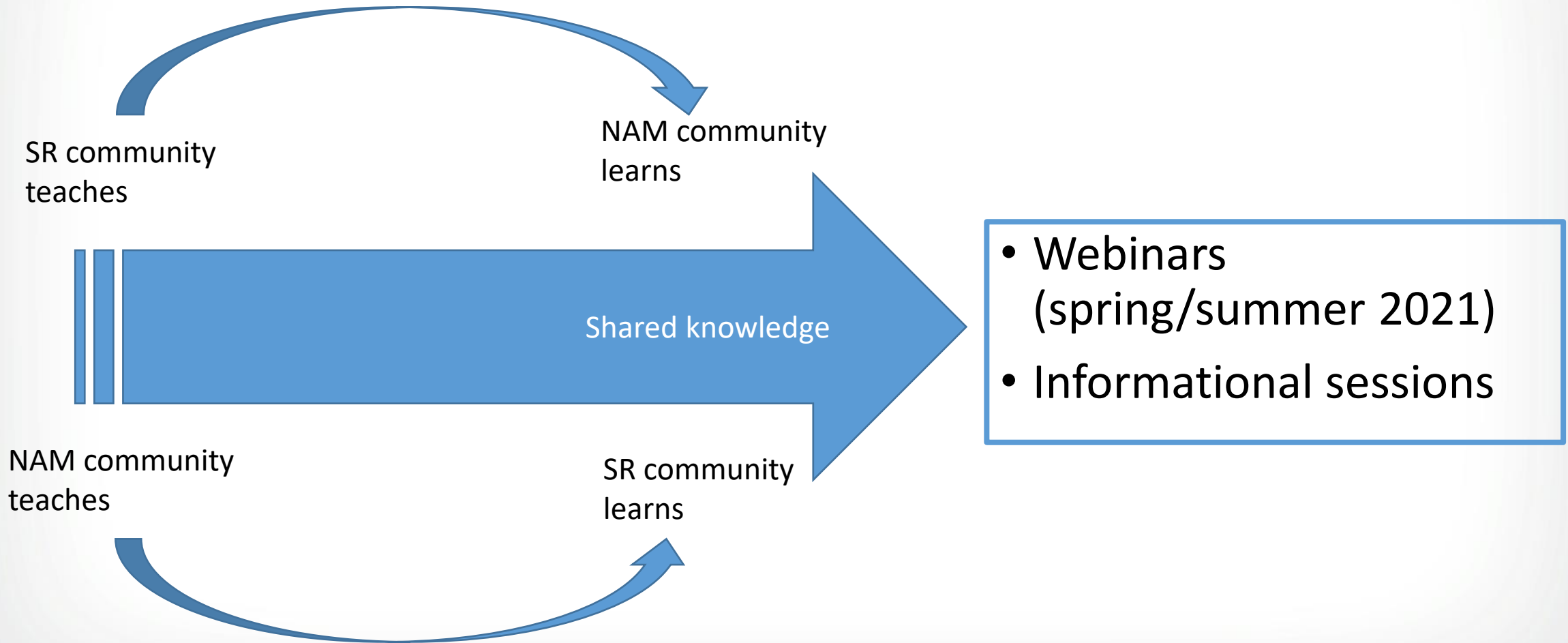


Introduction to Systematic Review in the Context of Environmental Health Assessments

EPA NAM and SR CoPs

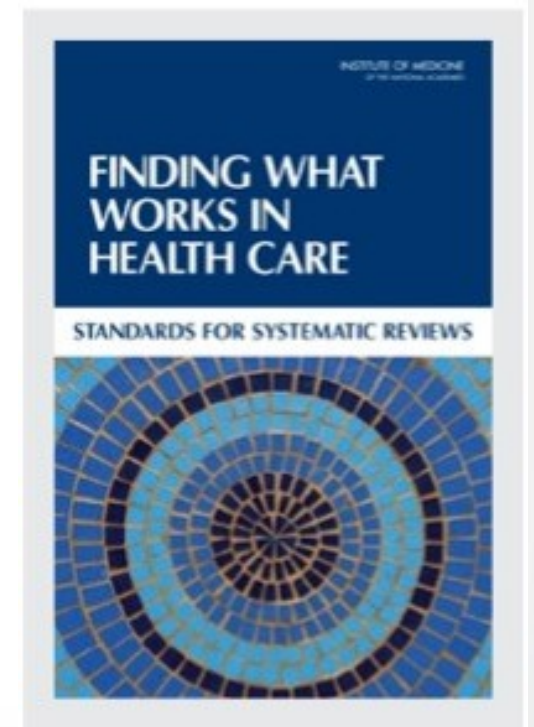
May 27, 2021



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 PERSPECTIVE

“Reviews must utilize systematic review methodologies...EHP does not publish narrative reviews...”

Reviews
Reviews present, contrast, and (when appropriate) synthesize studies to address a specific question or issue related to environmental health. Reviews must utilize systematic review methodologies to identify, appraise, and synthesize 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.

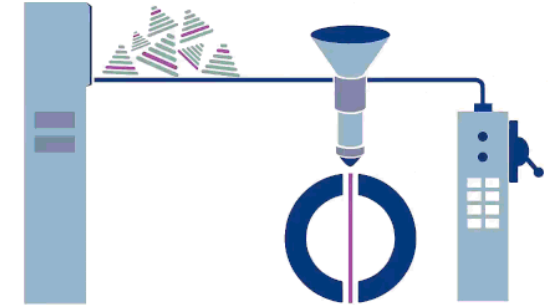
Note: For full systematic reviews, authors are expected to conform to appropriate guidelines, such as [PRISMA](#) (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

