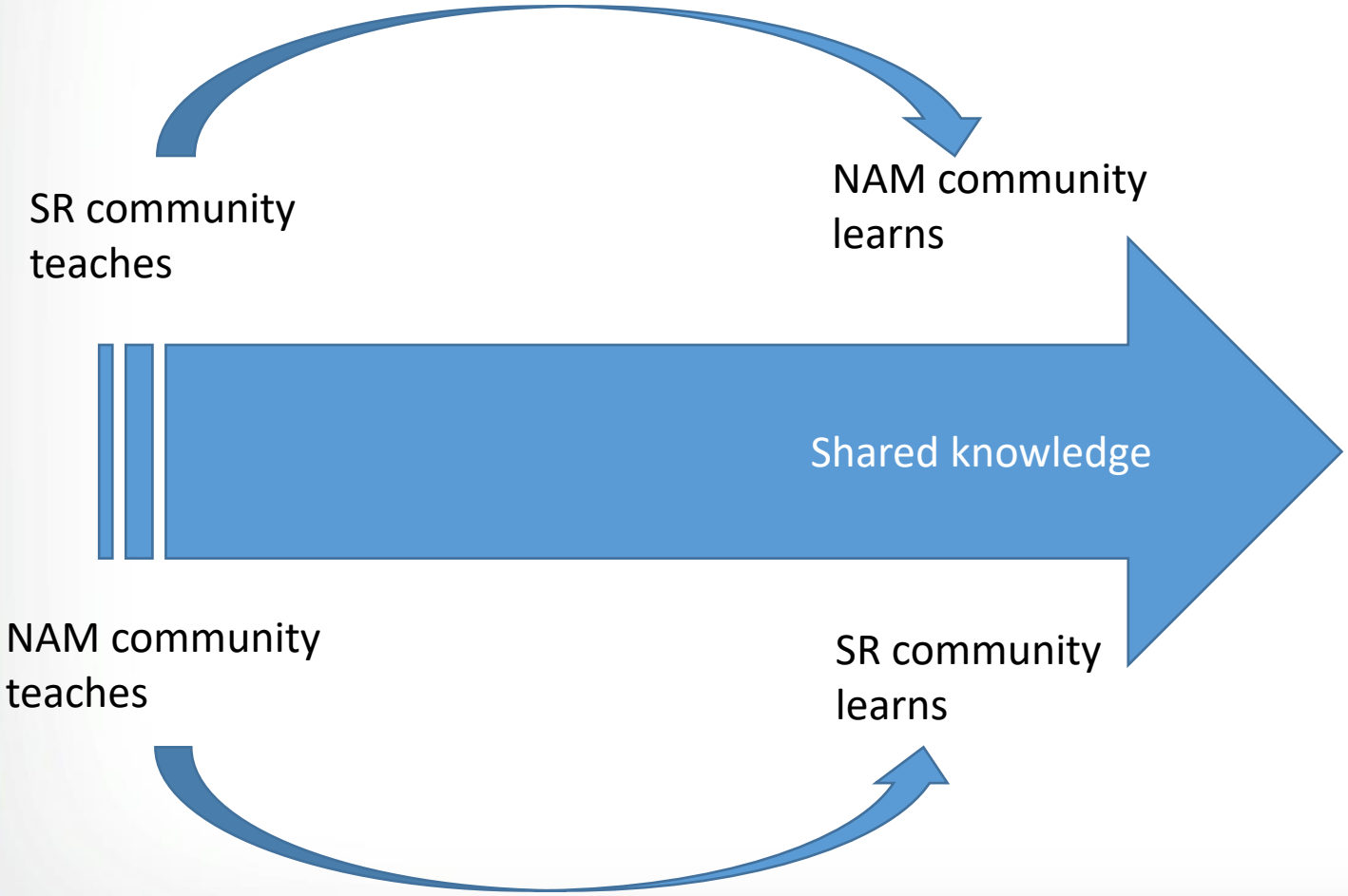
Introduction to Systematic Review in the Context of Environmental Health Assessments

EPA NAM and SR CoPs

May 27, 2021

NAMs & SR



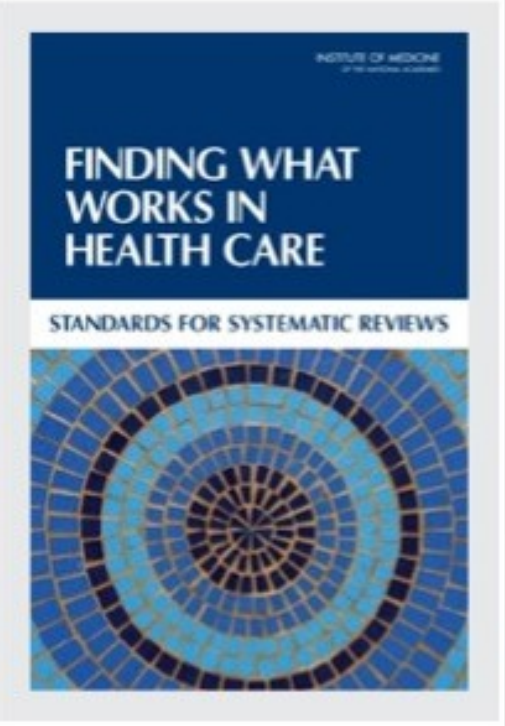
- Webinars (spring/summer 2021)
- Informational sessions

Systematic Review

A structured and documented process for transparent literature review

"… systematic review is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. The goal of systematic review methods is to ensure that the review is complete, unbiased, reproducible, and transparent."

IOM (Institute of Medicine). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/13059/finding-what-works-in-health-care-standards-for-systematic-reviews



Why Systematic Review?

- Enhances **transparency** and **minimizes bias**
- Issues with narrative reviews:
  - Unclear approach to choice of studies
  - No consistent evaluation of study quality
  - No clear framework for synthesizing and integrating evidence
  - Difficult to reproduce
- State of the science: becoming difficult to publish narrative reviews

ehp ENVIRONMENTAL HEALTH PERSPECTIVES

"Reviews must utilize systematic review methodologies…EHP does not publish narrative reviews…"

Reviews

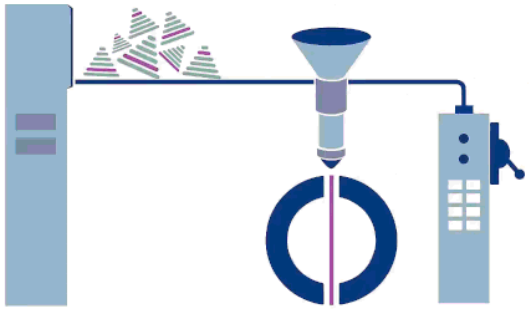
Reviews present, contrast, and (when appr[illegible] studies to address a specific question or issue related to environmental health. Reviews must utilize systematic review methodologies to [illegible] relevant scientific literature, including clearly defined search strategies and study eligibility criteria as needed to capture the current state of knowledge in an unbiased and comprehensive manner. A variety of review formats may be considered by *EHP*, such as state-of-the-science reviews, scoping reviews, evidence maps, full systematic reviews, and meta-analyses. *EHP* does not publish narrative reviews or reviews based on meetings (meeting summaries or reports). Regardless of review type, authors should integrate and critically analyze information from previous research, identify information gaps so as to make recommendations for future research, and draw conclusions based on the stated purpose of the review.

Note: For full systematic reviews, authors are expected to conform to appropriate guidelines, such as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Suggested length is < 10,000 words, excluding the text in the abstract, references, tables, figure legends, acknowledgments, and Supplemental Material.

Systematic Review Origins

- Initially developed for evidence-based medicine (clinical trials)
  - **Cochrane:** a non-profit founded 1993 to conduct & share health intervention systematic reviews
- Growing importance in science and policy decisions in:
  - Public health
  - Social interventions
  - Economic evaluations
  - **Environmental science and toxicology**
    - Ecological impacts
    - Human health hazards
    - Exposure



http://www.cochranelibrary.com/

Campbell Collaboration
Better evidence for a better world

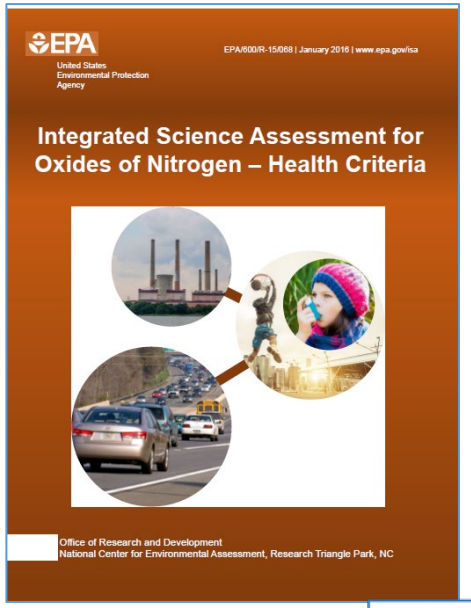
https://www.campbellcollaboration.org/library.html

Collaboration for Environmental Evidence

http://www.environmentalevidence.org/

Systematic Review (SR) at EPA

- EPA uses **"Fit-for-Purpose"** SRs: decision-making needs shape systematic review through scoping and problem formulation
- Examples of SR applications:
  1. Hazard/dose-response assessment
  2. Evidence mapping
  3. Identification of reference chemicals
  4. Meta-Analysis
  5. Ecological assessments



Endocrine Disruptor Screening Program (EDSP)

Prioritization

Chemical designated **High-Priority** for Risk Evaluation

Chemical designated **Low-Priority**

Risk Evaluation

EPA determination of **Unreasonable Risk**

EPA determination of **No Unreasonable Risk**

Risk Management

Impose Restrictions to **Eliminate the Unreasonable Risk**

SR 101 Webinar Agenda

Brandiese Beverly *NTP, Integrative Health Assessment Branch*	An overview of systematic review and evidence integration for environmental health
Kristina Thayer *EPA, Chemical Pollutant Assessment Division*	Rapid and Fit for Purpose Applications of Systematic Review Methods to Identify and Evaluate NAM Evidence
Michele Taylor *EPA, Chemical Pollutant Assessment Division*	Suite of Systematic Review Software Tools

Topics for future conversations

- Evidence appraisal
- Evidence integration

Acknowledgements

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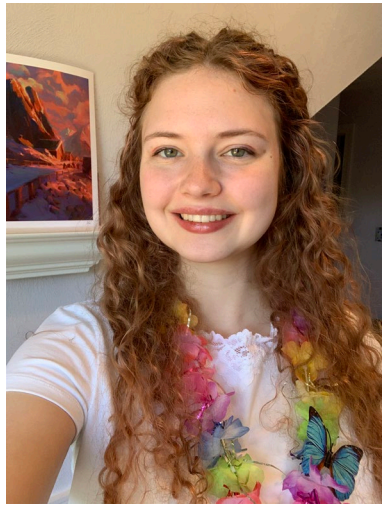
EPA/ORD/CPHEA



Grace Kaupas
EPA/ORD/CPHEA

Lucina Lizarraga
EPA/ORD/CPHEA

Kristan Markey
EPA/OCSPP/OPP

NTP
National Toxicology Program

An overview of systematic review and evidence integration for environmental health

Brandiese Beverly, PhD

Integrative Health Assessment Branch
Division of the National Toxicology Program
National Institute of Environmental Health Sciences

27 May 2021

Objectives of presentation

- Goals of SR and how they are applied to environmental health research.
- Major steps of the systematic review process and role of NAMs
- Highlight advantages, potential challenges, and key concepts

Integrative Health Assessment Branch (IHAB)

- IHAB (formally Office of Health Assessment and Translation – OHAT) serves as an environmental health resource for public and regulatory agencies
- Conduct literature-based evaluations to assess the evidence that environmental substances cause adverse health effects
  - Systematic review, evidence mapping
- Promote systematic review methods uptake in environmental health.
  - Encourage harmonization, communication

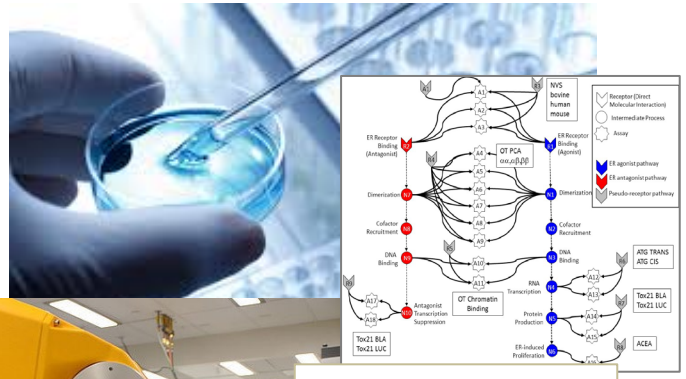
NTP Reports

NTP Monographs

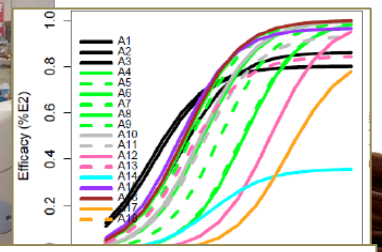
Workshops

Evidence-based Approaches for Environmental Questions

- **Challenges**
  - Needs to address the breadth of relevant data
  - Includes approach to reach hazard identification conclusions
  - Requires procedure to integrate evidence streams
    - Including new approach methodologies
  - Maintain transparent, critical evaluation of evidence
  - Find and translate “evidence” despite volume of research



ER Bioactivity Model

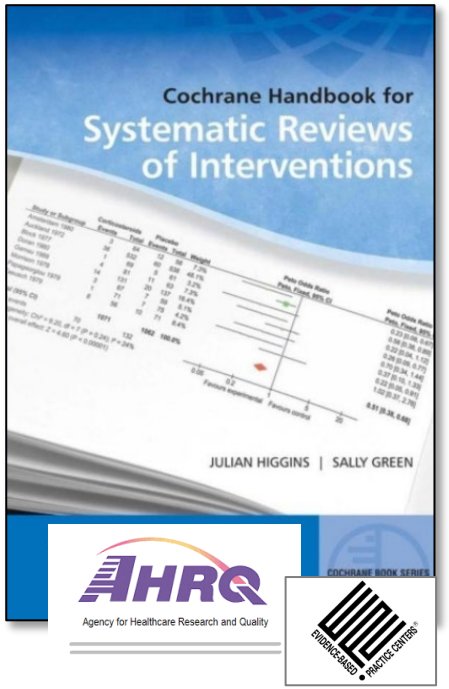


ER Bioactivity Model Response

What is Systematic Review and Why Use It?

Systematic Review

- Predefined, multistep process to identify, select, critically assess, and synthesize data from published studies to answer a specific question
- Explicit systematic methods
- Minimize Bias
- More reliable findings
- Transparency in reaching conclusion
- Inform decision-making



Systematic review has origins in clinical medicine and has been adapted for Environmental Health

Systematic Reviews in Environmental Health

- Published SR Frameworks or Methods in Envir./Public Health … **in last 5 years**
  - UCSF Navigation Guide
  - US NTP (ORoC and OHAT)
  - US EPA (IRIS Handbook)
  - Evidence Based Toxicology Collaboration
  - European Food Safety Authority
  - International Agency for Research on Cancer

Human Data

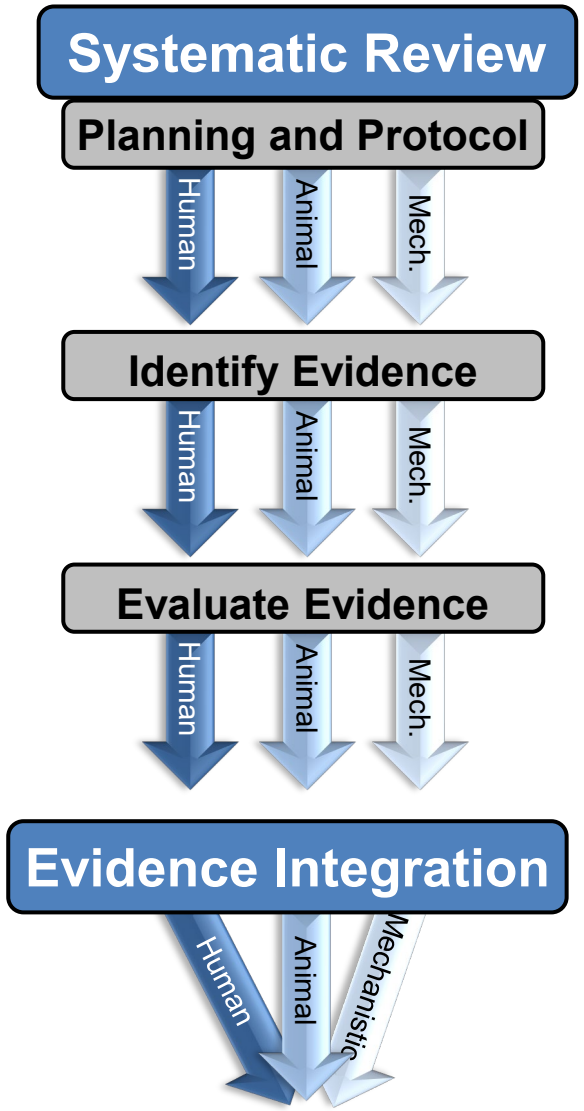
Experimental Animal Data

Mechanistic Data

Systematic Review and Evidence Integration Process

Stepwise Methods

- **Problem Formulation and Protocol Development**
  - Refine research question and develop systematic review protocol
  - Peer review and posting revised protocol
- **Identifying Evidence**
  - Perform comprehensive literature search
  - Select relevant studies
  - Extract data
- **Evaluating Evidence**
  - Assess individual study quality/risk of bias
- **Integrating Evidence**
  - Identify bodies of evidence
  - Develop confidence ratings for bodies of evidence
  - Translate confidence rating into levels of evidence
  - Develop hazard identification conclusion



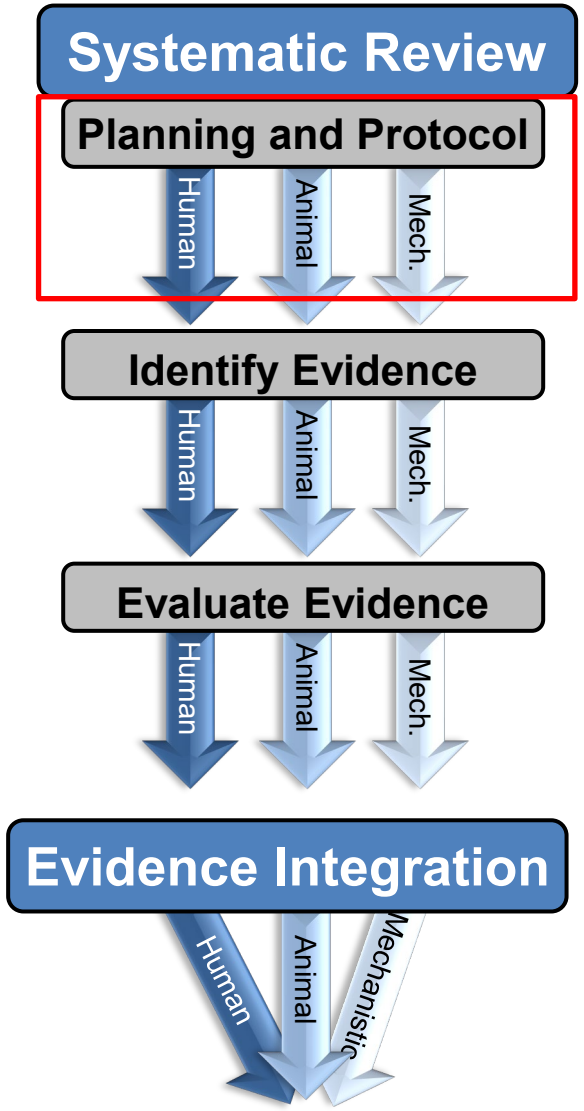
Planning: Problem Formulation

Identifies all factors critical to a conducting a review to address a specific research question

Considers:

- Purpose
- Scope
- Depth of analysis
- Approach
- Available resources
- Feasibility

