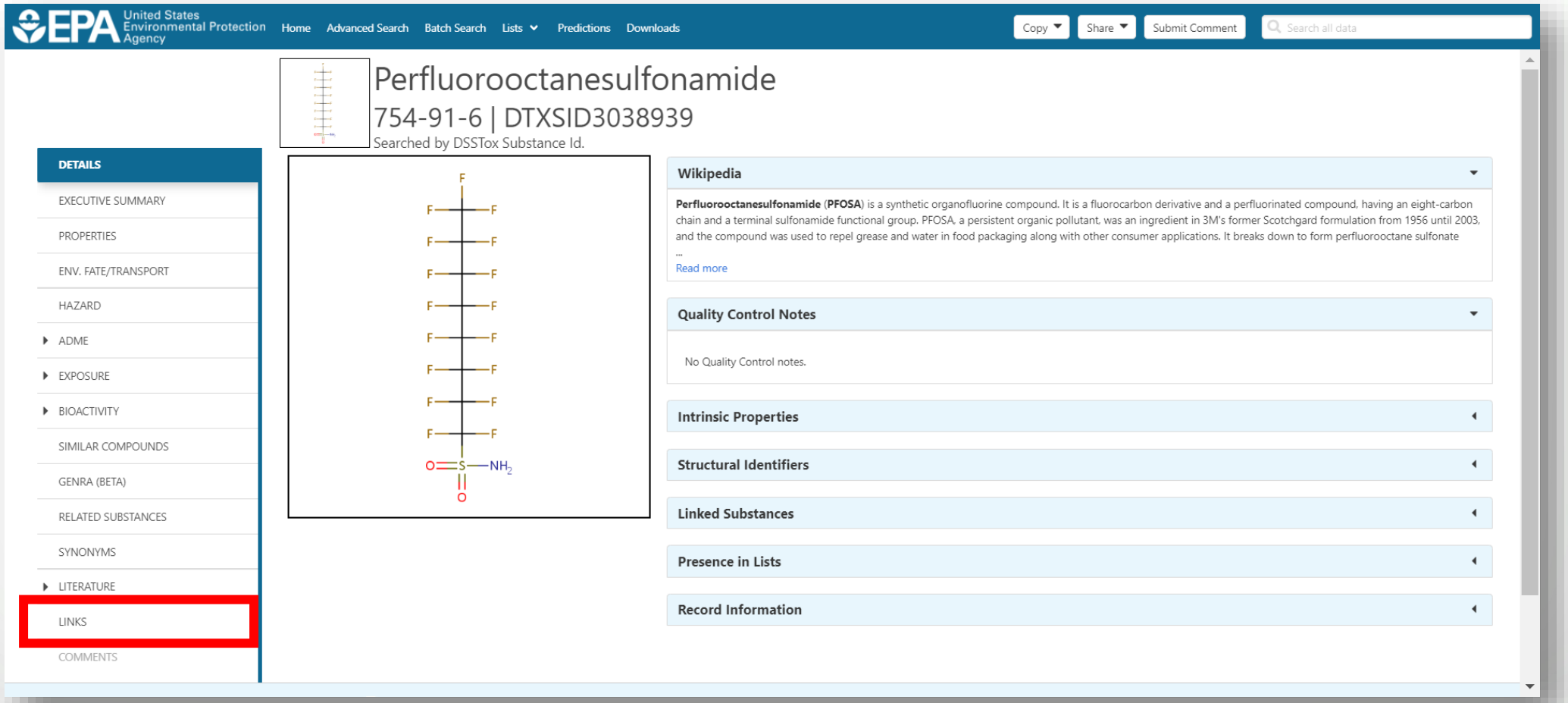


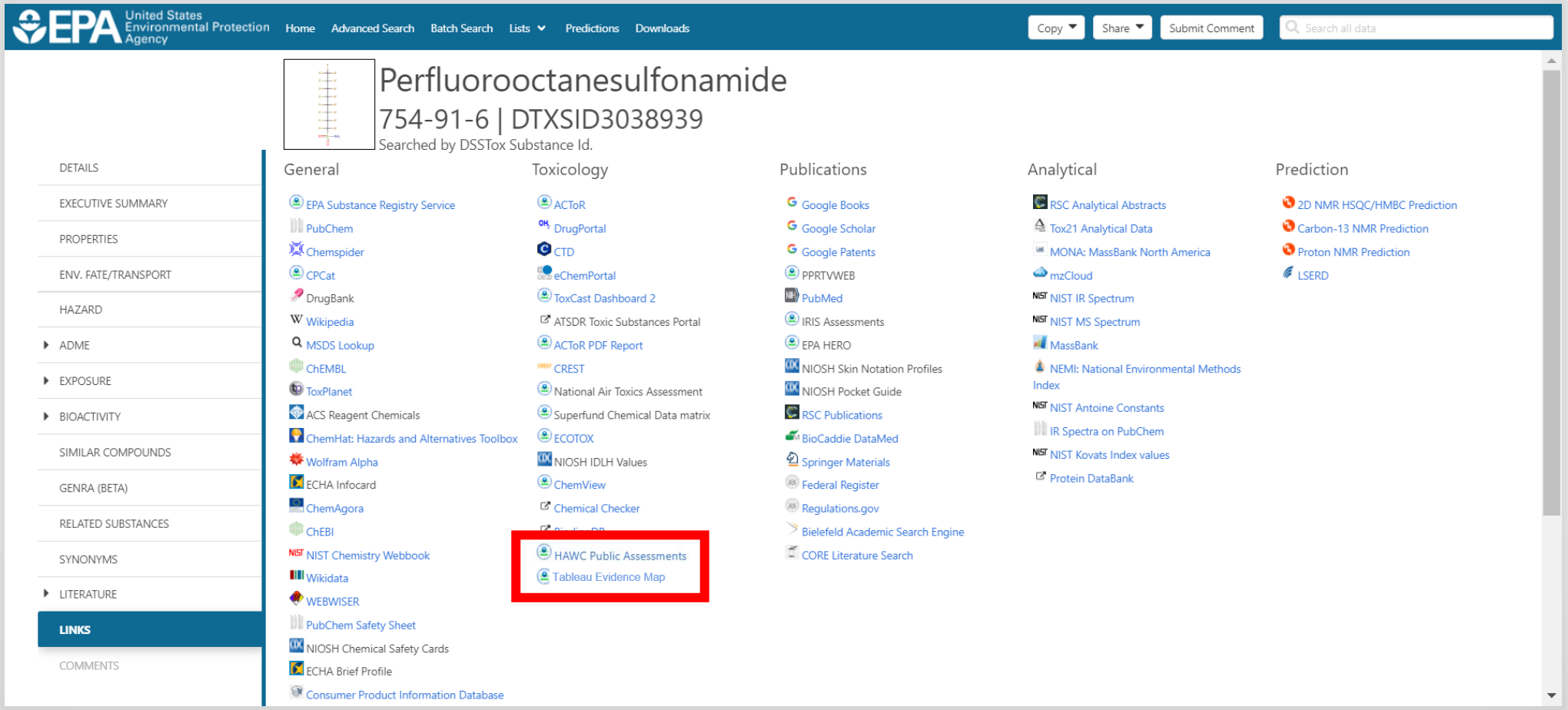
Linking SEMs to the EPA CompTox Chemicals Dashboard

Office of Research and Development
Center for Public Health and Environmental Assessment

Chemicals Dashboard – Links Tab



External Links



Questions?