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.cochrane.org/>



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

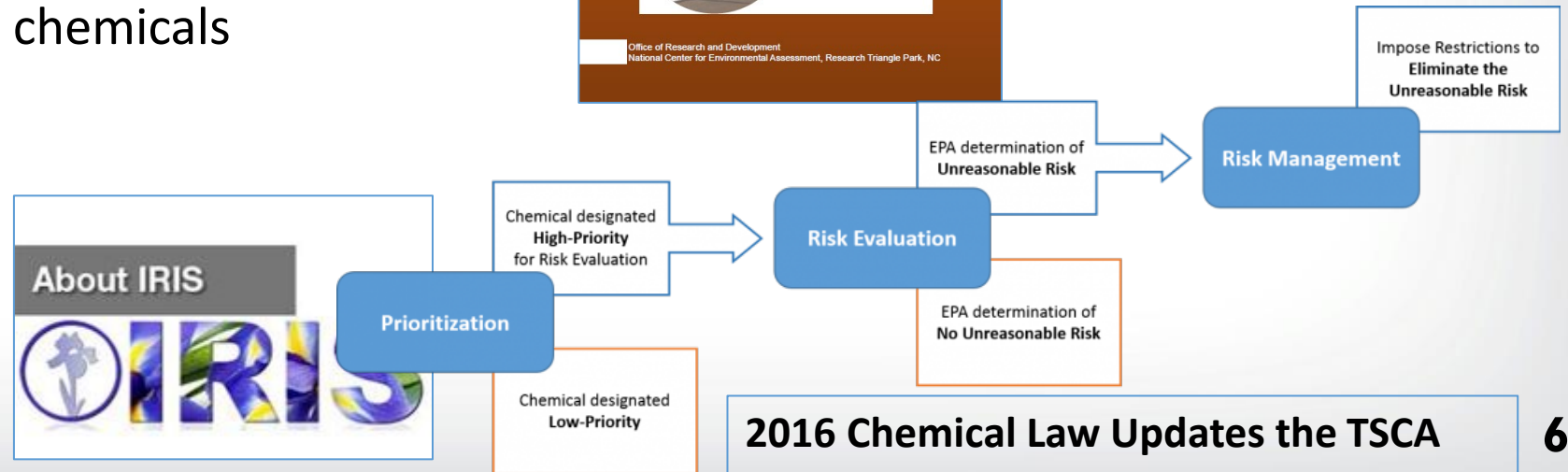
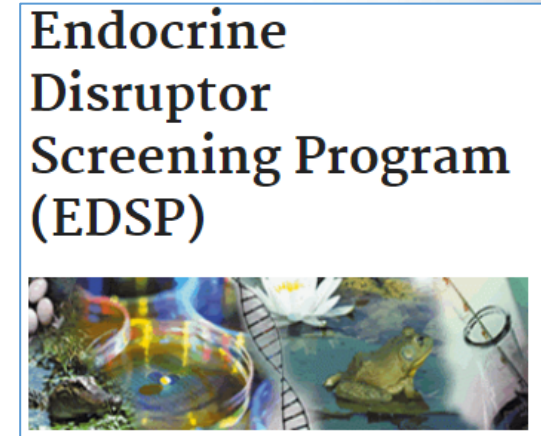
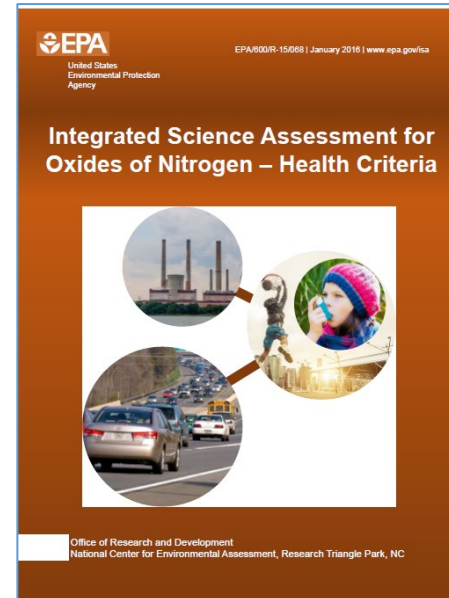