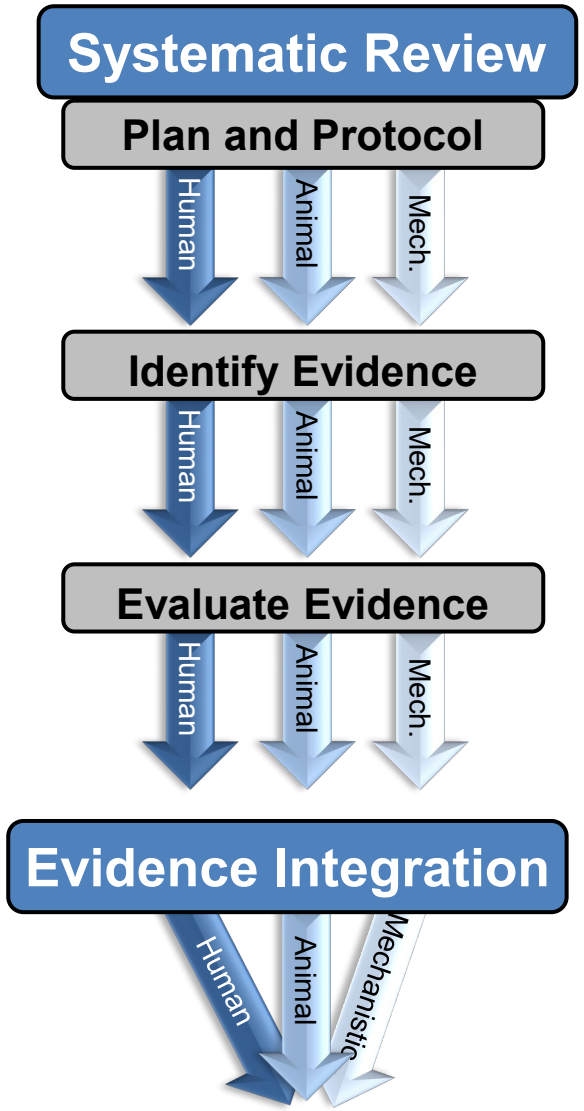
- **Scoping**
  - Define problem, rationale, objective(s)
  - Understand the literature
  - Analyses
  - Context
- **Framing**
  - Define research question(s)
  - Define literature search strategy



Planning: Considering Mechanistic Data

Using Data from New Approach Methodologies

- Problem Formulation
  - Outline proposed use of mechanistic/NAMs data
  - NAMs inform PECO and review question
    - Population
    - Exposure
    - Comparator
    - Outcome



Evidence Identification: SR and Evidence Integration

Stepwise Methods

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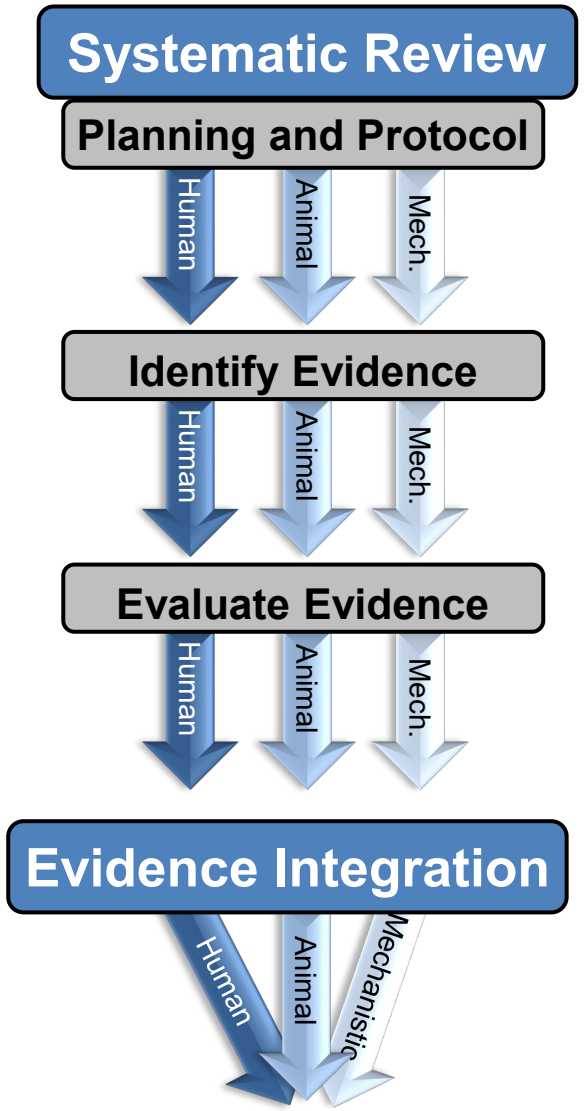
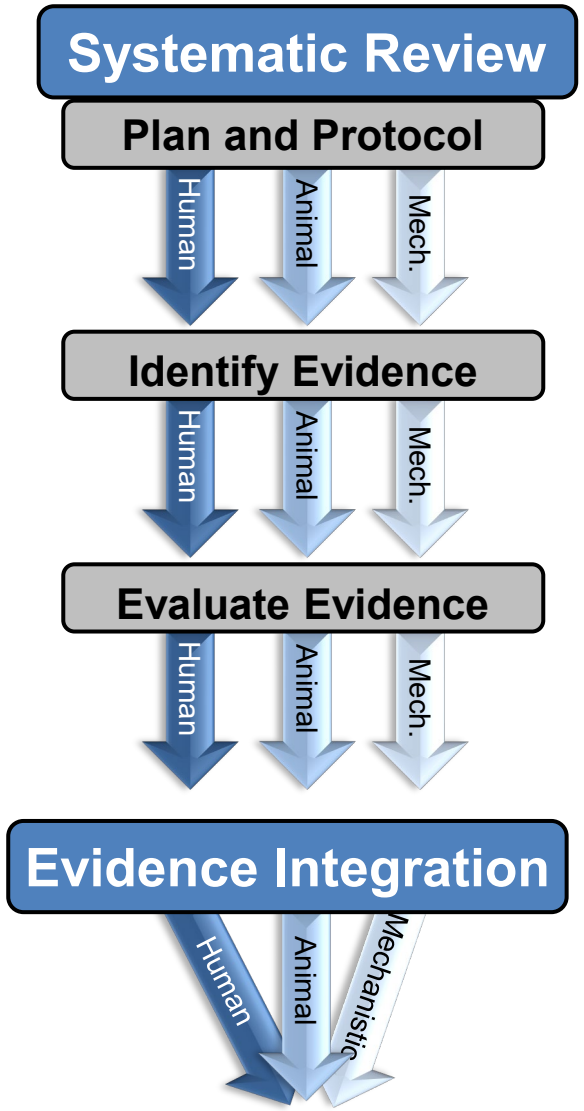


Evidence Identification: Considering Mechanistic Data

Using data from NAMs and in vitro studies

- Problem Formulation
  - Outline proposed use of mechanistic/NAMs data
  - NAMs inform PECO and review question

Identify
  - 1st focus on human and animal health effects data
  - 2nd mechanistic data relevant to human/animal health effects
    - Evidence-based decisions to dig deeper on cells, mechanisms, pathways
    - Planned, stepwise, targeted searches
    - Update protocol and planned approach at appropriate time



Evidence Evaluation: SR and Evidence Integration

Stepwise Methods

- **Problem Formulation and Protocol Development**
  - Refine research question and develop systematic review protocol
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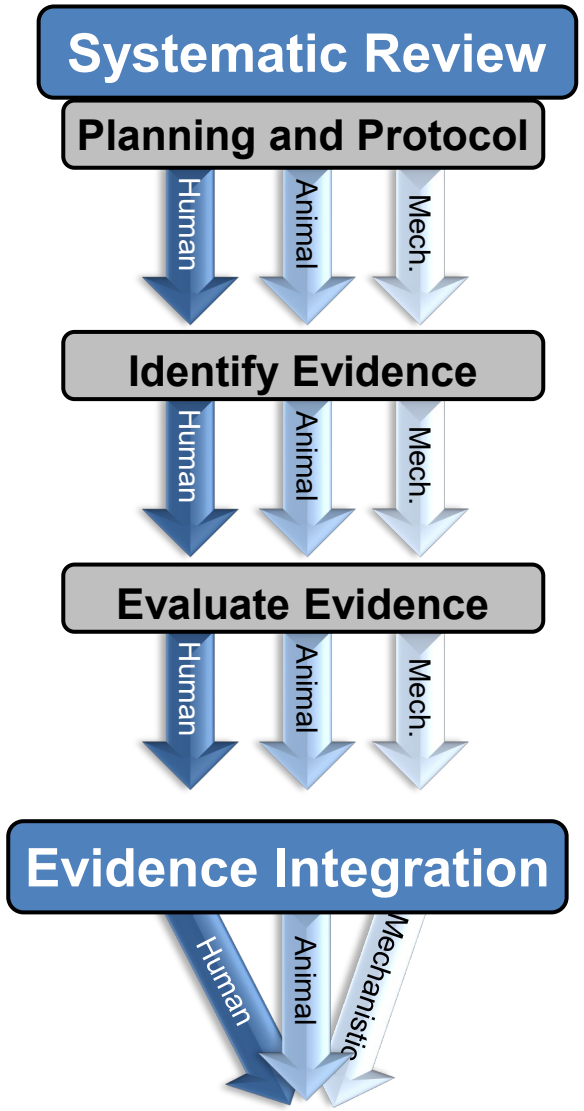


OHAT "Use-case" in PFOA Evaluation

A "parallel" approach across evidence streams

- Predefined set of questions address
  - Human studies
  - Animal toxicology studies
- Features of OHAT risk-of-bias tool
  - Study design determines which questions are applicable
  - Evaluation is endpoint specific

Use-case explored extending the risk of bias approach from experimental animal studies to studies with an in vitro exposure regime

Human Data

Experimental Animal Data

In Vitro Exposure Studies

https://ntp.niehs.nih.gov/go/749926

Study design determines which questions apply

1.Randomization of exposure (experimental animal studies)

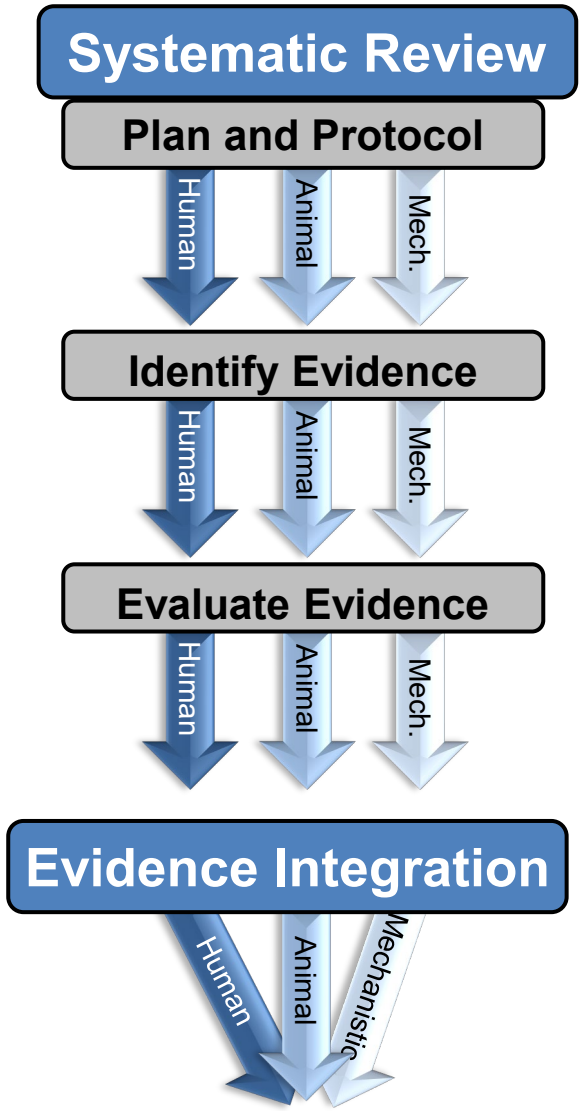
Risk-of-Bias Questions	Experimental Animal	Human Controlled Exposure	Cohort	Case-Control	Cross-Sectional	Case Series
1. Was administered dose or exposure level adequately randomized?	X	X				
2. Was allocation to study groups adequately concealed?	X	X				
3. Did selection of study participants result in the appropriate comparison groups?			X	X	X	
4. Did study design or analysis account for important confounding and modifying variables?			X	X	X	X
5. Were experimental conditions identical across study groups?	X					
6. Were research personnel blinded to the study group during the study?		X				
7. Were outcome data complete without attrition or exclusion from analysis?	X	X	X	X	X	
8. Can we be confident in the exposure characterization?	X	X	X	X	X	X
9. Can we be confident in the outcome assessment (including blinding of assessors)?	X	X	X	X	X	X
10. Were all measured outcomes reported?	X	X	X	X	X	X
11. Were there no other potential threats to internal validit	X	X	X	X	X	X

4. Confounding (observational studies)

Evidence Evaluation: Considering Mechanistic Data

Using Data from New Approach Methodologies

- Problem Formulation
  - Outline proposed use of mechanistic data
- Identify
  - Focused on endpoints with relevance to human and animal data
    - Stepwise, Evidence-based decisions based on human/animal
- Evaluate
  - Critical Assessment (Quality and Applicability)
    - NTP use-case: risk of bias method extended from animal approach
    - Ongoing research and discussion of current and best practices



Use-Case Adaptation Example

1) Was administered dose or exposure level adequately randomized?

- Assures that treatment is not given selectively based on potential differences in human subjects, animals, **cells**, **or tissues**
- Requires each human subject, animal, **or cell** had an equal chance of being assigned to any study group including controls
- **In vitro study considerations**
  - Potential difference between cells across groups
  - Dependence on study design
  - Example: homogeneous cell suspensions

NTP Monograph on Immunotoxicity Associated with Exposure to PFOA/PFOS *https://ntp.niehs.nih.gov/go/749926*

Stepwise Methods

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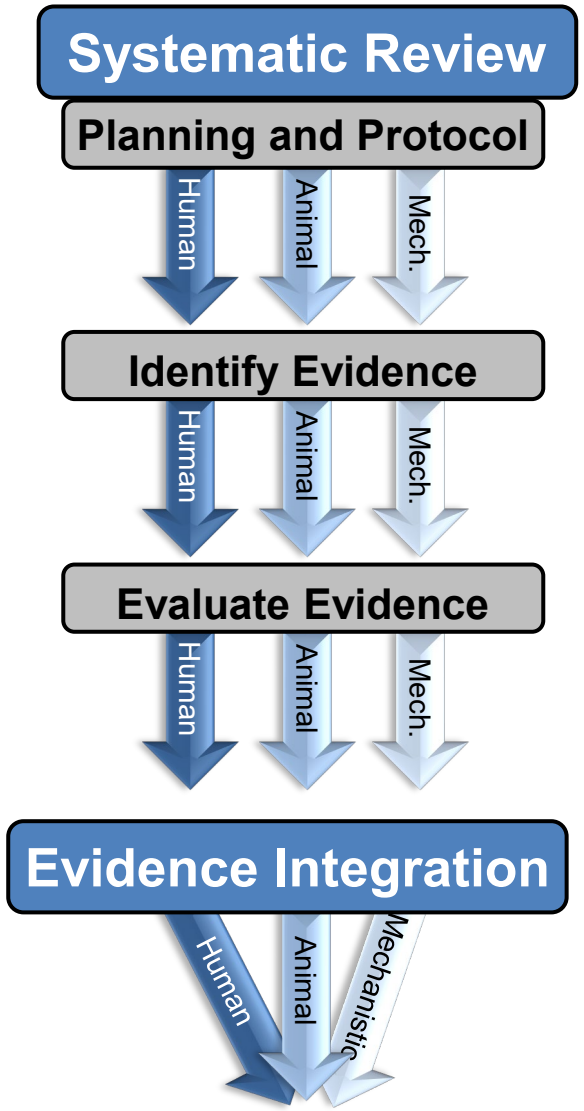

Evidence Integration: Considering Mechanistic Data

Using Data from New Approach Methodologies

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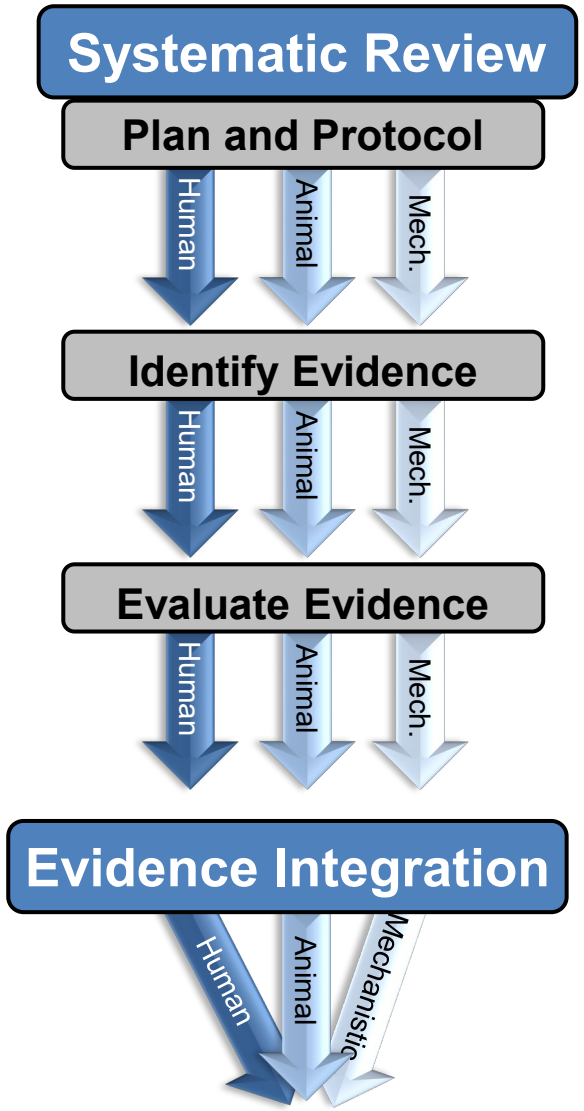
- Evaluate
  - Critical Assessment (Quality and Applicability)
    - NTP use-case: risk of bias method extended from animal approach
    - Ongoing research and discussion of current and best practices
- Evidence Integration
  - Biological plausibility