<http://www.environmentalevidence.org/>



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





SR 101 Webinar Agenda

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

- **Evidence appraisal**
- **Evidence integration**



Acknowledgements



Xabier Arzuaga
EPA/ORD/CPHEA



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EPA/ORD/CCTE



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EPA/ORD/CPHEA



Grace Kaupas
EPA/ORD/CPHEA



Lucina Lizarraga
EPA/ORD/CPHEA



Kristan Markey
EPA/OCSP/OPP

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

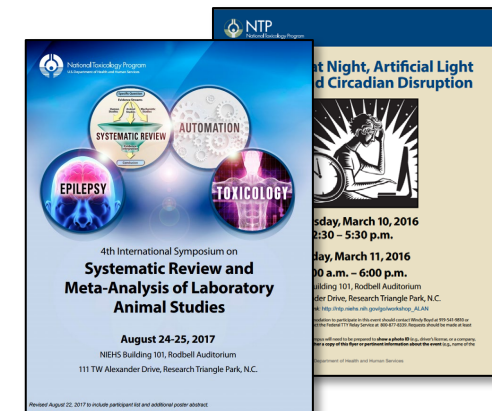
NTP Monographs



NTP Reports



Workshops



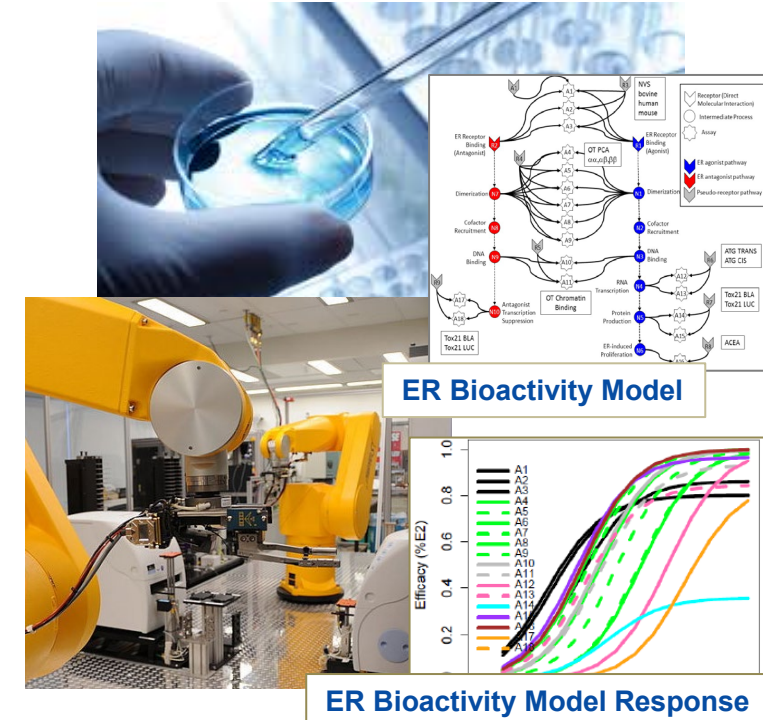


Human Health Assessments and Environmental Health

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

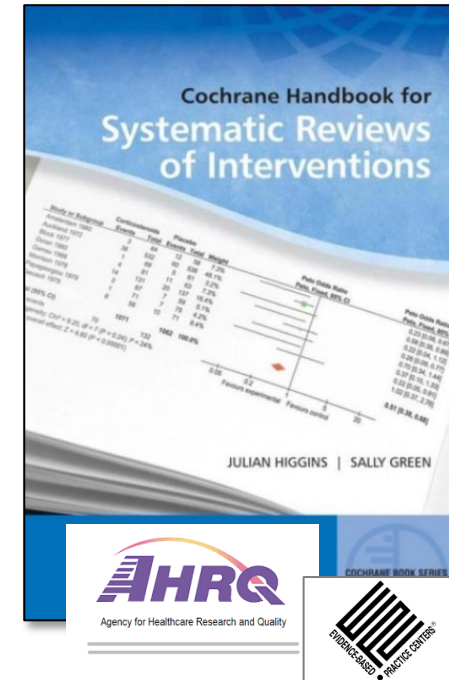




What is Systematic Review and Why Use It?

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

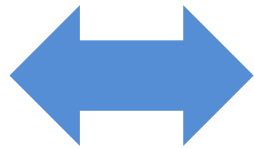


Systematic Reviews in Environmental Health

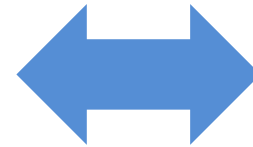
- Published SR Frameworks or Methods in Envir./Public Health ... **in last 5 years**
 - UCSF Navigation Guide
 - US NTP (ORoC and OHAT)
 - US EPA (IRIS Handbook)
 - Evidence Based Toxicology Collaboration
 - European Food Safety Authority
 - International Agency for Research on Cancer



Human Data



Experimental Animal Data



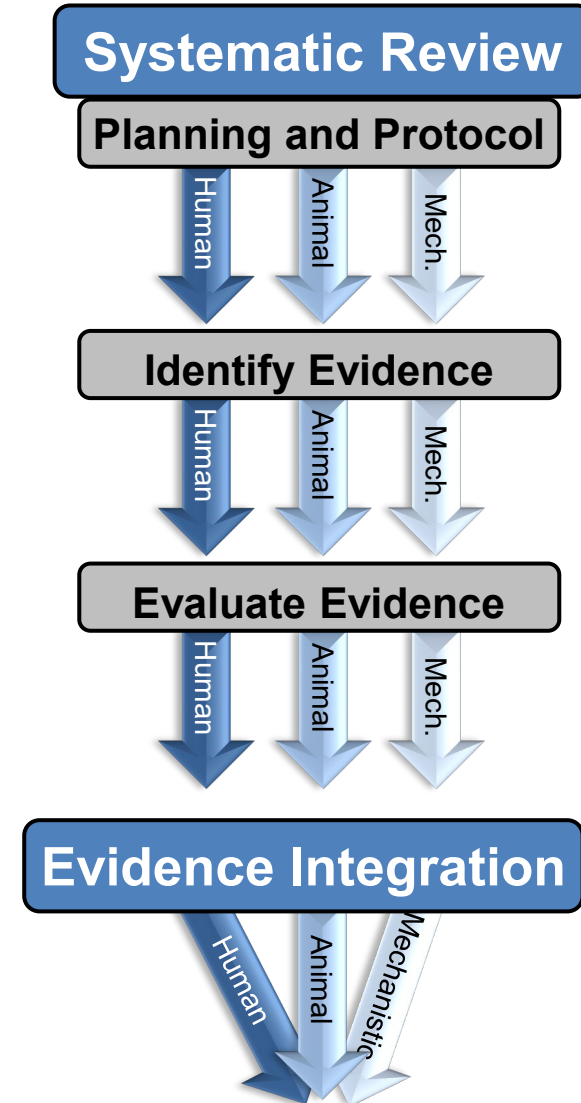
Mechanistic Data



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:

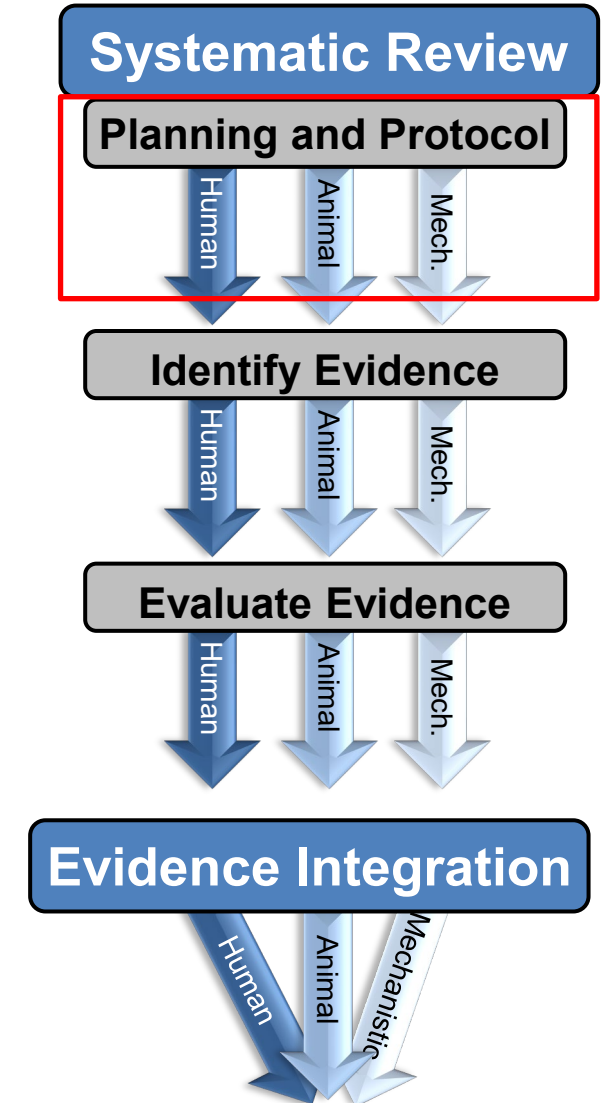
- Purpose
- Scope
- Depth of analysis
- Approach
- Available resources
- Feasibility

• Scoping

- Define problem, rationale, objective(s)
- Understand the literature
- Analyses
- Context

• Framing

- Define research question(s)
- Define literature search strategy





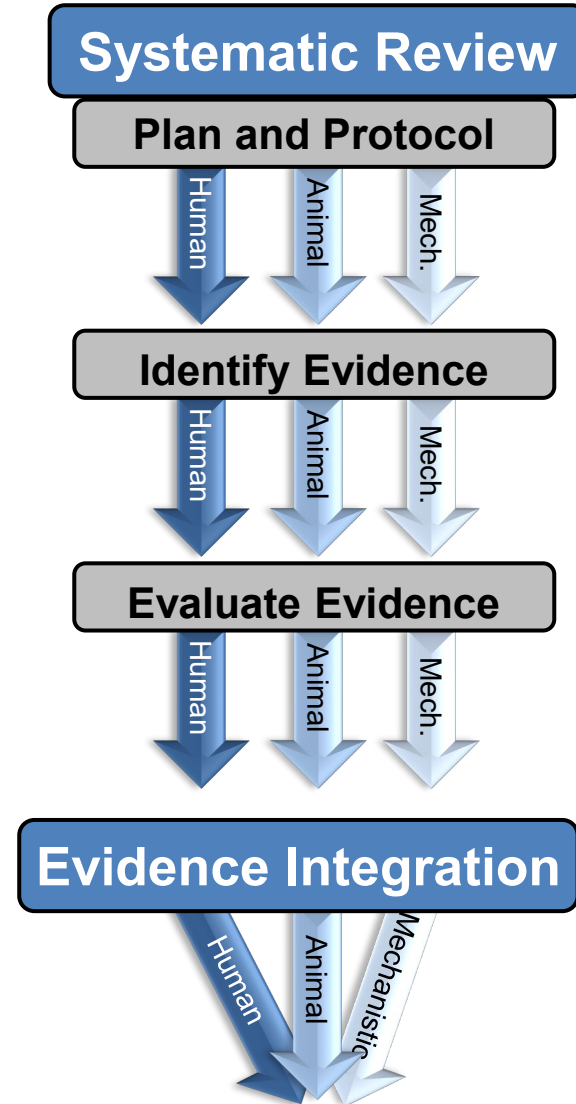
Planning: Considering Mechanistic Data

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

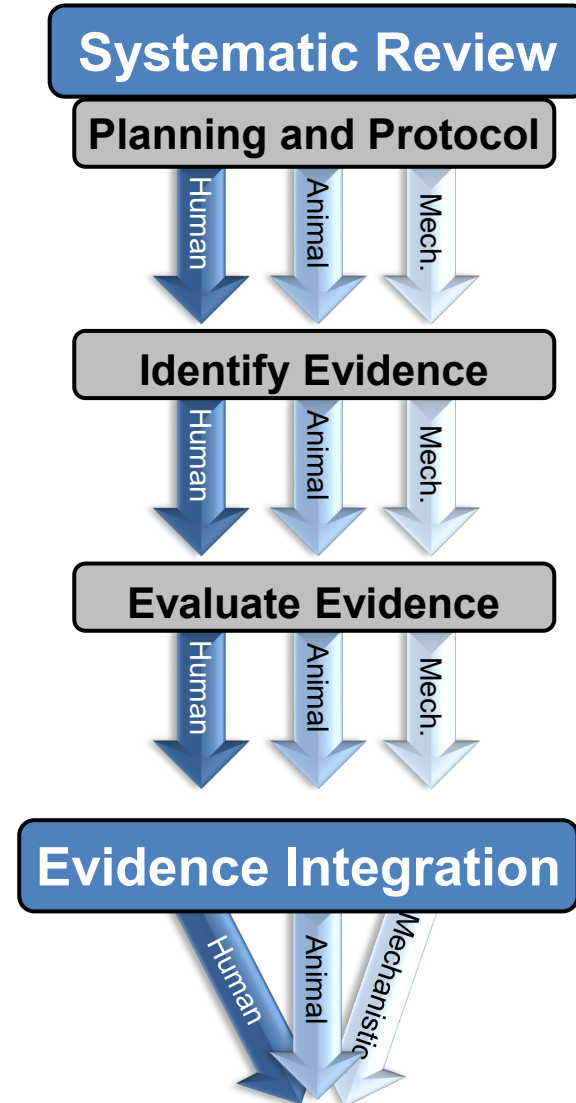




Evidence Identification: SR and Evidence Integration

Stepwise Methods

- **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





Evidence Identification: Considering Mechanistic Data

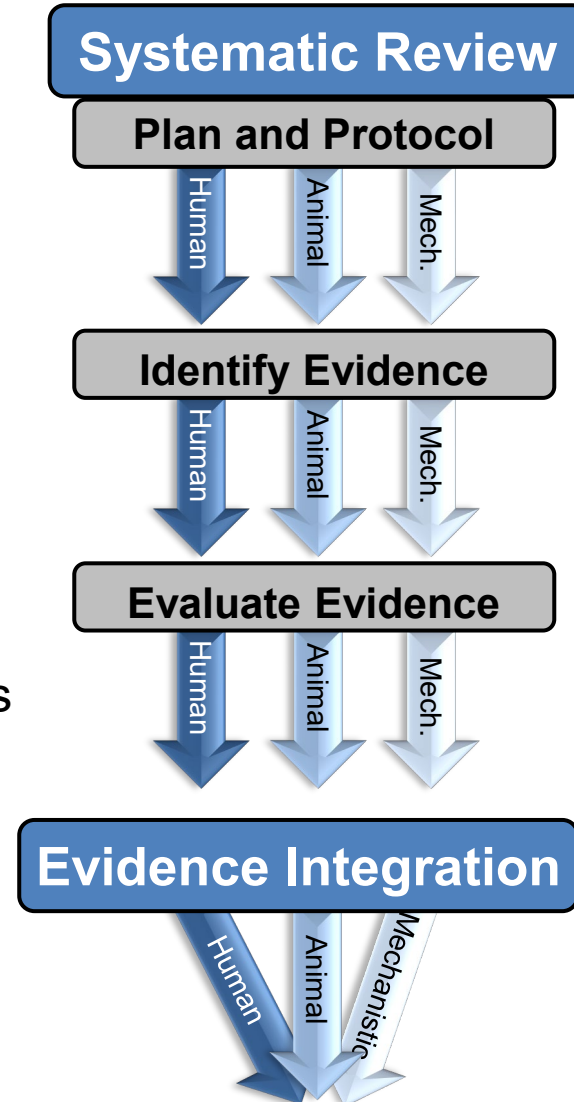
Using data from NAMs and in vitro studies

- 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

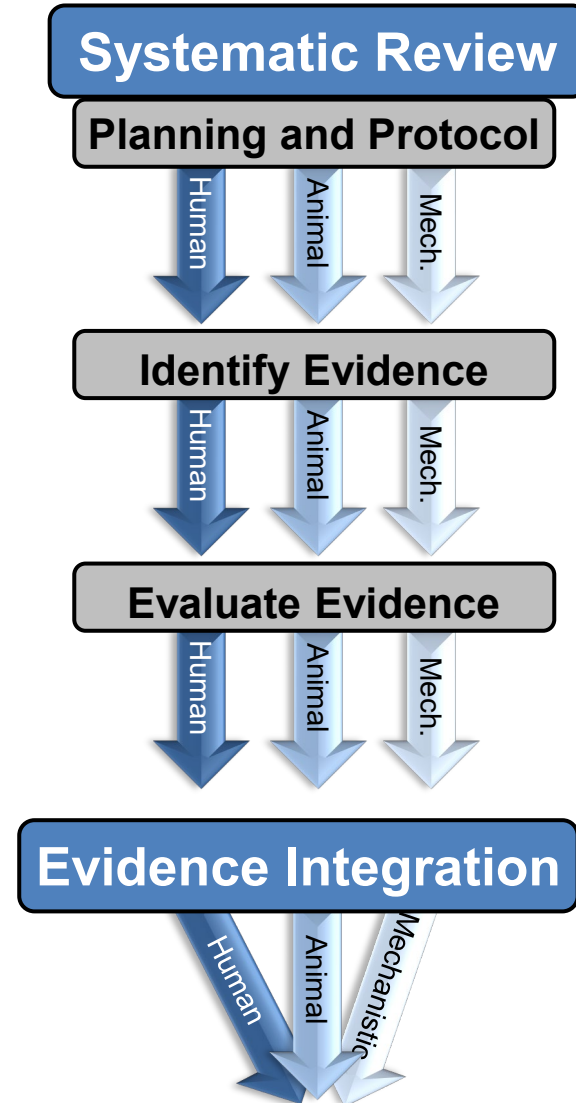