Integrate Evidence to Develop Hazard Conclusions

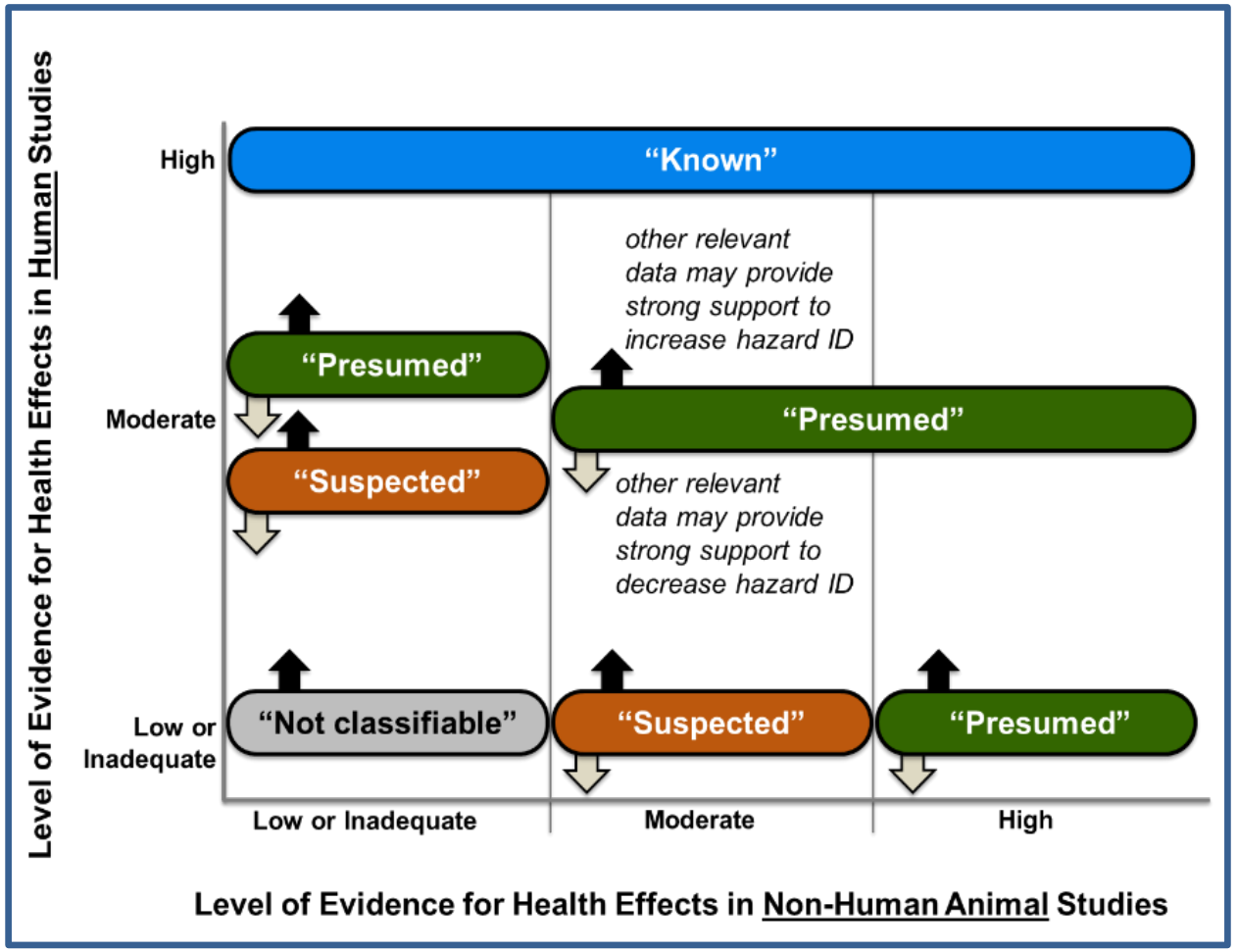
Initial Hazard Conclusion

Consider human and animal evidence together

- Known
- Presumed
- Suspected
- Not Classifiable

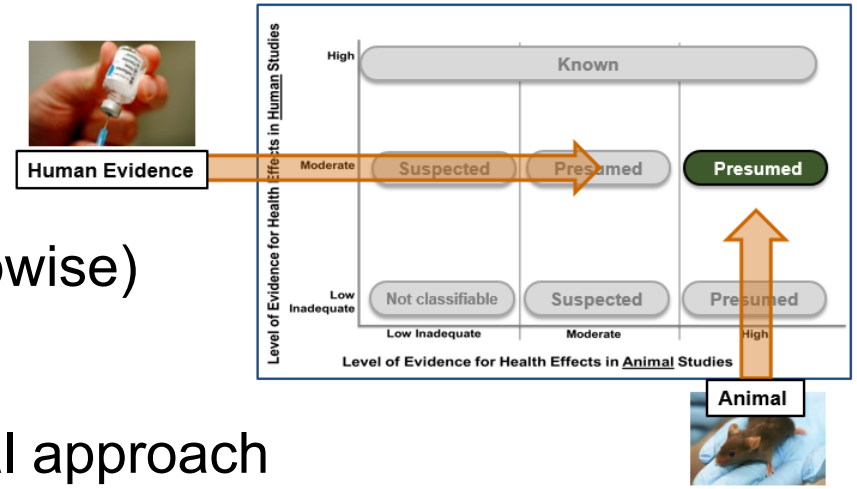
Final Hazard Conclusion

Consider impact of any relevant mechanistic data and biological plausibility of effect



Integration of Mechanistic Data

Considerations at multiple steps of the evaluation



- **Problem formulation**
  - Outline planned approach to mechanistic data
  - Inform and informed by human/animal evidence (stepwise)
- **Internal validity**
  - Assess with risk of bias method extended from animal approach
  - Only assess data directly relevant to human and animal health effects
- **External validity**
  - Critical to have plan for evaluating key mechanistic data
  - Dose and applicability were drivers in use of mechanistic data
- **Use-case represents an approach**
  - Emphasis on consistency within an evaluation
  - Flexibility across projects, active area of research, development, and discussion

Thank you

Questions?

United States Environmental Protection Agency

Rapid and Fit for Purpose Applications of Systematic Review Methods to Identify and Evaluate NAM Evidence

Computational Toxicology and Exposure Communities of Practice: Introduction to Systematic Review
Virtual Meeting (May 27, 2021)

Kristina Thayer (thayer.kris@epa.gov)
Director, Chemical Pollutant Assessment Division (CPAD)

Methods

- **Presented methods based on systematic evidence map (SEM) approaches used for problem formulation for IRIS and PPRTV toxicity value assessments. Methods also described in the IRIS Handbook which describes full assessment process.***
  - **Focus today is on searching, screening, displaying search results**
- **SEMs are pre-decisional analysis that use systematic review methods to identify and summarize evidence but do NOT reach assessment hazard or toxicity value conclusions**
  - **Generally quick to prepare (*days to weeks unless evidence base is large*)**
  - **Publishable in journals**
- **Used for:**
  - **Problem formulation (e.g., data poor or data rich evidence base?)**
  - **Need for assessment update?**
  - **Identify data gaps and prioritizing research needs**

*IRIS = EPA Integrated Risk Information System (https://www.epa.gov/iris); PPRTV = EPA Provisional Peer-Reviewed Toxicity Value (https://www.epa.gov/pprtv)
IRIS Handbook: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350086

Systematic Evidence Map

- Tailored to meet decision making needs
  - Include summarization of study designs, can also include study results and study evaluation
- Structured workflows
  - Facilitates rapid production and collaboration, enhances transparency and re-use of data
  - Availability of template reports reduce time to prepare and review (templates available upon request)
  - Reports are highly visual and graphics interactive
  - Workflows being designed to integrate with EPA CompTox Chemicals Dashboard
- Rapid production is facilitated by specialized software tools and use of artificial intelligence
  - Presented software tools are illustrative

Screening Criteria to Identify Key Evidence (PECO Criteria)

- **Presented screening criteria are illustrative based on IRIS/PPRTV assessments and should be customized to project**
- **Goal is to provide reproducible instructions on determining which studies are included, excluded, or considered supplemental**

Table 4. Example Populations, Exposures, Comparators, and Outcomes (PECO) Criteria

PECO element	Description
Populations	**Human:** Any population and lifestage (occupatio populations). **Animal:** Nonhuman mammalian animal species (lactation, peripubertal, and adult stages). Studies "potentially relevant supplemental material". *[O*
Exposures	Relevant forms: [chemical X] (*CAS number*) *Other forms of* [chemical X] *that readily dissociat* *Metabolites of interest, including metabolites use* *Occupations that may be considered surrogates c* **Human:** Any exposure to [chemical X] [via [oral o biomarkers of exposure are evaluated (e.g., meas exposure route is unclear or likely from multiple be tracked during title and abstract screening an *Specify if certain exposure assessment matrices o* **Animal:** Any exposure to [chemical X] via [oral or exposure during reproduction or development. S an experimental arm with exposure to [chemical tracked during title and abstract as "potentially r *Specify if certain exposures/study designs will NO* *tested in experimental animal studies is indicated*
Comparators	**Human, Example A (general SEM):** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits), or exposure for shorter periods of time, or cases versus controls, or a repeated measures design. However, worker surveillance studies are considered to meet PECO criteria even if no statistical analyses using a referent group is presented. Case reports or case series of > 3 people will be considered to meet PECO criteria, while case reports describing findings in 1–3 people will be tracked as "potentially relevant supplemental material." **Human, Example B (targeted SEM to identify studies suitable for dose response):** Studies reporting effect measures (e.g., relative risk, standardized mortality ratio, beta coefficients) based on a comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits), or cases versus controls, or a repeated measures design. *[Notes: Studies based exclusively on duration of exposure analyses (i.e., longer versus shorter exposure duration) are not likely to be informative for SEMs focused on identifying studies plausibly suitable for dose response.]* **Animal:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement, e.g., acute toxicity studies of mortality, or a repeated measures design).
Outcomes	All health outcomes (cancer and noncancer). In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes are considered to meet PECO criteria and prioritized for evidence synthesis over outcomes such as biochemical measures. *[Notes: Studies meeting PECO criteria may also contain supplemental mechanistic content that describes biological or chemical events associated with phenotypic effects. When this occurs, these studies are also tagged as having supplemental mechanistic information. This typically happens during full-text review or doing the literature inventory. Full-text retrieval is recommended for studies of transgenic model systems that meet E and C criteria because they may present phenotypic information in wildtype animals that meet P and O criteria but is not reported in the abstract.]*

Screening Criteria: Supplemental Material

- **Supplemental material falls outside of PECO but is not excluded**

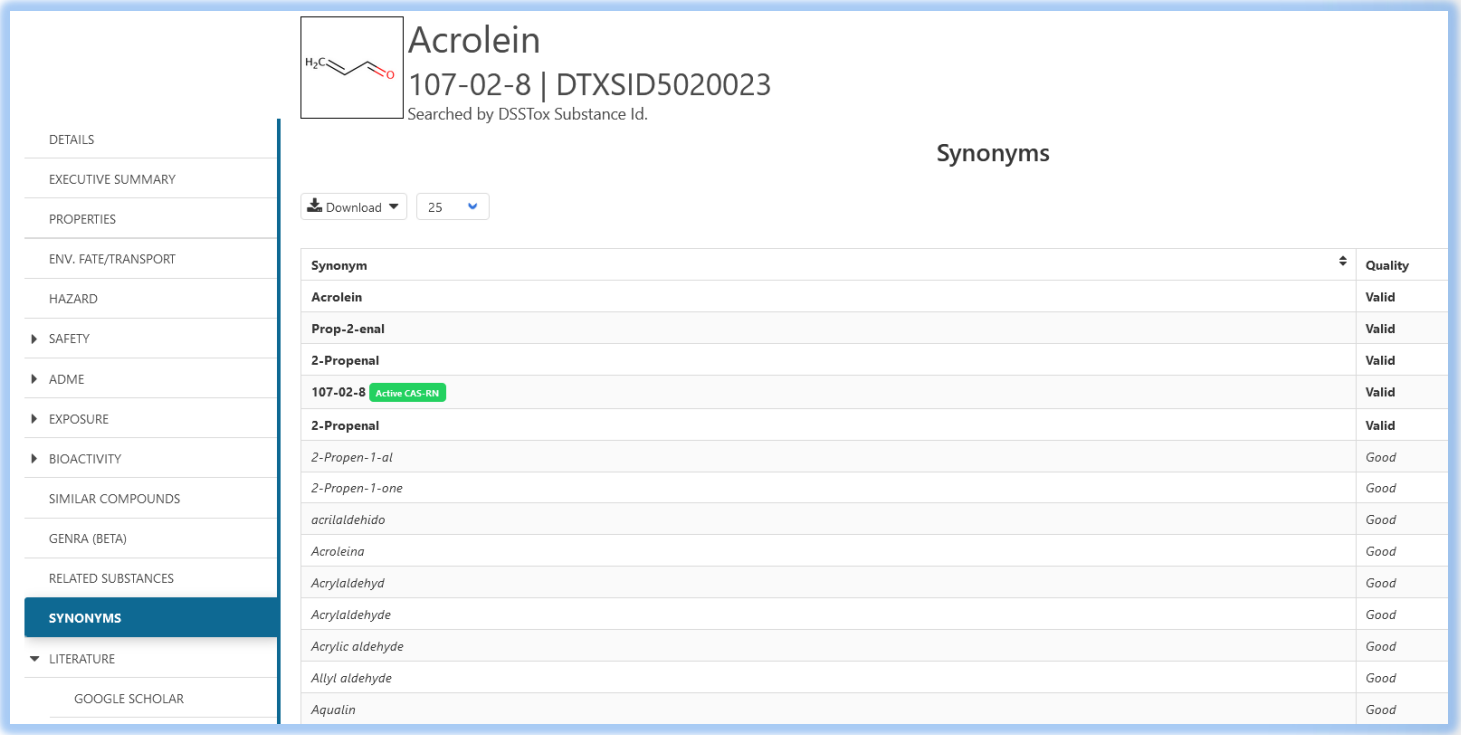
Table 5. Categories of Potentially Relevant Supplemental Material

Category	Evidence
Mechanistic information	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, in vivo (by any route of exposure, includes transgenic models), *ex vivo*, and *in silico* studies. Genotoxicity tests are considered "mechanistic." Studies where the chemical is used as a laboratory reagent generally do not need to be tagged (e.g., as a chemical probe used to measure antibody response). *[Notes:* • *Genotoxicity tests are considered "mechanistic" for the purposes of screening because they are typically used to reach mechanistic inferences in the IRIS and PPRTV Programs. However, some groups consider these endpoints suitable for dose response and may want to adjust PECO criteria to include them.* • *During screening, especially at the title and abstract (TIAB) level, it may not be readily apparent for studies that meet P, E, and C criteria if the endpoint(s) in a study are best classified as phenotypic or mechanistic with respect to the O criteria. In these cases, the study should be screened as "unclear" during TIAB screening and a determination made based on full-text review (in consultation with a content expert as needed). Full-text retrieval is recommended for studies of transgenic model systems that meet E and C criteria because they may present phenotypic information in wildtype animals that meet P and O criteria but is not reported in the abstract.]*
Nonmammalian model systems	Studies in nonmammalian model systems (e.g., fish, birds, *C. elegans*).

NAM evidence would often be in these categories for IRIS or PPRTV

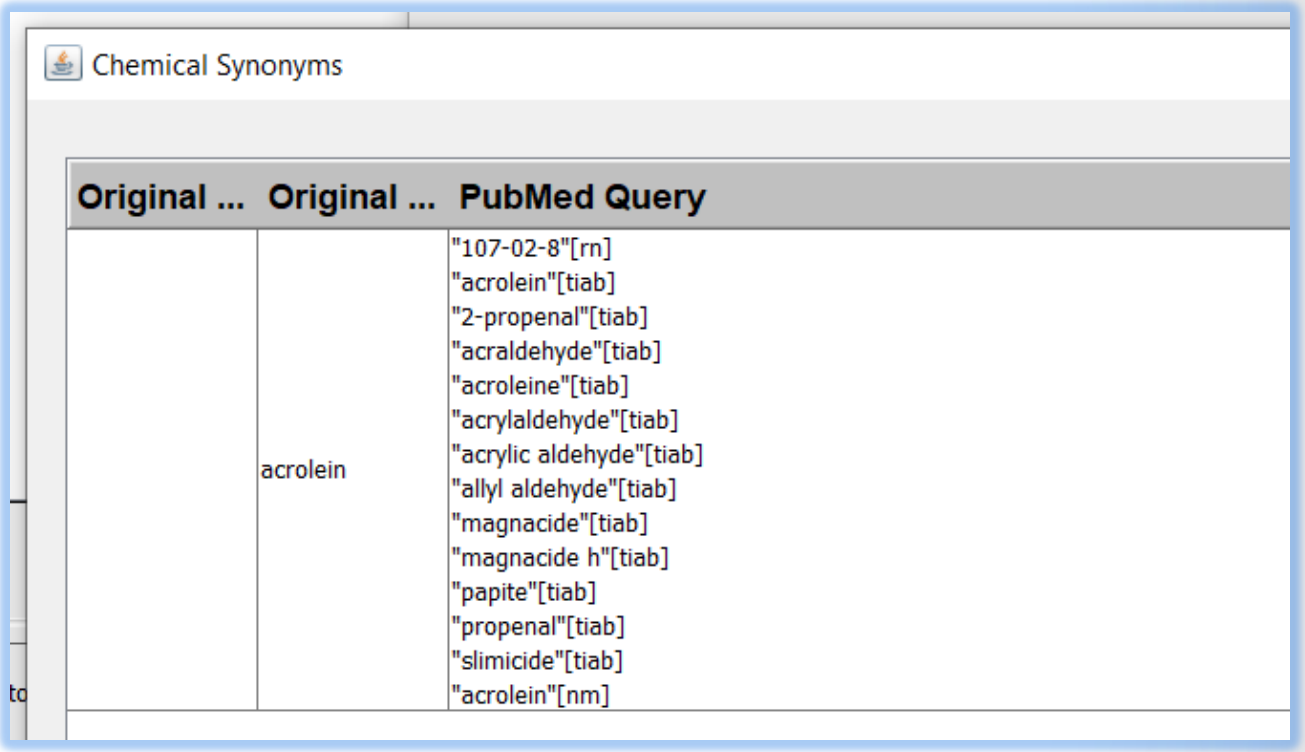
Literature Searching: Chemical Focused

- **Chemical name (and CASRN, synonyms, trade names, and metabolites/degradants of interest)**
- **Resources**
  - **Chemicals Dashboard (consider limiting synonyms to those marked as "valid" or "good")**



Literature Searching: Chemical Focused

- **Resources**
  - **SWIFT Review* "Find Chemical Synonyms" feature**
  - **Creates PubMed-formatted chemical search using (1) the common name as presented in the Tox21 chemical inventory list, (2) CASRN), (3) synonyms from the ChemIDPlus database, and (4) removal of ambiguous or short alphanumeric terms**


Chemical Synonyms

Original ...	Original ...	PubMed Query
	acrolein	"107-02-8"[rn] "acrolein"[tiab] "2-propenal"[tiab] "acraldehyde"[tiab] "acroleine"[tiab] "acrylaldehyde"[tiab] "acrylic aldehyde"[tiab] "allyl aldehyde"[tiab] "magnacide"[tiab] "magnacide h"[tiab] "papite"[tiab] "propenal"[tiab] "slimicide"[tiab] "acrolein"[nm]

*SWIFT Review is a free software application used to assist problem formulation. includes text mining and machine learning methods that allow users to uncover over-represented topics within the literature corpus and to rank order documents for manual screening. https://www.sciome.com/swift-review/

Literature Searching: Sources

- Should include multiple databases of published studies
  - e.g., PubMed, Web of Science, Scopus, ProQuest
- Should include "grey" literature
  - e.g., European Chemicals Agency (ECHA), EPA ChemView database
- Some sources may be especially important for data poor chemicals
  - ToxCast or Tox21 high throughput screening information
  - Comparative Toxicogenomics Database (CTD)
  - Gene expression studies (Gene Expression Omnibus https://www.ncbi.nlm.nih.gov/geo/ and ArrayExpress https://www.ebi.ac.uk/arrayexpress/)

Literature Searching: Narrowing Search Results

- Literature search filters deployed in SWIFT Review
  - Developed and refined by people (information scientists, bioinformaticians)
- Allows for rapid filtering of studies from a broad literature search

Literature Searching: Narrowing Search Results

SWIFT-Review - [C:\Users\KThayer\OneDrive - Environmental Protection Agency (EPA)\Profile\Desktop\SWIFT Review\PFAS 150 Full list 9-5-19 40740 records.stp]

File Tools Reports Help

Tag Browser | Search | Browse MeSH Tree | Heatmap Browser | Prioritized Lists

Evidence Stream

Tag	Count
Human	15076
Ecotoxicity (animal and plant)	13778
[No Tag]	13334
Animal (all)	10919
Animal (human health models)	7491
In Vitro	6635
Environmental Fate (beta)	5137
Plant	1375

Health Outcomes

Tag	Count
[No Tag]	2261
ADME (title + abstract)	6312
ADME (title only)	1779
Cancer	2442
Cardiovascular	5079
Developmental	5428
Endocrine	2586
Gastrointestinal	1951
Hematological and Immune	7470
Hepatic	2007
Mortality	2509
Musculoskeletal	3376
Neurological	4762
Nutritional and Metabolic	2958
Ocular and Sensory	3216
PBPK	259
Renal	1559
Reproductive	2150
Respiratory	6019
Skin and Connective Tissue	894

Document Preview | Pie Chart | Bar Chart

Sevoflurane downregulates insulin-like growth factor-1 to inhi and trigger apoptosis in glioma through the PI3K/AKT signalin

Gao, C.; He, X. F.; Xu, Q. R.; Xu, Y. J.; Shen, J.. *Anti-Cancer Drugs (2019)*

▼Abstract

Sevoflurane is a new type of inhalation anesthetic used widely in the clinic. It has the characteristics of rapid induction, rapid reco sevoflurane can affect the invasion and migration of a variety of malignant tumors. However, its effects on human glioma cells and were pretreated with sevoflurane. The effect of sevoflurane on proliferation was evaluated by MTT, and cell migration assay, cel assay, cell apoptosis, and Transwell assays. Insulin-like growth factor-1 (IGF-1) and PI3K/AKT signaling pathway gene expres blotting analysis, respectively. 5% sevoflurane significantly inhibited proliferation ability in both U251 and U87 cells. Sevoflurane apoptosis. Sevoflurane inhibited IGF-1 and promoted the expression of apoptosis-related proteins in glioma cells. In addition, se This study clarifies that sevoflurane inhibits proliferation, invasion, and migration, and promotes apoptosis in glioma cells. These e signaling pathway. These findings may be significant for the selection of anesthetic agents in glioma surgery to improve the progno