Evidence Evaluation: SR and Evidence Integration

Stepwise Methods

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





OHAT “Use-case” in PFOA Evaluation

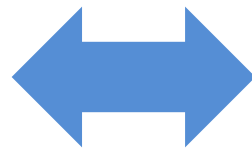
A “parallel” approach across evidence streams

- 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

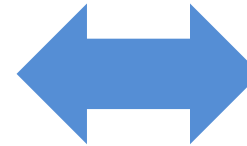
Use-case explored extending the risk of bias approach from experimental animal studies to studies with an in vitro exposure regime



Human Data



Experimental Animal Data



In Vitro Exposure Studies



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 validity?	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



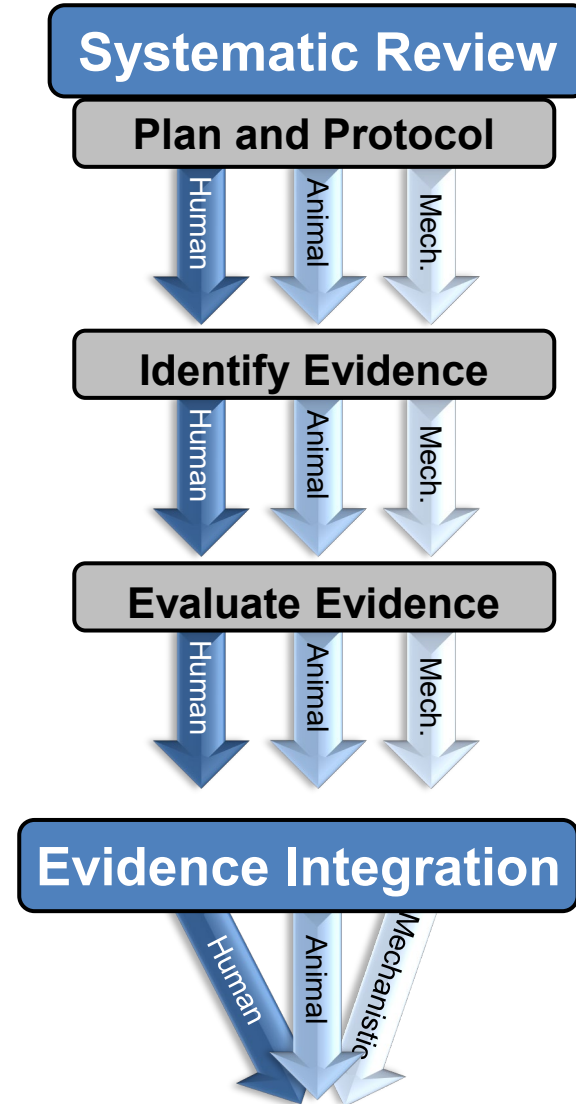
Identify

- 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?

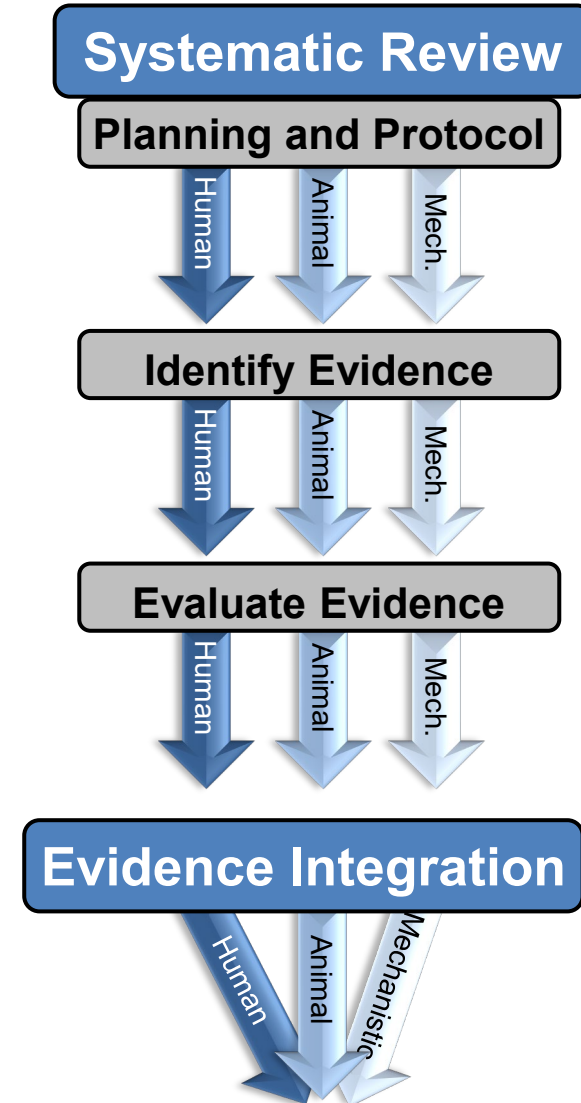
- Assures that treatment is not given selectively based on potential differences in human subjects, animals, **cells, or tissues**
- Requires each human subject, animal, **or cell** had an equal chance of being assigned to any study group including controls
- **In vitro study considerations**
 - Potential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





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
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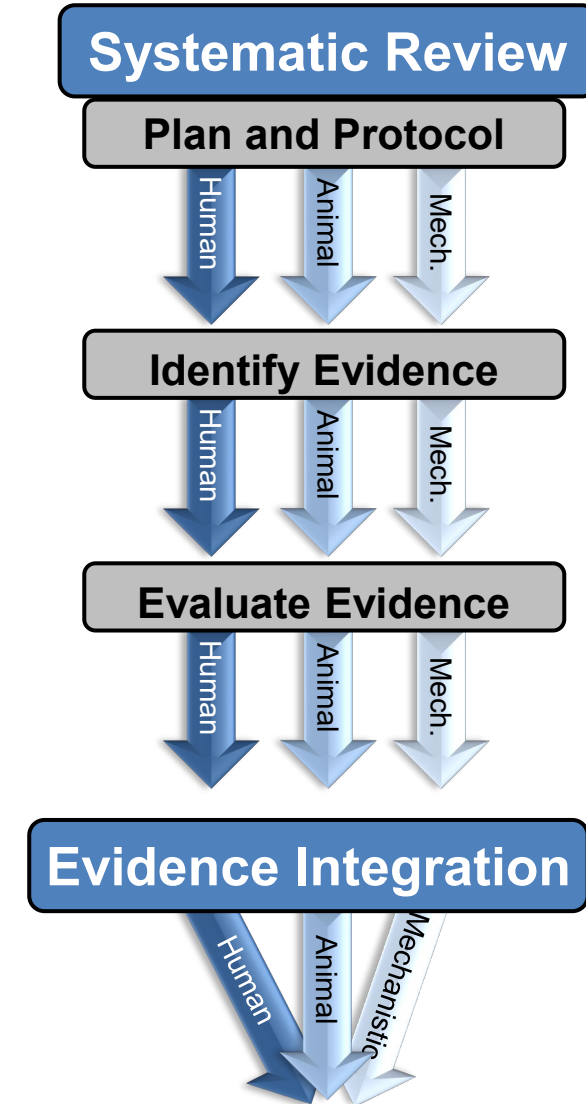




Evidence Integration: Considering Mechanistic Data

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
-  **Evidence Integration**
 - Biological plausibility