▼Health Outcomes

Cancer (65%)
Nutritional and Metabolic (15%)
Respiratory (10%)
Endocrine (7%)
ADME (title + abstract) (4%)

Showing 2442 of 40740 loaded documents (1 selected; 0 total included; 0 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Authors	Journ
0.132	☐	☐	s6227	Leydig cell hyperplasia and adenoma formation: Mechanisms and relevance to humans	1997	Clegg, E. D.; Cook, J. C.; Chapin, R. E.; Foster, P. M. D.; Daston, G. P.	Repro
0.132	☐	☐	s6446	Induction of Leydig cell adenomas by ammonium perfluorooctanoate: a possible endocrine-related mecha...	1992	Cook, J. C.; Murray, S. M.; Frame, S. R.; Hurtt, M. E.	Toxic
0.132	☐	☐	s16946	Synthesis and biological evaluation of 3,4-diphenyl-1,2-dihydroisoquinolines as a new tamoxifen analogue	1995	Kihara, M.; Ikeuchi, M.; Nagao, Y.	Drug

SWIFT Review – Behind the Tags

SWIFT REVIEW

Desktop Version (1.21)

Search Strategies

swift-review@sciome.com

Ecotoxicity (animal and plant)

tiab :("Norway Rat" OR "Rattus norvegicus" OR "Rainbow Trout" OR "Oncorhynchus mykiss" OR "Water Flea" OR "Daphnia magna" OR "Zebra Danio" OR "Danio rerio" OR "Fathead Minnow" OR "Pimephales promelas" OR "House Mouse" OR "Mus musculus" OR "Common Carp" OR "Cyprinus carpio" OR "Bluegill" OR "Lepomis macrochirus" OR "Domestic Chicken" OR "Gallus domesticus" OR "Japanese Medaka" OR "Oryzias latipes" OR "Mallard Duck" OR "Anas platyrhynchos" OR "Goldfish" OR "Carassius auratus" OR "Corn" OR "Zea mays" OR "African Clawed F

"Honey Bee" OR "

max"

OR "Northern Bo

Nile Tilapia" OR "Oreochromis niloticus" OR "Rice" OR "Oryza sativa" OR "Channel Catfish" OR "Ictalurus punctatus" OR "Yellow Fever Mosquito" OR "Aedes aegypti" OR "Earthworm" OR "Eisenia fetida" OR "Silver

Based on searches used for EPA's ECOTOXDB. Full search strategy is ~130 pages long

Sciome

Enabling Science via Analytical Informatics

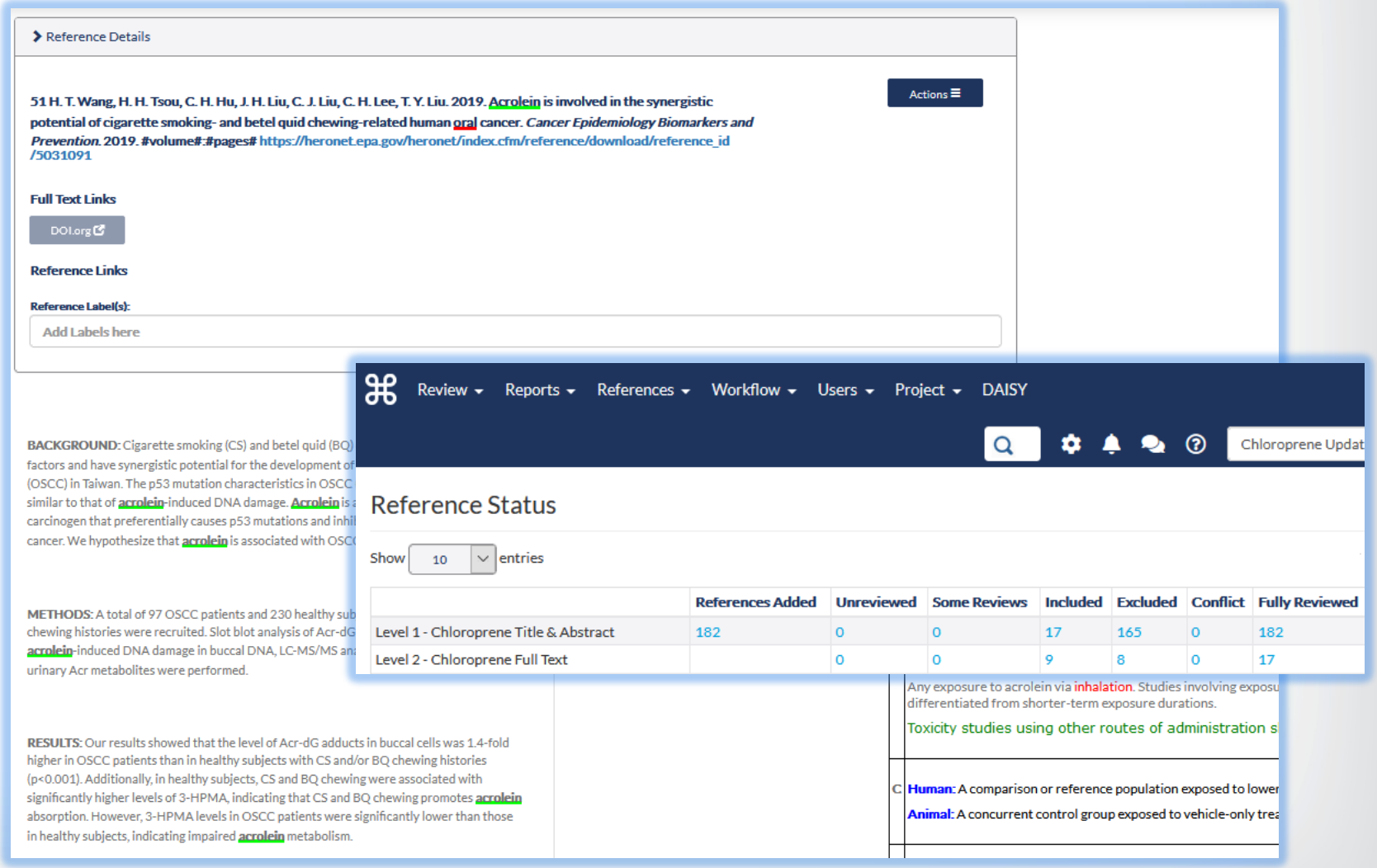
Page **81** of **210**

Screening Studies: Best Practices

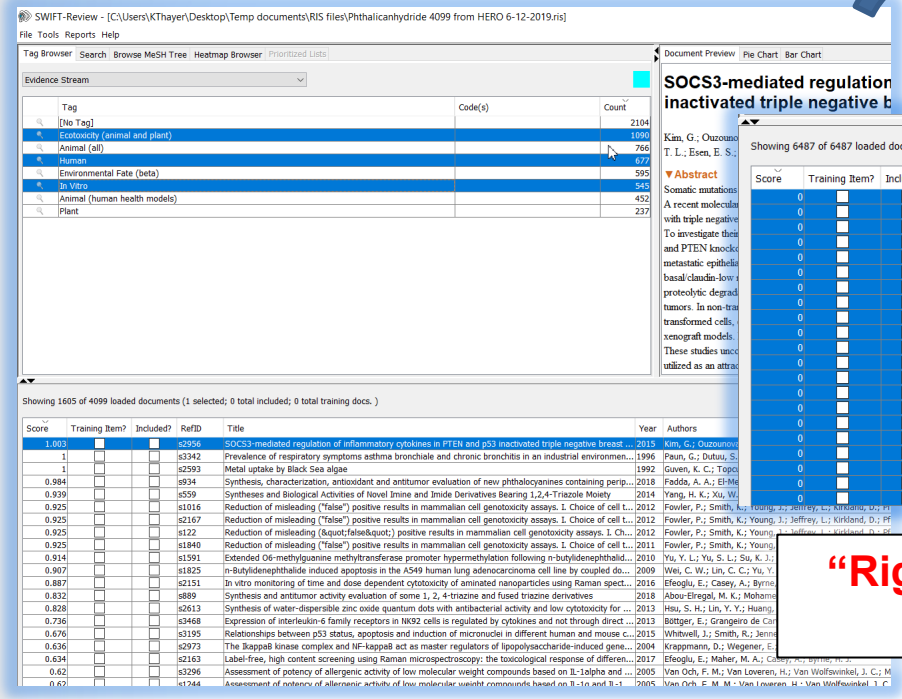
- Two independent reviewers per record (at title/abstract and full-text levels) and a process to resolve conflicts
- Requirement for public availability depends on decision-making context
- Document reason for exclusion (at least at full-text level)
- Best practices is NOT to apply language restrictions
- Most studies identified from search get excluded at the title and abstract level
- Many screening tools available (both manual and machine-learning based)
  - A focus in the field is to make tools interoperable

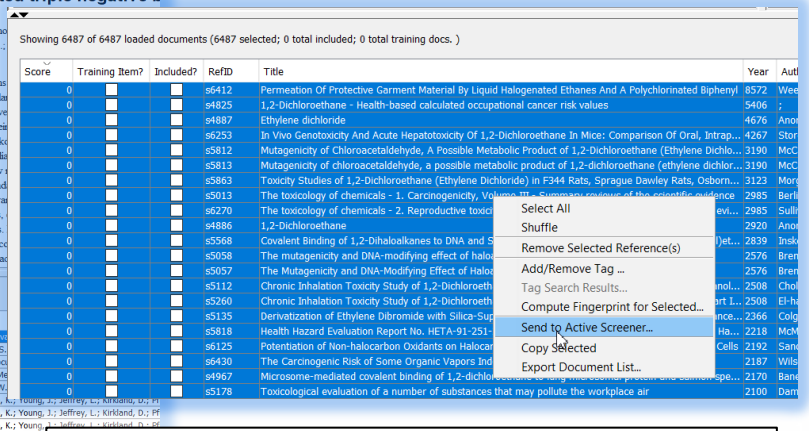
Screening Studies: Example Form

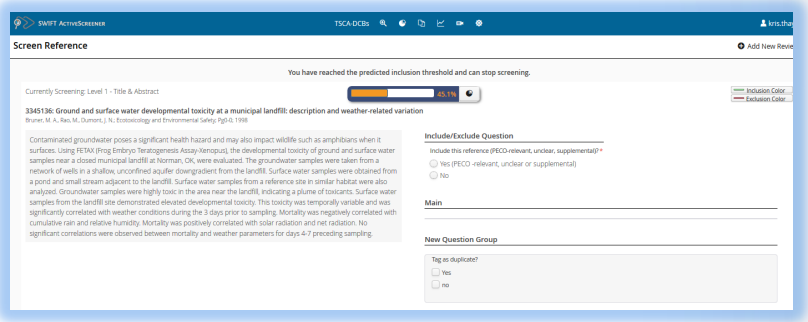
- 5-10 seconds per study at title/abstract level
- 30 seconds to 1-2 minutes at full-text level
- For most projects the majority of studies are excluded at title and abstract level



SWIFT Review + SWIFT Active Workflow



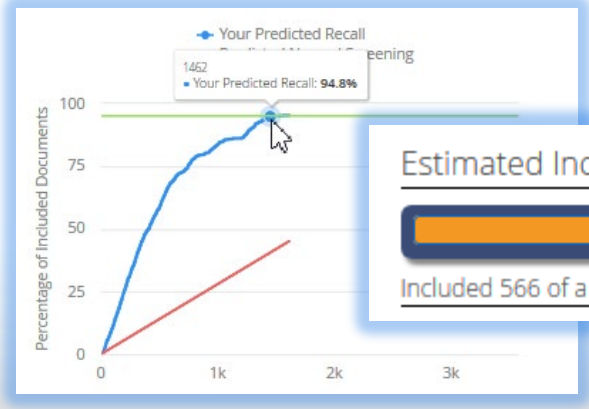


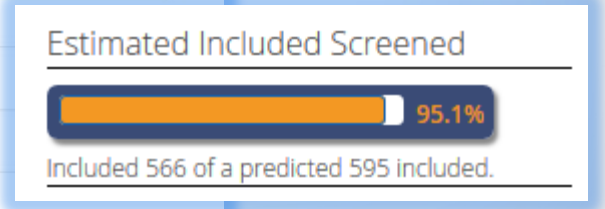


SWIFT Review to identify hazard records

"Right click" to move to SWIFT Active

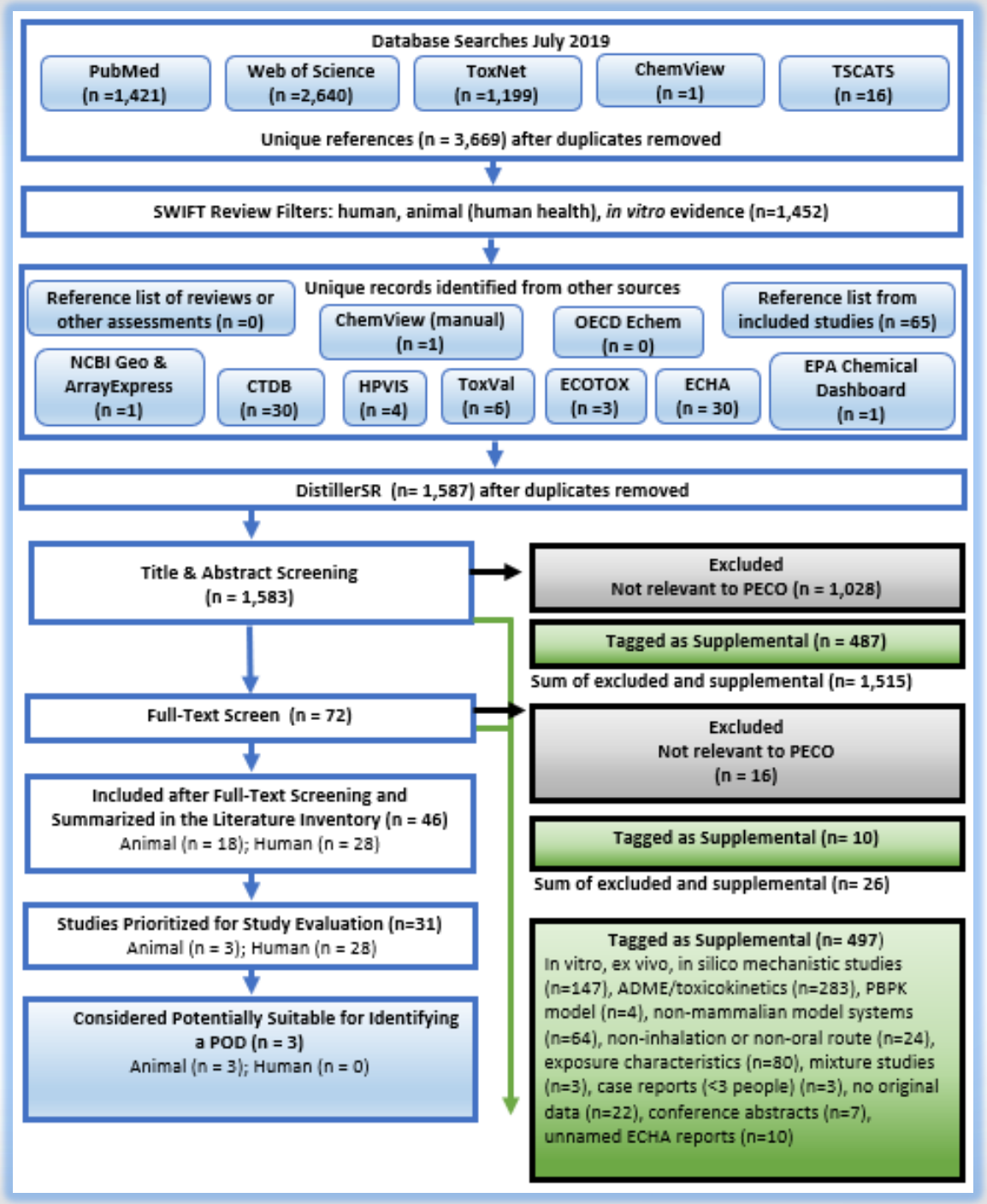
Machine-learning based screening



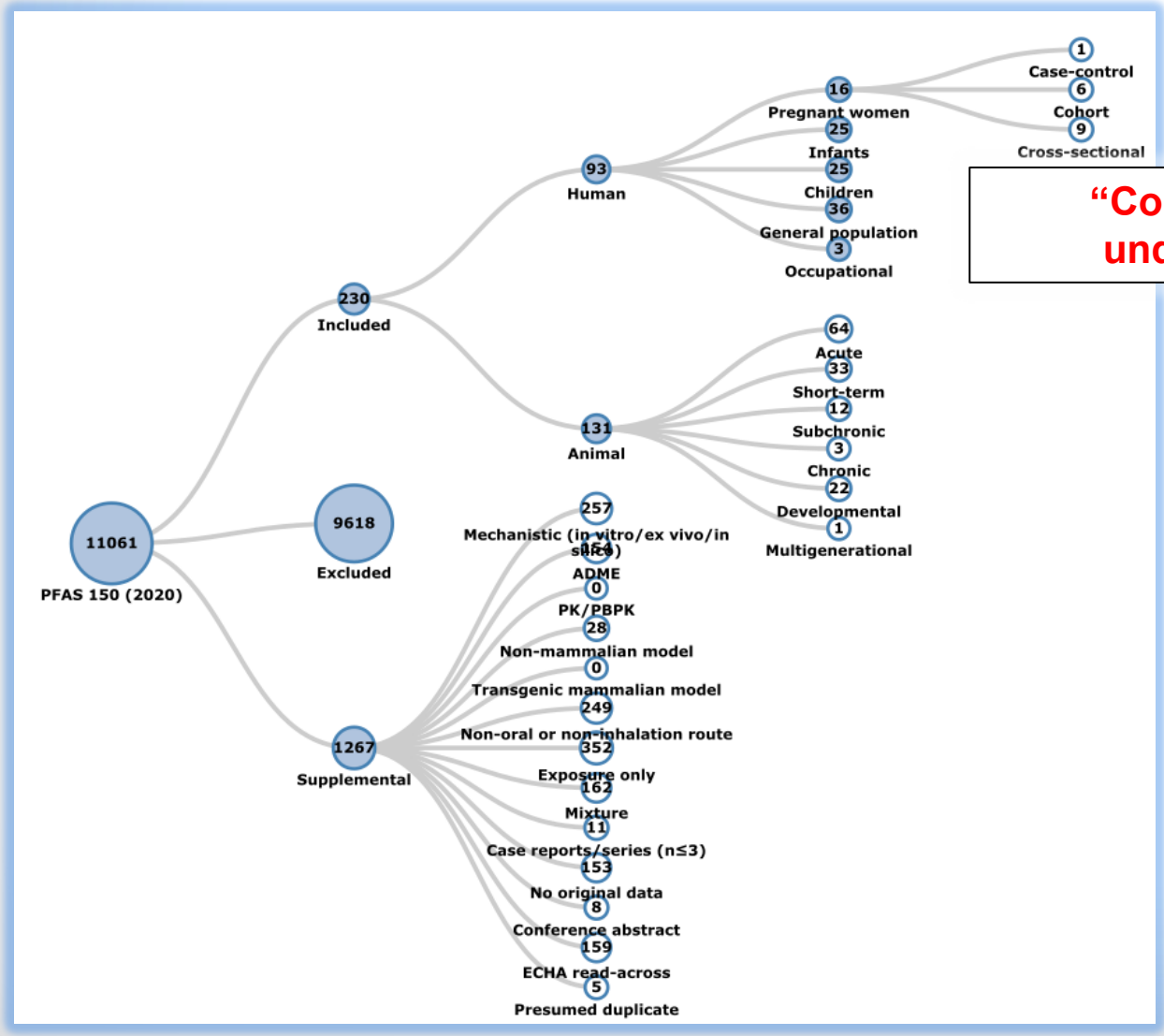


- **Only 45% of studies needed to screened (40-60% reduction typical)**
- **Software tells screeners when they can stop**
- **Review of grey literature resources, reference list of included studies, references cited in other assessments, and public comment mitigate concern for missing "key" studies**