Integrate Evidence to Develop Hazard Conclusions

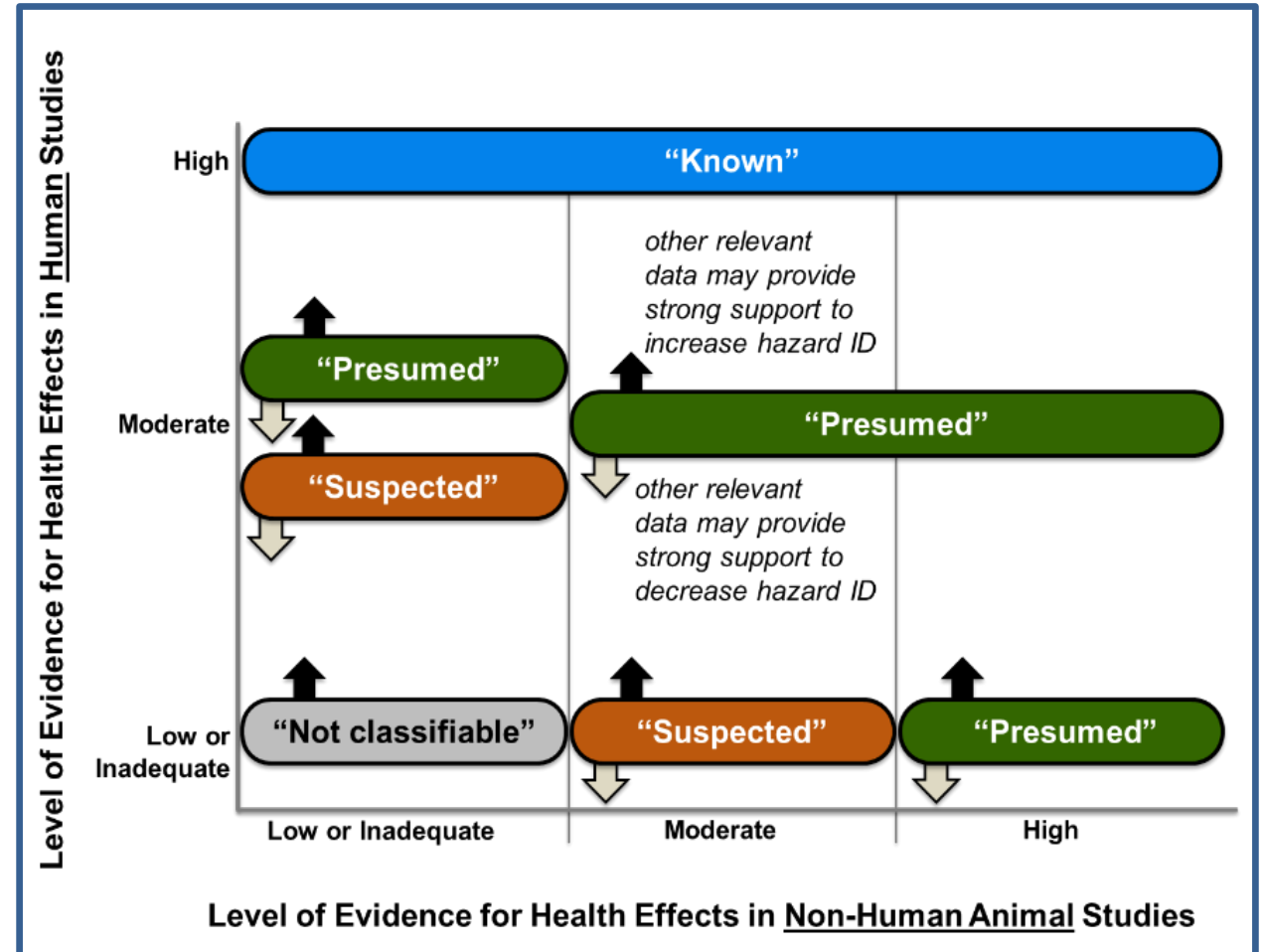
Initial Hazard Conclusion

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**

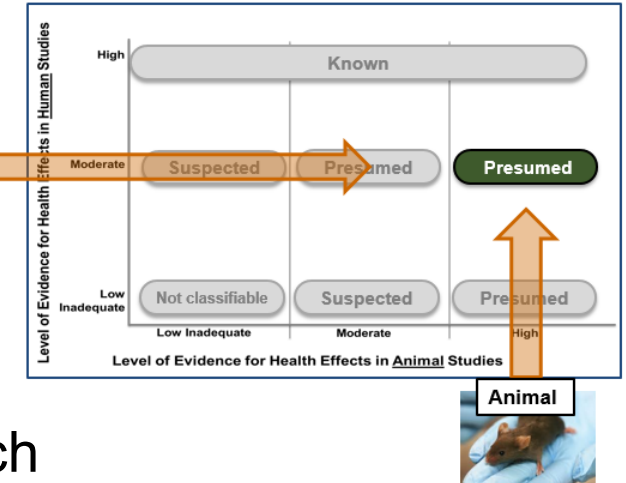
- Critical to have plan for evaluating key mechanistic data
- Dose and applicability were drivers in use of mechanistic data

- **Use-case represents an approach**

- Emphasis on consistency within an evaluation
- Flexibility across projects, active area of research, development, and discussion



Human Evidence





Thank you Questions?



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>) **32**

IRIS Handbook: https://cfpub.epa.gov/ncea/iris_drafts/recorddisplay.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	<p>Human: Any population and lifestage (occupation populations).</p> <p>Animal: Nonhuman mammalian animal species (lactation, peripubertal, and adult stages). Studies “potentially relevant supplemental material”. [O]</p>
Exposures	<p>Relevant forms: [chemical X] (CAS number) Other forms of [chemical X] that readily dissociate Metabolites of interest, including metabolites used Occupations that may be considered surrogates of Human: Any exposure to [chemical X] [via [oral or biomarkers of exposure are evaluated (e.g., mea: exposure route is unclear or likely from multiple be tracked during title and abstract screening and Specify if certain exposure assessment matrices o</p> <p>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</p>
Comparators	<p>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.”</p> <p>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.]</p> <p>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).</p>
Outcomes	<p>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.</p> <p>[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.]</p>