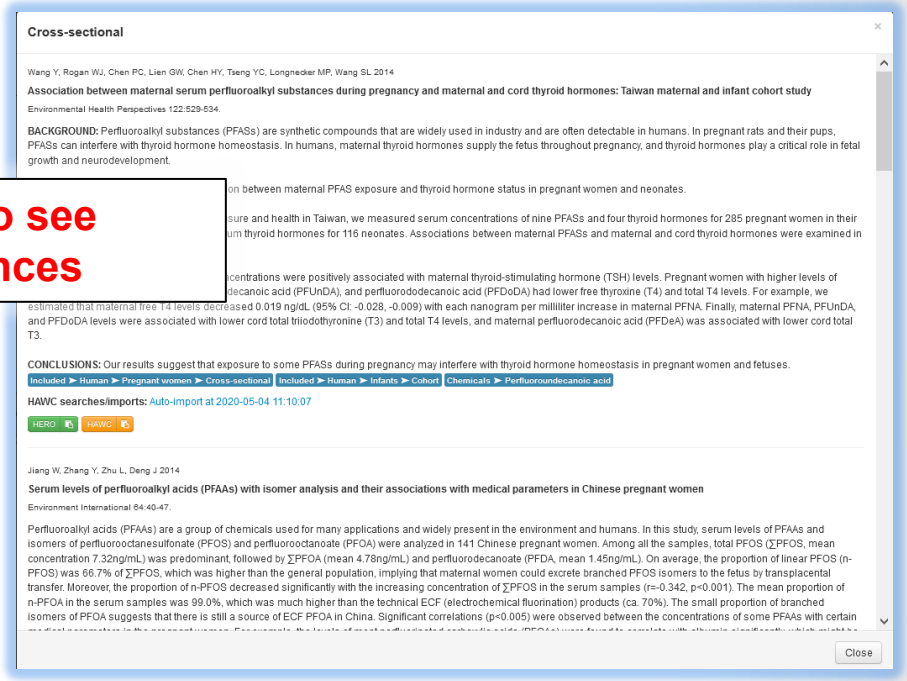
Displaying Search and Screening History: Study Flow Diagram



HAWC Literature Trees



"Control + click" to see underlying references



EPA and EPA contractors: https://hawcprd.epa.gov
Non-EPA: https://hawcproject.org/ (free and open source)
*Deployments share same source code

Literature Inventories to Show Extent and Nature of the Evidence

Health effect category	Adults	Adults and children	Children <18 y
Cancer	3		
Cardiovascular	9	2	
Developmental			
Endocrine	6	2	
Gastrointestinal			
Hematologic			
Hepatic	3		
Immune	1		
Metabolic	10	2	
Nervous			
Other		1	
Renal	4		
Reproductive, female	4	1	
Reproductive, male	4	1	

Population	Chemical		Outcome	
	PFUnDA	86	Birth size	17

Reference	Chemical	Endpoint	Sub-pop	N				
3M (2000)	POSF	bladder cancer	full sample	208				
		liver cancer	full sample	208				
Aimuzi et al. (2019)	PFUnDA	FT3	full sample	568				
			males	305				
		FT4	males	305	median=0.40 ng/mL (IQR: 0.31-0.54)	change in FT4 per standardized unit increase in PFUA	0.033	-0.007	0.069

ReadMe | Animal Studies | Human Studies

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

Heat Map

	acute							short-term			subchronic		chronic	
	rat	mouse	dog	guinea pig	hamster	rabbit	not reported	rat	mouse	not reported	rat	mouse	rat	mouse
Cancer													2	
Cardiovascular	3		4					10			6	2	2	
Dermal	1							2			2			
Developmental														
Endocrine								11			7		2	
Exocrine	1													
Gastrointestinal	7							7			5		1	
Hematologic								12			10	2	2	
Hepatic	8	1	1	1				16	6		9	2	2	
Immune	4							12	3		9	1	2	
Lymphatic									1					
Metabolic								3			3	1		1
Musculoskeletal/Connect..								7			3			
Nervous	6	2						10			7	2	2	
Not reported (but NOAEL..								3		3				
Ocular	3	1						4			9	1	2	
Renal	8	1						12	2		9	2	2	

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
Cancer	chronic	inhalation	rat	both	Haskell Laboratories (1995)
					Malley et al. (1998)
Cardiovascular	acute	inhalation	rat	male	DuPont (1992b)
			dog	male	DuPont (1992d)

References

- 3M (1999)
- Anand et al. (2012)
- Apollo Scientific Ltd. (2019) (ECHA Summ..
- Bodin et al. (2016)
- Bomhard and Loser (1983)
- Case et al. (2001)
- Covance Laboratoroes (2000)
- DuPont (1990a)

Chemicals Evaluated - by Name

1-Butanesulfonic acid, 1,1,2,2,3,3,..	1
1H,1H,2H-Perfluorocyclopentane	6
1H,1H,5H-Perfluoropentanol	1
2-Chloro-1,1,1,2-tetrafluoroethane	13
3-Methoxyperfluoro(2-methylpent..	3
3,3,4,4,5,5,6,6,6-Nonafluorohexene	5

Chemicals Evaluated - by CASRN

76-05-1	14
307-35-7	1
335-27-3	2
335-99-9	2
338-83-0	1

Chemicals Evaluated - by DTXSID

DTXSID0036926	2
DTXSID0059879	1
DTXSID0061826	8
DTXSID1032646	2
DTXSID1074915	4

Study Evaluation & Evidence Analysis

- Study evaluation tools available for epidemiology, animal toxicology, and in vitro studies, but pragmatic approaches need to considered for NAM
  - Study evaluation is a high level of effort
  - Fewer tools for in silico evidence
- Structured frameworks for evidence synthesis and integration recommended in systematic review to reach weight of evidence conclusions
  - Existing frameworks underdeveloped for application to mechanistic/NAM evidence
  - Active area of discussion and interest

Take Home Message

- Any literature-based analysis requires searching for existing evidence
- Use of systematic review methods to identify evidence brings transparency and rigor to the process
- Use of defined workflows and specialized software to identify literature makes the process efficient, i.e., unclear if process takes longer than non-systematic methods (may be faster)
- More discussion and method development warranted for study evaluation and evidence synthesis/integration for NAM-based analyses

Acknowledgements

Template Systematic Evidence Map (SEM) Report Format and Methods Used for the US EPA Integrated Risk Information System (IRIS) Program, Provisional Peer Reviewed Toxicity Value (PPRTV) Program, and Other "Fit for Purpose" Analyses

Kristina A. Thayer[1], Michelle Angrish[1], Xabier Arzuaga[1], Laura M. Carlson[1], Allen Davis[1], Laura Dishaw[1], Ingrid Druwe[1], Catherine Gibbons[1], Barbara Glenn[1], Ryan Jones[2], J. Phillip Kaiser[1], Channa Keshava[1], Nagalakshmi Keshava[1], Andrew Kraft[1], Lucina Lizarraga[1], Amanda Persad[1], Elizabeth G Radke[1], Glenn Rice[1], Brittany Schulz[3], Teresa Shannon[1], Andrew Shapiro[2], Shane Thacker[2], Suryanarayana Vulimiri[1], Antony J. Williams[4], George Woodall[1], Erin Yost[1] Robyn Blain[5], Katherine Duke[5], Ali Goldstone[5], Pam Hartman[5], Kevin Hobbie[5], Brandall Ingle[6], Courtney Lemeris[5], Cynthia Lin[5], Alex Lindahl[5], Kristen McKinley[5], Parnian Soleymani[5], Nicole Vetter[5]

[1]Center for Public Health and Environmental Assessment, Chemical & Pollutant Assessment Division, US EPA, NC, USA; [2]Center for Public Health and Environmental Assessment, Health & Environmental Effects Assessment Division, US EPA, NC, USA; [3]Oak Ridge Associated Universities, TN, USA; [4]Center for Computational Toxicology and Exposure, US EPA, NC, USA; [5]ICF, VA, USA; [6]Office of Pesticide Programs, US EPA, NC, USA

Questions?

United States Environmental Protection Agency

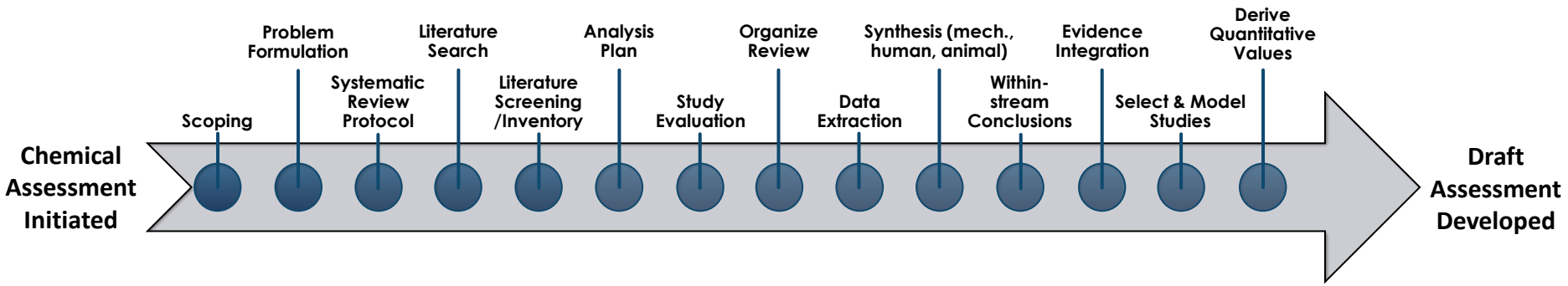
Suite of Systematic Review Software Tools

Michele M. Taylor
Chemical Pollutant Assessment Division

Computational Toxicology and Exposure Community of Practice:
Introduction to Systematic Review
May 27, 2021

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

Overview of the SR Workflow



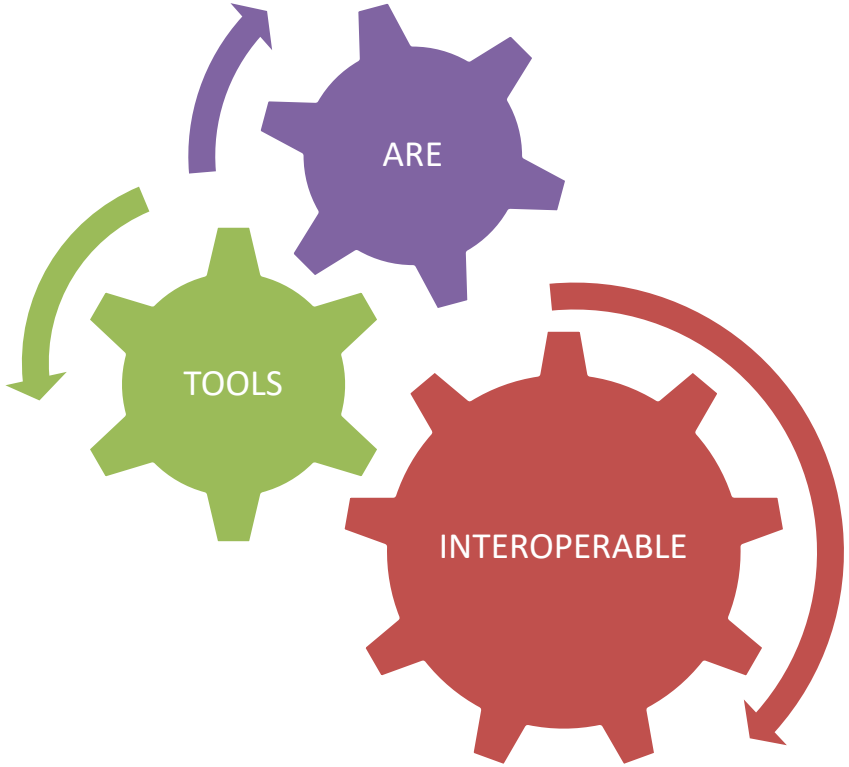
- Develop problem formulation and scope of the systematic review
- Search journal databases (PubMed, WoS, Toxline, etc.) and grey literature using database specific search strings
- Use specialized SR software to:
  - focus on topics of interest
  - leverage machine-learning to rapidly screen
  - document reviewer decisions
  - store extracted data
  - compile/summarize/visually display the relevant evidence base

Suite of Systematic Review Software Tools

Search HERO

DistillerSR

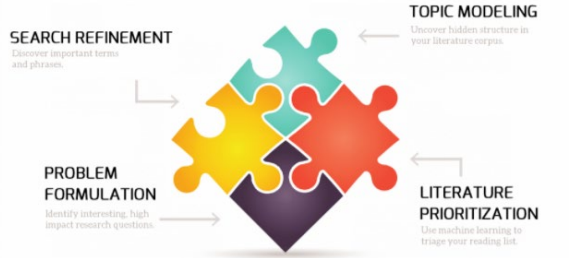
HAWC
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE



SWIFT REVIEW

SWIFT-Review (SWIFT is an acronym for "Sciome Workbench for Interactive computer-Facilitated Text-mining") is a freely available interactive workbench which provides numerous tools to assist with problem formulation and literature prioritization. SWIFT-Review puts the systematic review expert in the driver's seat by providing several features that can be used to search, categorize, and prioritize large (or small) bodies of literature in an interactive manner. SWIFT-Review utilizes newly developed statistical text mining and machine learning methods that allow users to uncover over-represented topics within the literature corpus and to rank order documents for manual screening.

For more information about SWIFT-Review, and other Sciome products and services please contact us at swift-review@sciome.com.



SWIFT-ACTIVESCREENER

SWIFT-Active Screener is a web-based, collaborative systematic review software application. Active Screener was designed to be easy-to-use, incorporating a simple, but powerful, graphical user interface with rich project status updates. What makes Active Screener special, however, is its behind-the-scenes application of state-of-the-art statistical models designed to save screeners time and effort by automatically prioritizing articles as they are reviewed, using user feedback to push the most relevant articles to the top of the list.

Health and Environmental Research Online (HERO)

- Online library and tool that supports risk assessments and other research, backed by a team of trained librarians and specialists

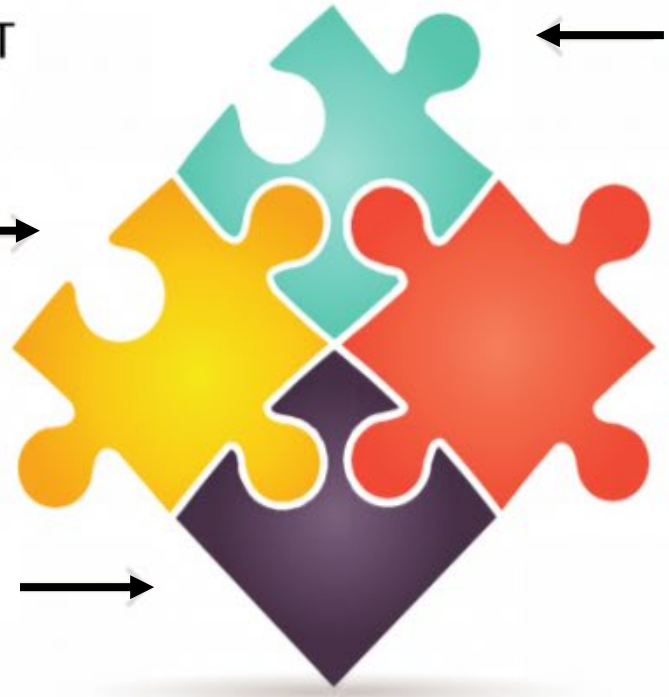
- The HERO database includes more than four million scientific references and associated data from the peer-reviewed literature used by EPA to develop reports that support critical agency decisions

- HERO team works with assessors to develop literature search strategies

- Interoperates with other SR tools

Sciome Workbench for Interactive Computer Facilitated Text Mining (SWIFT Review)

Can be used to screen studies according to the PECO statement



TOPIC MODELING

Uncover hidden structure in your literature corpus

SEARCH REFINEMENT

Discover important terms and phrases

Built-in *and* user-defined search queries allow targeted surveys of the literature corpus

PROBLEM FORMULATION

Identify interesting high impact research questions

LITERATURE PRIORITIZATION

Use machine learning to triage your reading list

Machine learning prioritizes relevant literature, reducing the screening burden by at least 50%

SWIFT REVIEW

Howard et al. Systematic Reviews (2016) 5:87
DOI 10.1186/s13643-016-0263-z

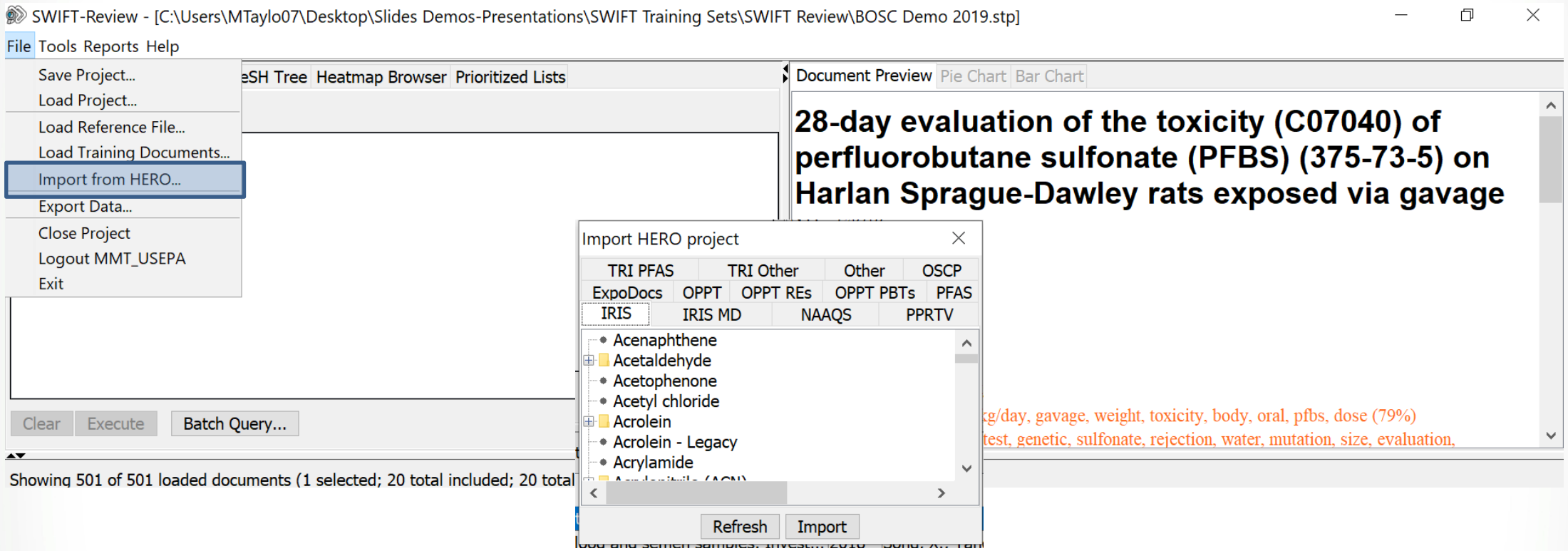
Systematic Reviews

METHODOLOGY Open Access

SWIFT-Review: a text-mining workbench for systematic review

Brian E. Howard[1*], Jason Phillips[1], Kyle Miller[1], Arpit Tandon[1], Deepak Mav[1], Mihir R. Shah[1], Stephanie Holmgren[2], Katherine E. Pelch[3], Vickie Walker[3], Andrew A. Rooney[3], Malcolm Macleod[4], Ruchir R. Shah[1] and Kristina Thayer[3]

SWIFT – HERO Interoperability



Import literature directly from HERO

Merge with existing project

Start a new project

Data Mining and Visualization

SWIFT-Review - [C:\Users\mtaylo07\Desktop\SWIFT Review\NAS Session 3.stp]

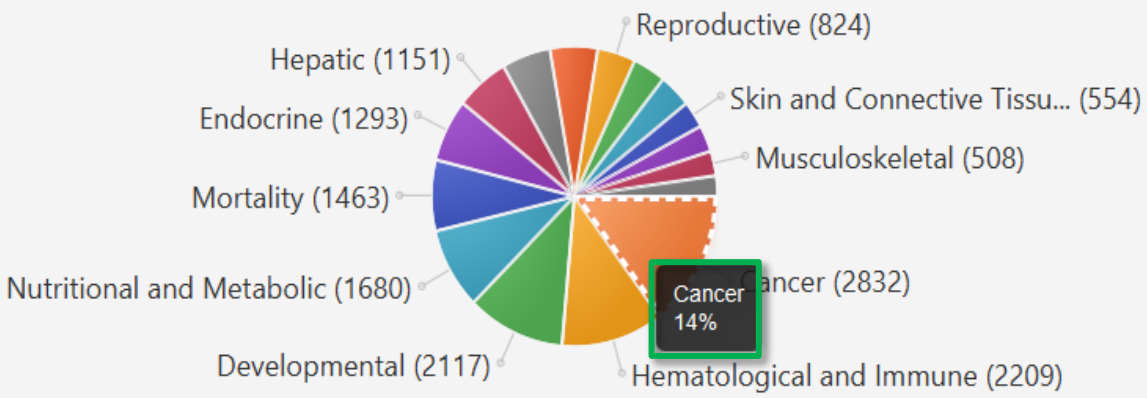
File Tools Reports Help

Tag Browser | Search | Browse MeSH Tree | Heatmap Browser | Prioritized Lists

Health Outcomes

Tag	Code(s)	Count
Cancer		2832
Hematological and Immune		2209
[No Tag]		2130
Developmental		2117
Nutritional and Metabolic		1680
Mortality		1463
Endocrine		1293
Hepatic		1151
Respiratory		1051
Gastrointestinal		1032
Reproductive		824
Renal		713
Neurological		698
Skin and Connective Tissue		554

Document Preview | Pie Chart | Bar Chart



Showing 2832 of 9150 loaded documents (1 selected; 21 total included; 40 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Authors	Journal
0.95	☐	☐	h1021972	Mutagenicity study of carbon tetrachloride and...	1998	Sasaki, T.; Suzuki, M.; Noda, K.; ...	Journal of Toxicological Sciences
0.95	☐	☐	h630464	Advances in research on carcinogenic and gen...	1993	Daniel, F. B.; Meier, , J. R.; Deang...	Annali dell'Istituto superiore di sa...
0.95	☐	☐	h1024901	Cytosine attack by free radicals arising from br...	1993	Castro, G. D.; Castro, J. A.	Teratogenesis, Carcinogenesis, an...
0.95	☑	☑	h1010308	International Commission for Protection Again...	1992	Lohman, P. H. M.; Mendelsohn, M...	Mutation Research: Fundamental a...
0.95	☑	☑	h1024875	International Commission for Protection Again...	1992	Mendelsohn, M. L.; Moore, D. H.; ...	Mutation Research

Downloadable Data - Heatmaps

Choroform 5 Year.xlsx - Excel

	1940-1944	1945-1949	1950-1954	1955-1959	1960-1964	1965-1969	1970-1974	1975-1979	1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2017
Cancer	0	1	1	0	0	1	3	47	36	19	266	230	256	258	231	116
Cardiovascular	0	1	2	0	0	0	0	13	2	0	46	29	60	77	94	34
Developmental	0	0	0	2	1	1	0	24	17	6	252	220	288	322	323	152
Endocrine	0	0	0	0	2	2	9	38	31	6	98	107	145	134	124	61
Gastrointestinal	0	0	0	0	1	2	0	20	4	3	61	60	114	131	172	82
Hematological and Immune	0	0	1	1	3	2	4	34	26	6	156	158	333	368	377	142
Hepatic	0	0	1	2	4	12	13	38	37	13	205	139	145	127	109	46
Mortality	0	2	2	2	1	3	9	36	29	5	244	220	201	203	197	96
Musculoskeletal	0	0	0	0	1	1	0	10	2	0	47	30	65	87	117	45
Neurological	0	0	0	0	0	0	1	19	8	2	83	55	103	116	131	58
Nutritional and Metabolic	0	0	0	0	2	8	11	38	36	5	167	137	273	267	273	117
Ocular and Sensory	0	0	0	0	0	0	2	9	0	2	52	54	86	101	113	41
Renal	0	1	0	3	2	4	4	24	19	8	111	79	104	83	65	33
Reproductive	0	0	0	0	0	0	1	13	7	4	82	56	109	91	111	52
Respiratory	0	0	1	3	3	0	8	28	12	8	151	134	137	155	141	62
Skin and Connective Tissue	0	0	0	0	0	0	0	8	1	0	57	45	70	70	100	34

Semi-Automated Priority Ranking

SWIFT-Review - [C:\Users\mtaylo07\Desktop\SWIFT Review\NAS Session 3.stp]

File Tools Reports Help

Prioritize...
Classify...
Build Topic Model...
Reset Automatic Taggers...
Find Chemical Synonyms...
Options

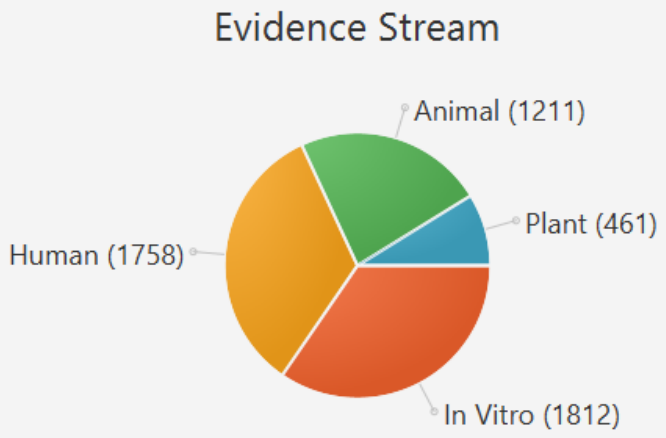
Tree Heatmap Browser Prioritized Lists

Evidence Stream

Tag	Count
In Vitro	1812
Human	1758
Animal	1211
Plant	461

[No Tag]	2130
Developmental	2117
Nutritional and ...	1
Mortality	1
Endocrine	1
Hepatic	1
Respiratory	1051

Document Preview Pie Chart Bar Chart



Seed the model to priority rank

Showing 1758 of 9150 loaded documents (1 selected; 21 total included; 40 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Author	
0.269	☐	☐	h699241	The relationship between multiple myeloma a...	2010	Gold,	
0.261	☐	☐	6759108	Epidemiological evidence of carcinogenicity of ...	1982	Cantor	
0.243	☐	☐	h3719592	Toxic potentials of ten herbs commonly used f...	2015	Abuda	
0.241	☐	☐	h3698164	Application of ultrasound-assisted emulsificati...	2014	Asgha	
0.241	☐	☐	h1292499	Antioxidant, genotoxic and antigenotoxic activi...	2012	Chaab	
0.24	☐	☐	h1068198	Genotoxicity and toxicity assessment in urban ...	2006	Cardozo, T. R.; Rosa, D. P.; Feide...	Mutation Research
0.24	☐	☐	h3698004	The use of endemic Iranian plant, Echium am...	2015	Uysal, H.; Kızılet, H.; Ayar, A.; Ta...	Toxicology and Industrial Health
0.24	☐	☐	11518606	Classification of carcinogenic chemicals in the ...	2001	Greim, H; Reuter, U	Toxicology
0.238	☐	☐	h1024786	In vitro protective effects of Terminalia arjuna ...	2002	Pasquini, R.; Scassellati-Sforzolini,...	Journal of Environmental Patholo...

- **Priority ranking helps triage your literature**
- **Screening burden reduced 50-60%**
- **Direct export to SWIFT Active**

Improved Ranking Model

SWIFT-ACTIVESCREENER

- Web-based, real-time, collaborative
- Reduced screening burden
- Statistical models prioritize articles ***as they are being reviewed***
- Algorithm improves from screener-input without training "seeds" further increasing efficiency
- Tells reviewer when to stop
- Interface provides project status updates
- User-defined screening levels (1-3) using customizable forms

Use of Machine-Learning to Screen

- **Track reviewer conflicts**
- **Machine-learning can decrease the screening burden by 40-60%**

Environment International 138 (2020) 105623

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

SWIFT-Active Screener: Accelerated document screening through active learning and integrated recall estimation

Brian E. Howard[a,*], Jason Phillips[a], Arpit Tandon[a], Adyasha Maharana[a], Rebecca Elmore[a], Deepak Mav[a], Alex Sedykh[a], Kristina Thayer[c], B. Alex Merrick[b], Vickie Walker[b], Andrew Rooney[b], Ruchir R. Shah[a]

[a] Sciome LLC, 2 Davis Drive Durham, NC 27709, USA
[b] National Toxicology Program (NTP)/National Institute of Environmental Health Sciences (NIEHS), 111 T.W. Alexander Drive RTP, NC 27709, USA
[c] Integrated Risk Information System (IRIS) Division, Environmental Protection Agency, 109 T.W. Alexander Drive RTP, NC 27709, USA

3572056: Nrf2 Signaling Elicits a Neuroprotective Role Against PFOS-mediated Oxidative Damage and Apoptosis

Sun, P., Nie, X., Chen, X.; Neurochemical Research; Pg2446-2459; 2018

Perfluorooctanesulfonate (PFOS) may cause neurotoxicity through the initiation of oxidative stress. In the current study, we investigated the role of anti-oxidant nuclear factor erythroid 2-related factor 2 (Nrf2) pathway in PFOS-induced neurotoxicity. We found that human neuroblastoma SH-SY5Y cells exhibited significant apoptotic cell death following PFOS exposure, and this process was accompanied with apparent accumulation of reactive oxidative species (ROS). In addition, we revealed that PFOS exposure caused marked activation of Nrf2 pathway and the expression of Nrf2 transcription target heme oxygenase-1. We further found that pre-treatment with ROS scavenger N-acetyl-L-cysteine (NAC) dramatically ameliorated PFOS-induced ROS production and Nrf2 signaling. In keeping with these findings, western blot and Cell Counter Kit-8 analyses revealed that pre-incubation with NAC suppressed PFOS-induced expression of pro-apoptotic proteins and impairment of neuronal viability. Moreover, antagonizing Nrf2 pathway with Nrf2 inhibitor brusatol resulted in increased ROS production and enhanced PFOS-induced expression of apoptosis related proteins. Finally, we showed that PFOS exposure altered mitochondrial transmembrane potential and disrupted normal mitochondrial morphology in SH-SY5Y cells. Whereas treatment with NAC ameliorated PFOS-induced mitochondrial disorders, co-incubation with brusatol augmented PFOS-induced mitochondrial deficits, consequently contributing to neuronal apoptosis. These results manifest that Nrf2 pathway plays a protective role in PFOS-induced neurotoxicity, providing new insights into the prevention and treatment of PFOS-related toxicities.

Include/Exclude Question

Include this reference? *

- Yes, include the reference (it's PECO or supplemental material)
- No, exclude the reference

Main

Supplemental Material Tags

what type of supplemental content

- in vitro/ex vivo/in silico studies
- Non-mammalian model systems
- Non-oral or non-inhalation route of administration
- ADME and toxicokinetic
- Exposure characteristics (no health outcome assessment)
- Mixture studies (only use for experimental studies)

Save and Next

Instructions

P

Human: Any population and lifestage (occupational or general population, including children and other sensitive populations).

Animal: Nonhuman mammalian animal species (whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).

Screener note: Mechanistic information including in-vitro assays will be tagged as supplemental material

E

Relevant forms:

All PFAS chemicals. Many common names and synonyms should appear as keyword green highlighting, but also include no abstract studies where the title mentions PFAS (or other words such as perfluorinated) but does not mention specific chemicals.

Human: Any exposure to PFAS via the oral and inhalation routes. Studies will also be included if biomarkers of PFAS exposure are evaluated (e.g. measured PFAS in tissues or bodily fluids) but the exposure route is unclear or reflects multiple routes. Other exposure routes, including dermal will be tracked during title and abstract screening and tagged as "potentially relevant supplemental information."

Animal: Any exposure to PFAS (including mixtures containing PFAS) via the oral and inhalation routes. Studies involving exposures to mixtures will be included only if they include an arm with exposure to a PFAS alone. Other exposure routes, including dermal or injection, will be tracked during title and abstract screening and tagged as "potentially relevant supplemental information."

C

Reviewer Input Updates the Model

SWIFT ActiveScreener | Chloroform | MMT_USEPA

Screening References

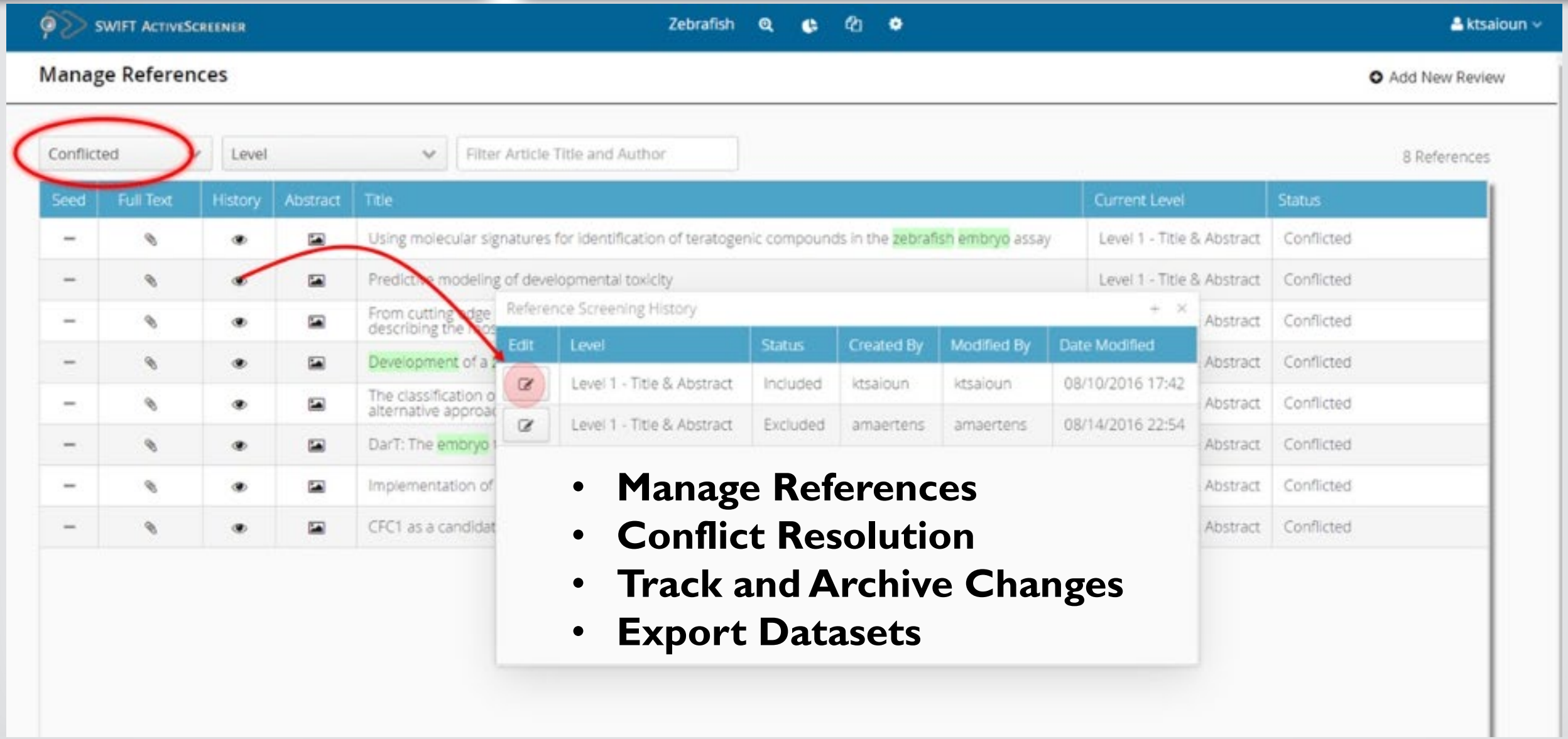
Add New Review

0.3%

Level 1 - Title & Abstract

Include	Exclude	Detailed Screen	ID	Title
			1619902	Hepatotoxicity and lethality of halomethanes in Mongolian gerbils pretreated with chlordecone, phenobarbital or mirex
			1619890	Central nervous effect and blood level regressions on exposure time paralleled in solvents (toluene, carbon tetrachloride and chloroform)
			1619889	DNA damage as a consequence of chloroform-induced cytotoxicity in male F344 rat and B6C3F1 mouse hepatocytes in vitro
			1619865	Suppression of pulmonary host defenses and enhanced susceptibility to respiratory bacterial infection in mice following inhalation exposure to trichloroethylene and chloroform
			1619857	Carcinoembryonic antigen, alpha-fetoprotein, and prostate-specific antigen in the sera of industrial workers exposed to phenol, formaldehyde, urea, and mixed vapors
			1619856	Ranking of chemicals for carcinogenic potecya comparative study of 13 carcinogenic chemicals and an examination of some of the issues involved
			1619852	Metabolism of haloforms to carbon monoxide: II in vivo studies
			1619846	A painless burn: systemic toxicity after dermal exposure to chloroform
			1619844	U.S. Environmental Protection Agency's revised cancer guidelines for carcinogen risk assessment

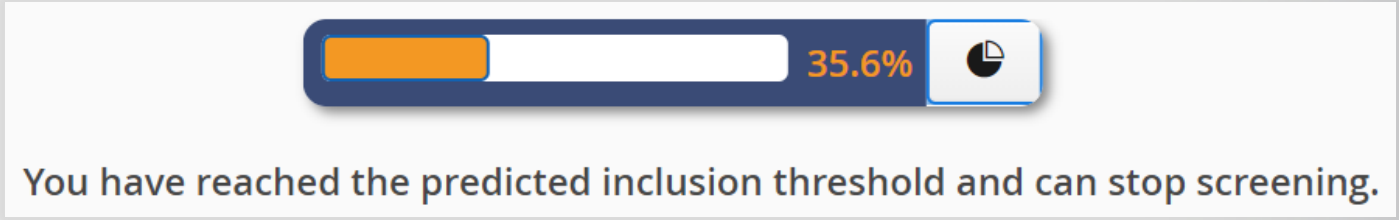
Increased Efficiency and Transparency



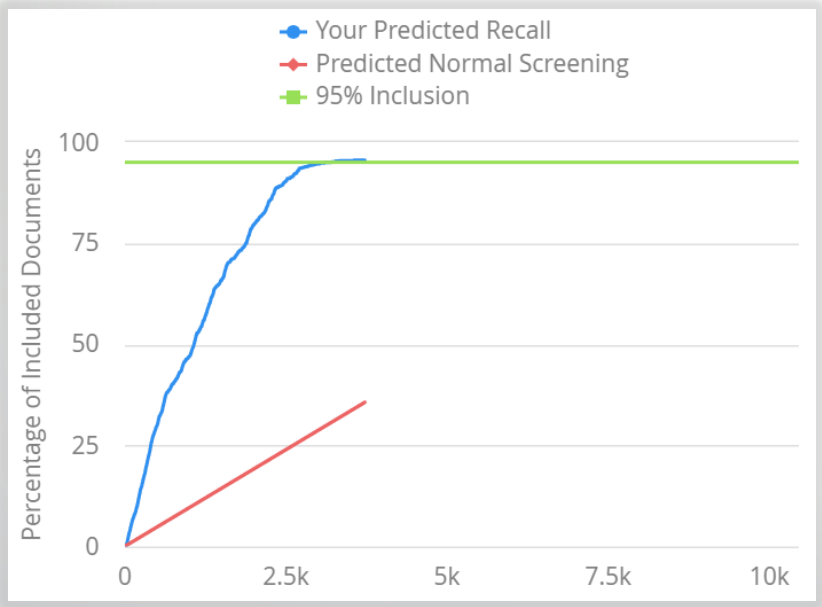
- **Manage References**
- **Conflict Resolution**
- **Track and Archive Changes**
- **Export Datasets**

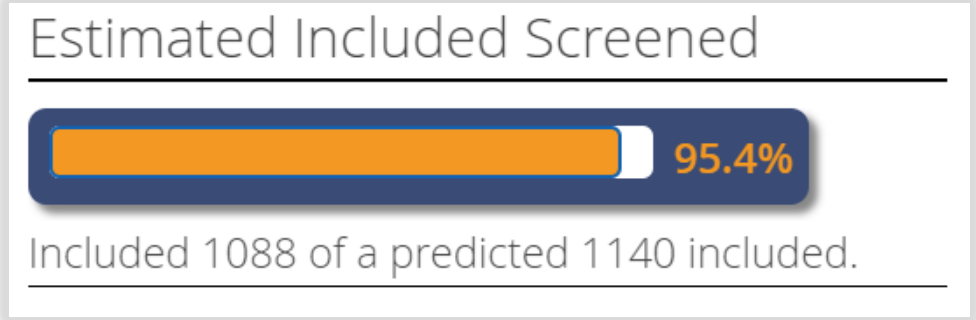
SWIFT-Active Screener Metrics

- **Total screened by humans = 35.6% (3,725 out of 10,458)**
  - **1,088 includes + 2637 excludes**



- **1,088 includes represented 95.4% of the predicted 1,140 includes**





Review of grey literature resources, reference list of included studies, references cited in other assessments, and public comment mitigate concern for missing "key" studies

SWIFT-Active Screener Metrics

Start Date:	10/2/2019
End Date:	10/16/2019
Duration:	10 workdays
Number of screeners:	20

	Included Reference	Excluded Reference	All References
Screening Time per Abstract			
Average (seconds)	73.8	69.9	71.8
Min (seconds)	0	26.5	0
Max (seconds)	141.0	148.7	148.7
Total Screening Time (hours)	32.5	60.9	93.4
Average screening time per screener (hours)	1.6	3.0	4.7

Export PECO-relevant to Distiller for full-text screening or compiling literature inventory

Evidence Partners – Distiller SR

- Customizable forms to capture information:
  - Literature screening
  - Study evaluation
  - Literature inventories
  - Data extraction
- Project status management (QC, audit logs, conflict resolution)
- Interoperable with other tools
  - Import with HERO tags
  - Link to HERO PDFs
  - Export reports to HAWC, Tableau

Web-Based Forms for Literature Inventory

Submit All

Animal Literature Inventory

1. **FORM STATUS**

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

Select an Answer

2. **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).

3. **ANIMAL SPECIES**

Enter details on the animal species, strain and sex below. If multiple species and/or sexes are evaluated seperately, create new lines as needed.

Add | Edit | Delete | Clone | New Row — Search:

Animal Species Name	Species	Strain	Sex
No data available in table			

Showing 0 to 0 of 0 entries

4. **ANIMAL EXPOSURE**

Enter details on the study design and chemical exposure below. If multiple study designs were evaluated, create new lines as needed.

Add | Edit | Delete | Clone | New Row — Search:

Animal Exposure Name	Chemical Form	Study Design	Route	Dose Levels	Dose Units	Dose Duration
No data available in table						

Showing 0 to 0 of 0 entries

5. **HEALTH OUTCOMES**

Enter details on the health outcomes evaluated below. If multiple health outcomes were evaluated, create new lines as needed.

Add | Edit | Delete | Clone | New Row — Search:

Health Outcome Name	Health Outcome System	Evaluated Endpoints
No data available in table		

Showing 0 to 0 of 0 entries

6. **ANIMAL DATA EXTRACTION**

Combine data from the subforms above and extract the NOEL/LOAEL. Use as many lines as needed.

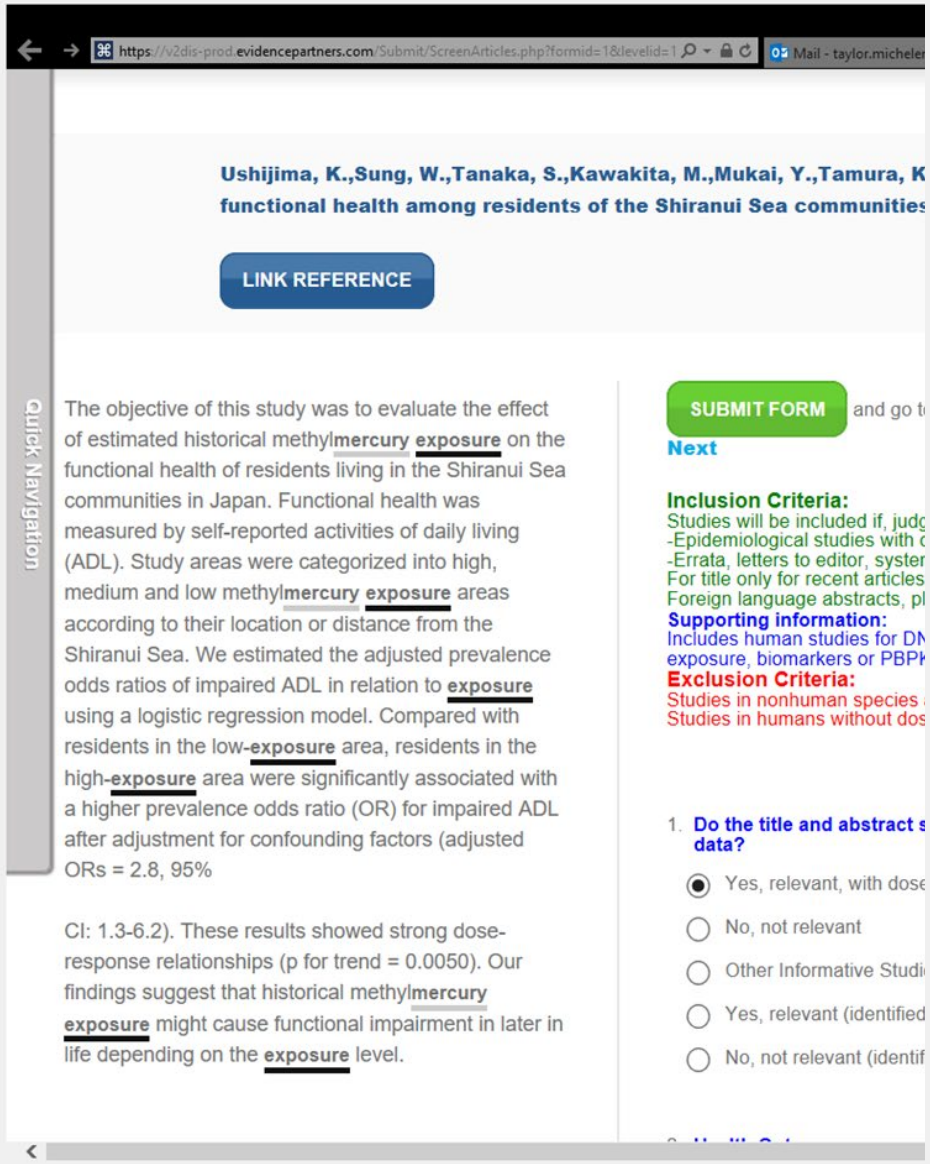
Add | Edit | Delete | Clone | New Row — Search:

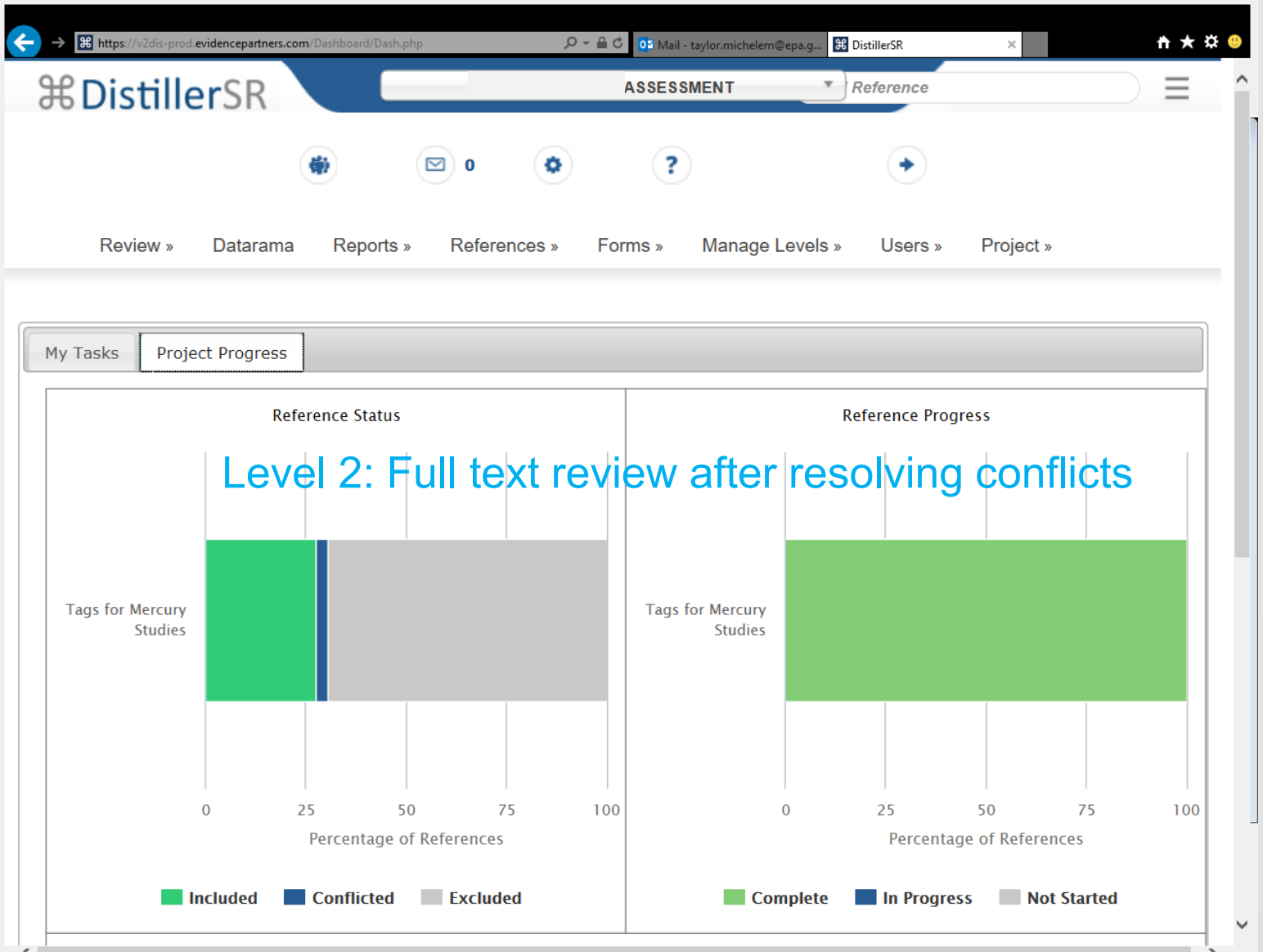
Animal Species	Animal Exposure	Health Outcome	Health Effect Findings	NOEL/NOEC Dose Level	LOEL/LOEC Dose Level	Description of Effect	Extract Study?	Extraction Location	Extraction Explanation	Comments
No data available in table										

Showing 0 to 0 of 0 entries

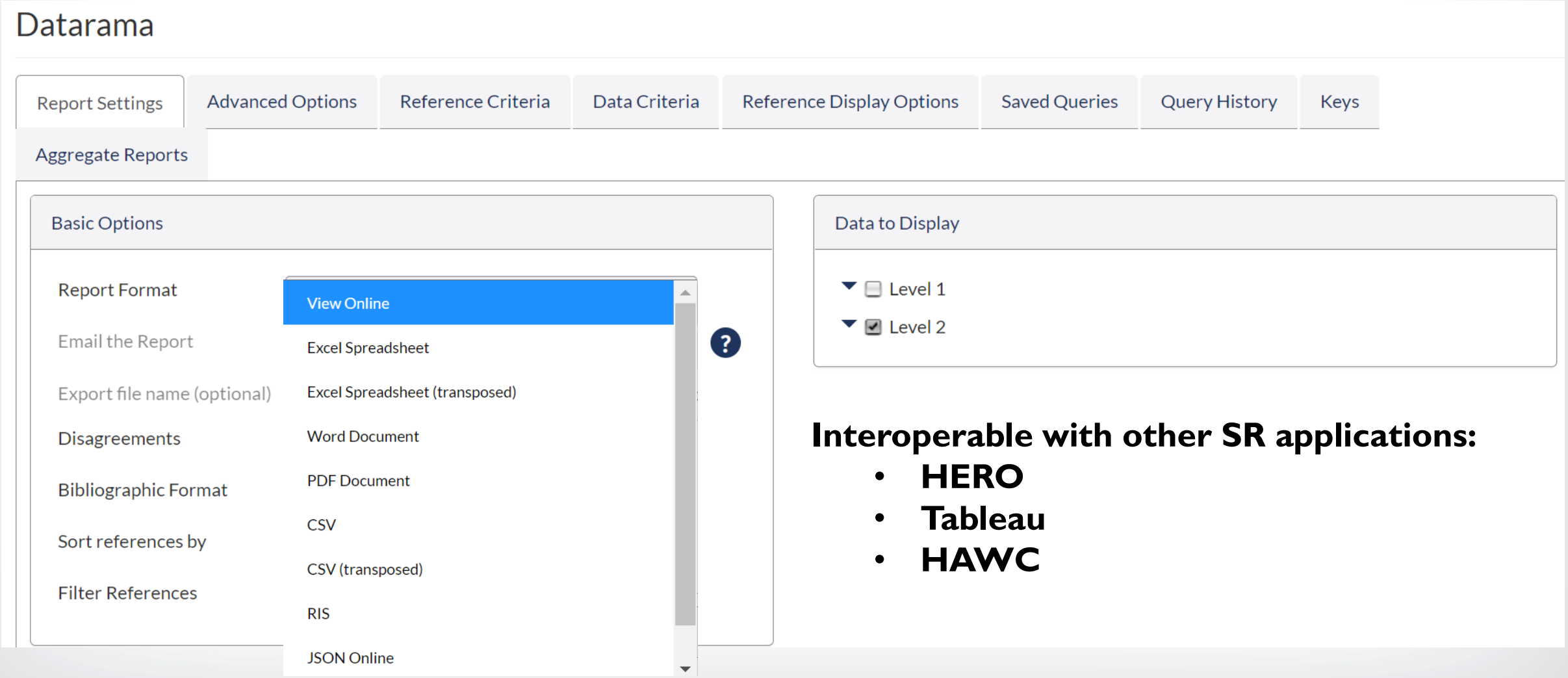
- **Customizable forms to compile and screen relevant study information**
- **High levelAnimal species, exposure, health outcomes**
- **Export to visualization tools (Tableau)**

Full Text Screening





Download Data in Multiple Formats



Interoperable with other SR applications:

- **HERO**
- **Tableau**
- **HAWC**

Health Assessment Workspace Collaborative (HAWC)

- Free and open source
- Fit for purpose content management
- Animal bioassay, epidemiological, and in vitro structured data extraction and visualization
- Interactive “click to see more” graphics
- Study evaluation
- Literature trees
- Modular and interoperable with other tools
- Can be made publicly available

Study Evaluation Process & Resources

Exposure Assessment

Characterization of the exposure to the compound of interest

Reviewer 1

++

Good

The inhalation chambers are well described and include dynamic airflow conditions. Atmosphere of exposure chamber was generated by metering chloroform at known rate with precision syringe pump into vaporization flask and then drawn into the airstream being drawn into exposure chamber. Concentration of chloroform was measured continuously during each day of exposure period. Time weighted analytical concentrations are reported for each group and are very close to the nominal targeted concentration of 100 ppm (avg 97-99 ppm)..

Reviewer 2

+

Adequate

Adequate: Source was reported, but purity of the test compound was not described. Levels of the test compound was monitored: "The concentration of chloroform in the chamber was monitored continuously by infrared spectrophotometry each day during the exposure period."

Final Reviewer

+ Create new override

Score

Adequate

+

Bias direction

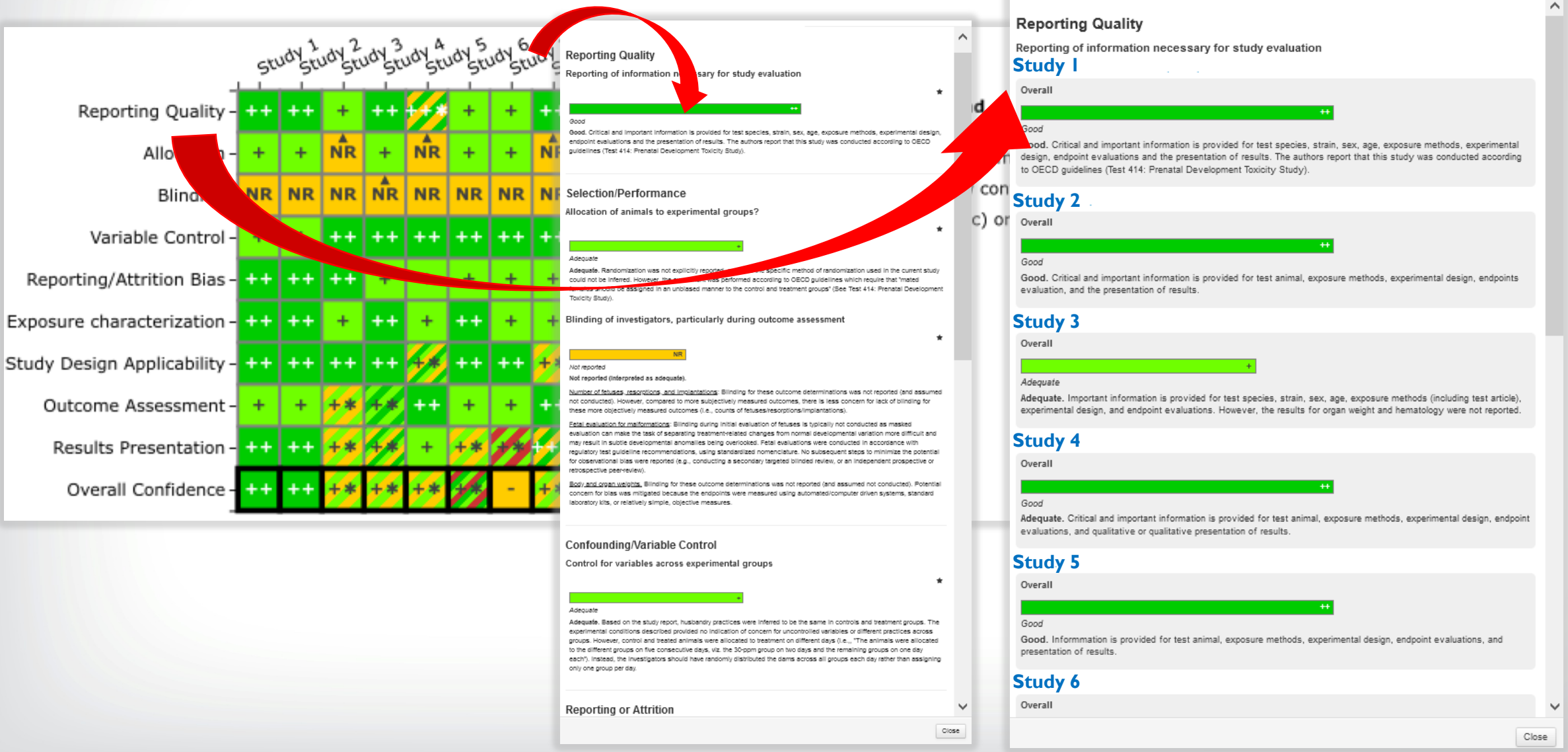
? (Unknown/not specified)

Normal B I U

Adequate. Test compound source was reported, but purity was not provided. Levels of the test compound in the inhalation chamber were monitored. The authors reported, "The concentration of chloroform in the chamber was monitored continuously by infrared spectrophotometry each day during the exposure period." Time-weighted analytical concentrations were very close to the nominal targeted concentration of 100 ppm (i.e., avg 97-99 ppm).

Study Evaluation Tips - Histopathology v20190130	Study Evaluation tips - histopathology endpoints. Drafted by GTIC Workgroup. January 30, 2019 version	Edit Delete
Study Evaluation Tips - Clinical Chemistry v20190130	Study evaluation tips - clinical chemistry endpoints. Drafted by GTIC Workgroup. January 30, 2019 version	Edit Delete
Example answers to the animal study evaluation domains		Edit Delete

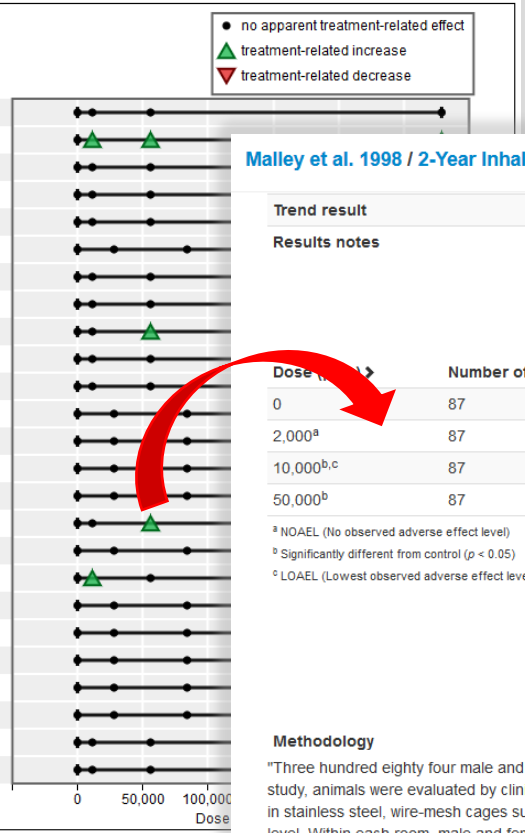
Study Evaluation Interactive Visuals



HAWC: Data Extraction Visual

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)

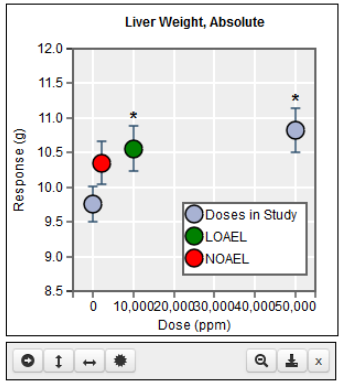


Malley et al. 1998 / 2-Year Inhalation Study in Rats / Female Crl:CD BR Rat / Liver Weight, Absolute

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 (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
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

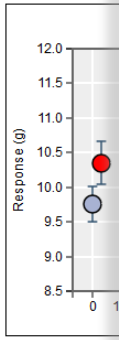
Dose-Response Analysis

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
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, study, animals were evaluated by clinical observations and body weight determinations during a 3-week quarantine period. in stainless steel, wire-mesh cages suspended above cage boards. Rats were housed in four laminar flow animal rooms wi level. Within each room, male and female rats were housed on separate cage racks. A system of rotation was employed to week and to reposition the cages on the rack every two weeks. Animal rooms were targeted at a temperature of 23+/- 2°C were artificially illuminated (fluorescent light) on a 12-hour light/dark cycle. Throughout the test period, except during expos were supplied with a feeder filled daily with approximately 50 or 70g of irradiated Purina Rodent Chow #5056 (chunk), resp sacrifice, the amount of chow was adjusted according to the number of animals remaining in a cage. Rats were allowed fre

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

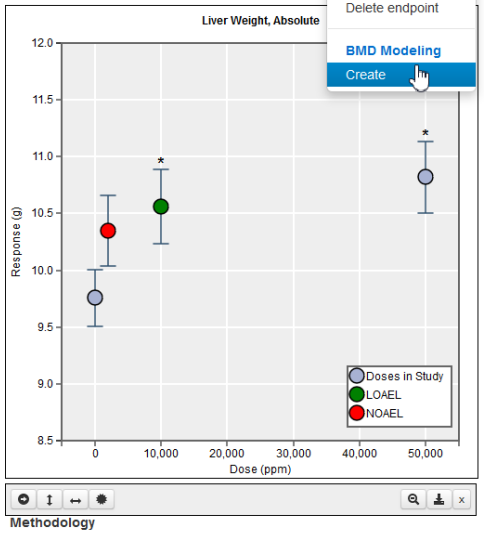
Actions

- 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

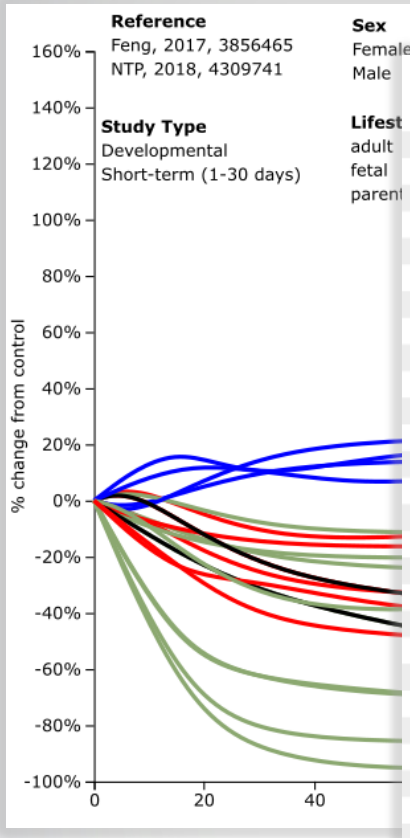
Plot



Methodology

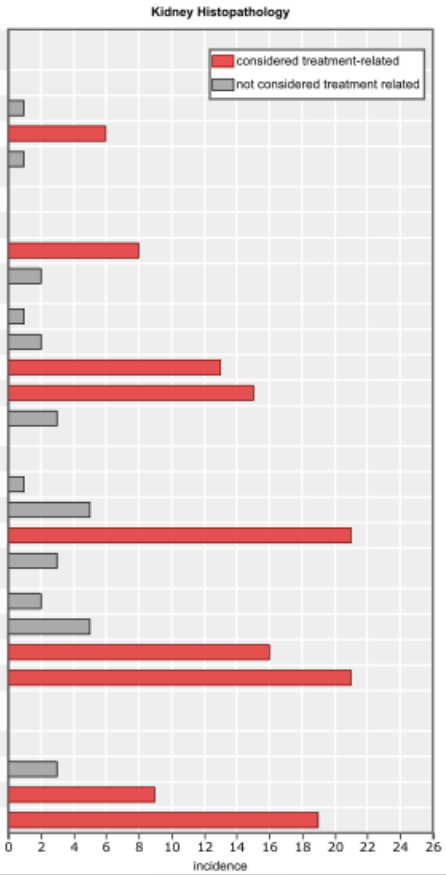
"Three hundred eighty four male and 384 female weanling Crl:CD BR rats were received from Charles River Laboratories, Inc., Portage, Michigan. Prior to being

Looking at Patterns Across Studies



Study	Confidence	Route	Study Design	Animal Description	Units	Dose (mg/kg-day)
NTP, 2018, 4309741	|high confidence|	oral gavage	28 days	Rat, Harlan Sprague-Dawley (♀, N=1-10)	ng/dL	0
						62.6
Feng, 2017, 3856465	|high confidence|	oral gavage	GD1			

Study	Confidence	Study Design	Route	Description	Endpoint	Dose (mg/kg-day)	Incidence
Lieder, 2009, 1578546	|high confidence|	subchronic (90 days)	oral gavage	Rat, Crl:Cd@(Sd)Igs Br Vaf/Plustm (♀, N=10)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	0	0/10 (0.0%)
						60	0/10 (0.0%)
						200	1/10 (10.0%)
						600	6/10 (60.0%)
				Rat, Crl:Cd@(Sd)Igs Br Vaf/Plustm (♂, N=10)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	0	1/10 (10.0%)
						60	0/10 (0.0%)
						200	0/10 (0.0%)
						600	8/10 (80.0%)
Lieder, 2009, 1578545	|high confidence|	reproductive	oral gavage	F1 Rat, Sprague-Dawley (♀, N=30)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	0	2/30 (6.7%)
						30	1/30 (3.3%)
						100	2/30 (6.7%)
						300	13/30 (43.3%)
						1,000	15/30 (50.0%)
				F1 Rat, Sprague–Dawley (♂, N=30)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	0	3/30 (10.0%)
						30	0/30 (0.0%)
						100	1/30 (3.3%)
						300	5/30 (16.7%)
						1,000	21/30 (70.0%)
				P0 Rat, Sprague-Dawley (♀, N=30)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	0	3/30 (10.0%)
						30	2/30 (6.7%)
						100	5/30 (16.7%)
						300	16/30 (53.3%)
						1,000	21/30 (70.0%)
				P0 Rat, Sprague-Dawley (♂, N=30)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	0	0/30 (0.0%)
						30	0/30 (0.0%)
						100	3/30 (10.0%)
						300	9/30 (30.0%)
						1,000	19/30 (63.3%)



Harmonize Terms Increase Interoperability

Update Alanine Aminotransferase (ALT), Blood

Update an existing endpoint. The Environmental Health Vocabulary (EHV) is enabled for this assessment. Browse to view controlled terms, and whenever possible please use these terms.

Endpoint/Adverse outcome*

Alanine Aminotransferase (ALT), Blood

☐ Use controlled vocabulary

Short-text used to describe the data in this form. Please use a controlled vocabulary term if possible and if enabled for your assessment. A separate field, "Endpoint Name in Study", captures the name of endpoint as reported. If no preferred term matches the data extracted, type in the desired description. Do not add units — units are summarized in a separate extraction field. If the endpoint is a repeated measure, indicate the time in parentheses, e.g., running wheel activity (6 wk), using the abbreviated format: seconds = sec, minutes = min, hours = h, days = d, weeks = wk, months = mon, years = y.

System

Hepatic

Selected term: 888 | Hepatic

☑ Use controlled vocabulary

The affected biological system. Please use a controlled vocabulary term if possible and if enabled for your assessment. Multi-system and Whole Body are options for wide-spread effects. If the Endpoint is measured in Blood, Urine or biological media other than the affected system, it should be captured in the Effect Subtype field.

Organ/Tissue/Region

Liver

Selected term: 889 | Liver

☑ Use controlled vocabulary

Please use a controlled vocabulary term if possible and if enabled for your assessment. Tissue should be used for same tissues affected in multiple organs/regions (e.g., epithelial, mesothelium). Region (e.g., head, abdomen, limb) are common for developmental endpoints. Multi-organ and Whole Body are options for wide-spread effects.

Effect

Enzyme Activity

Selected term: 969 | Enzyme Activity

☑ Use controlled vocabulary

Please use a controlled vocabulary term if possible and if enabled for your assessment (eg., Malformation, Neoplastic [Non-Neoplastic] Lesions, Organ Weight, Abnormal Appearance).

Effect subtype

Clinical Chemistry

Selected term: 970 | Clinical Chemistry

☑ Use controlled vocabulary

The method used for the measuring the Effect (e.g., Histopathology, Clinical Observation, Clinical Chemistry, Hematology). For Developmental Malformation effects, values may be Skeletal Structural Abnormality, Skeletal Ossification Abnormality, External Abnormality, or Visceral Abnormality. For Organ Weights, may be Absolute or Relative (absolute can be inferred when it's not explicitly stated). When a determination cannot be made, use [Null] or leave empty.

Additional tags

+

Any additional descriptive-tags used to categorize the outcome

Endpoint Name in Study

ALT

List the endpoint/adverse outcome name as used in the study. This will help during QA/QC of the extraction to the original study in cases where the endpoint/adverse outcome name is adjusted for consistency across studies or assessments.

- **Research to develop and harmonize terminologies and ontologies**
- **Research to develop/refine artificial intelligence algorithms to extract information from full-text**
- **Work closely with ECOTOX Knowledgebase**

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

Download Data Sets

Home / PFAS 150 (2020) / Downloads /

SELECTED ASSESSMENT x

PFAS 150 (2020)

AVAILABLE MODULES

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

DOWNLOADS

- Download datasets

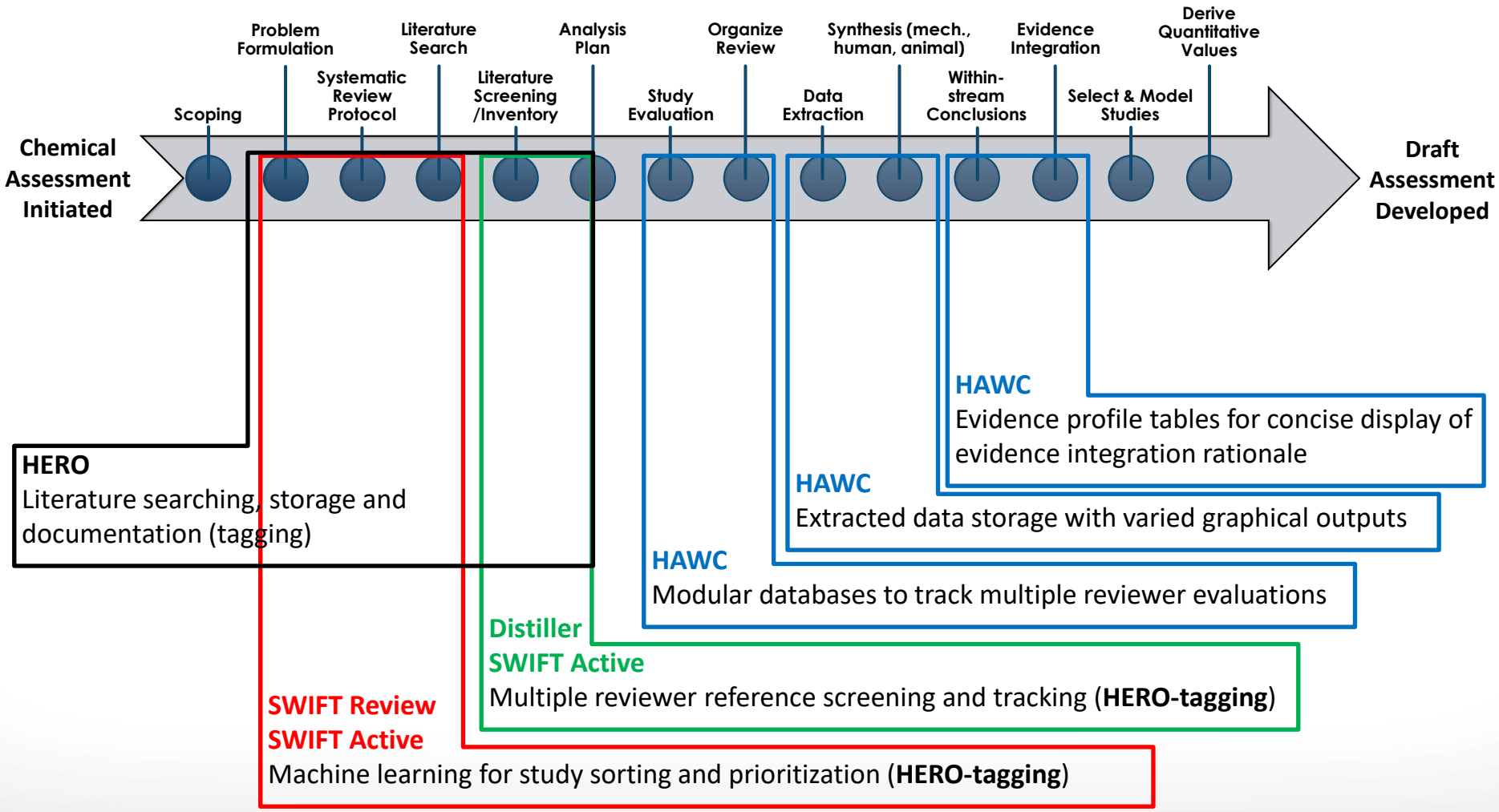
PFAS 150 (2020) downloads

All data from HAWC are exportable into Excel. Developer exports in JSON format are also available (please contact us for more information).

- **Literature-review**
  Download
  Microsoft Excel spreadsheet
- **Study evaluation report**
  Download
  (no individual reviews)
  Download complete
  (includes individual reviews - team-members and higher only)
  Microsoft Excel spreadsheet
- **Animal bioassay data**
  Complete export | Endpoint summary
  Microsoft Excel spreadsheet

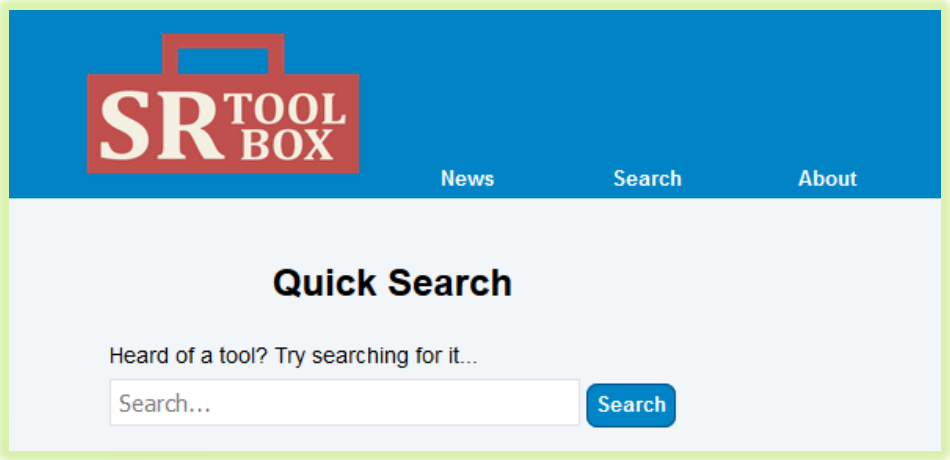
- **Entire database for an assessment**
- **Study evaluation report**
- **BMD results**
- **Visualizations**

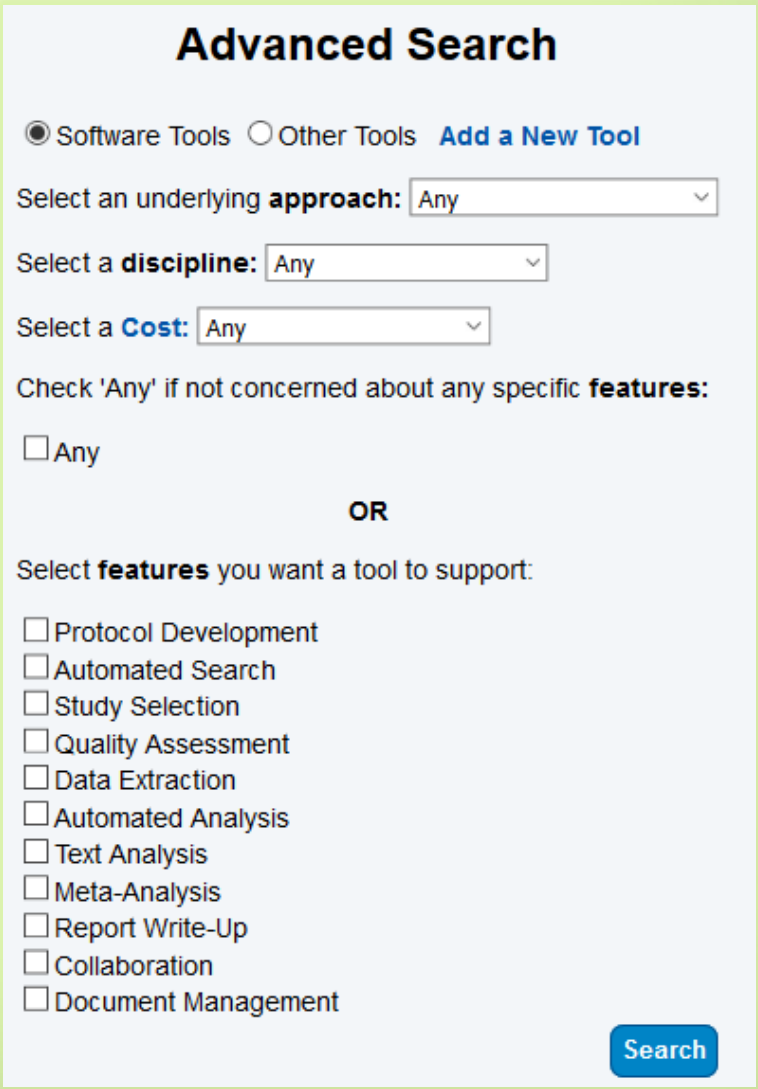
Tools Supporting the SR Workflow



Specialized Software Tools

- Rapidly-growing field
- Machine-learning methods for screening (fairly mature)
- Topic modeling for clustering (fairly mature)
- Electronic extraction from full-text (developing rapidly)
- Text analytics for automated evidence mapping (in development)





http://systematicreviewtools.com/

United States Environmental Protection Agency

QUESTIONS??