Screening Criteria: Supplemental Material

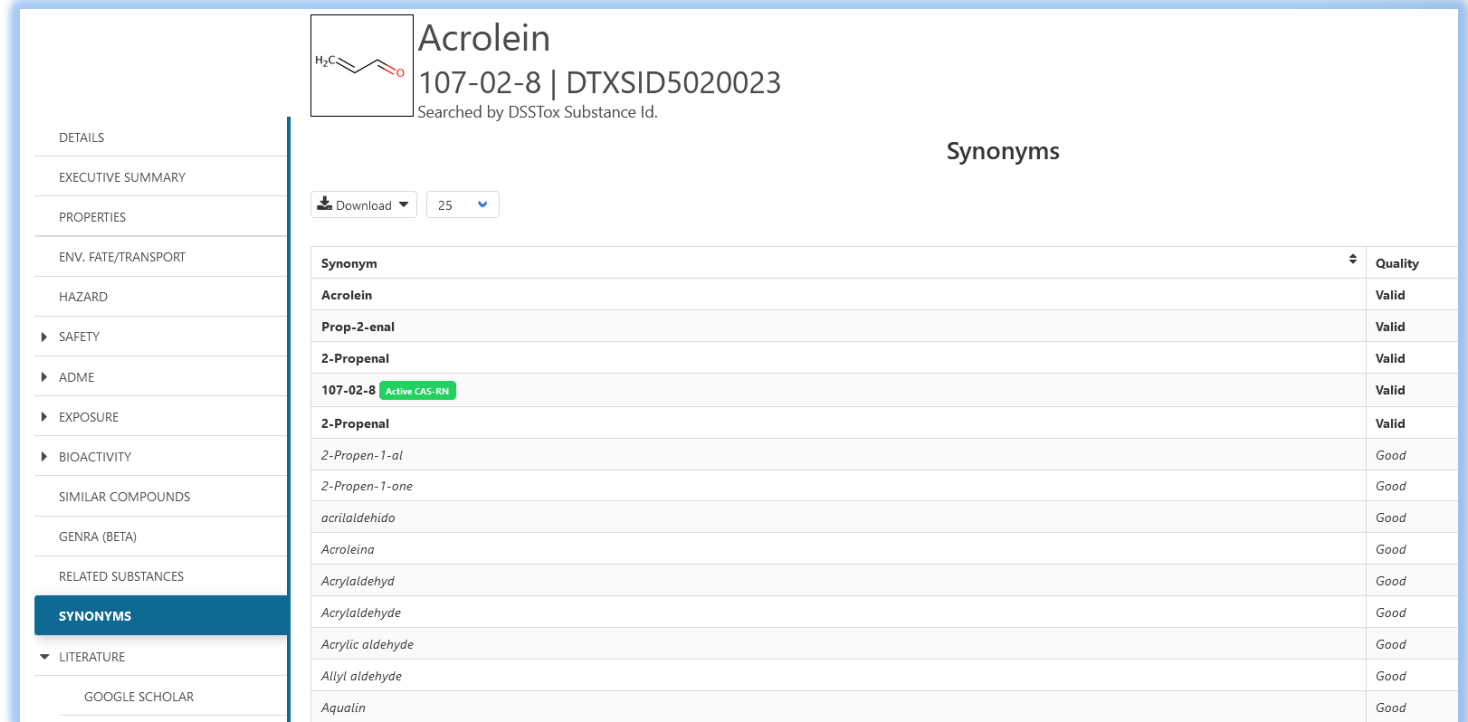
- Supplemental material falls outside of PECO but is not excluded

Table 5. Categories of Potentially Relevant Supplemental Material

Category	Evidence
Mechanistic information	<p>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 <i>in vitro</i>, <i>in vivo</i> (by any route of exposure, includes transgenic models), <i>ex vivo</i>, and <i>in silico</i> 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).</p> <p><i>[Notes:</i></p> <ul style="list-style-type: none">• <i>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.</i>• <i>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.]</i>
Nonmammalian model systems	Studies in nonmammalian model systems (e.g., fish, birds, <i>C. elegans</i>).

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

- **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”)**

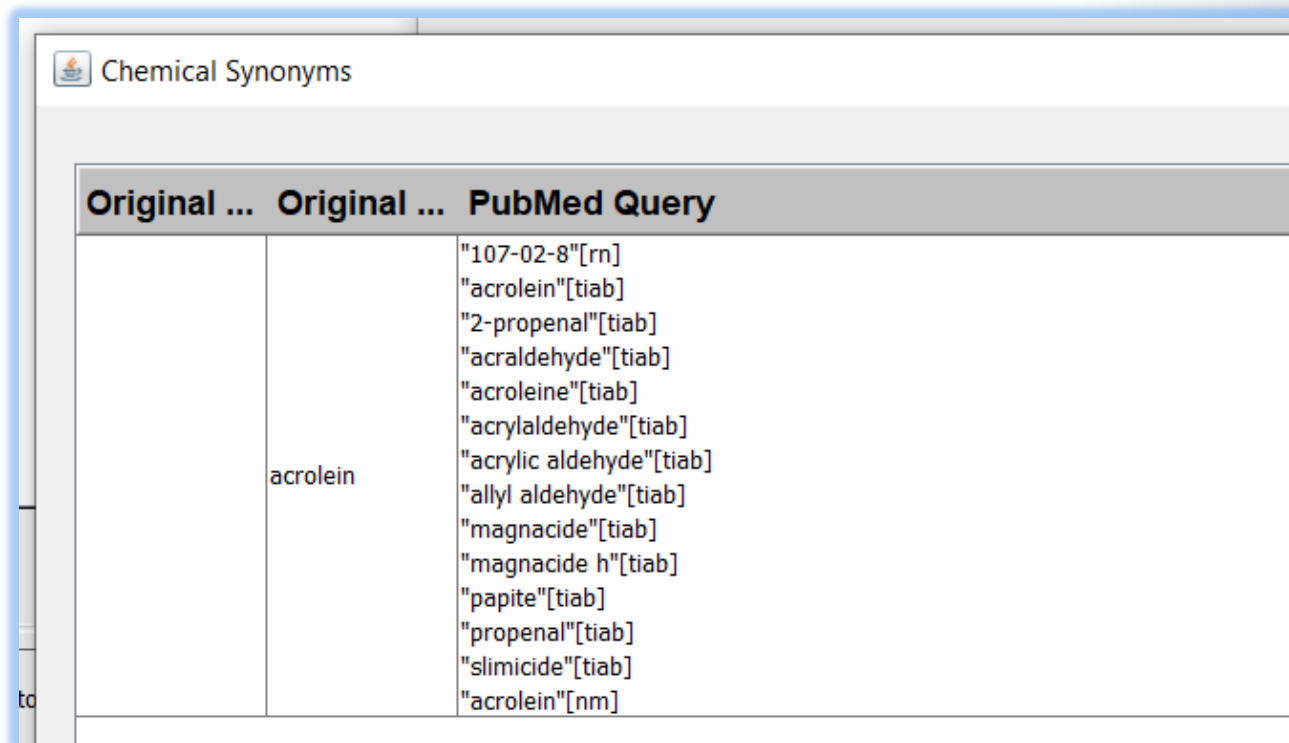


The screenshot shows the EPA Chemicals Dashboard for Acrolein. The chemical structure is C=CC=O. The CASRN is 107-02-8, and the DTXSID is 5020023. The search was performed using the DSSTox Substance Id. The dashboard includes a sidebar with navigation options: DETAILS, EXECUTIVE SUMMARY, PROPERTIES, ENV. FATE/TRANSPORT, HAZARD, SAFETY, ADME, EXPOSURE, BIOACTIVITY, SIMILAR COMPOUNDS, GENRA (BETA), RELATED SUBSTANCES, SYNONYMS (selected), LITERATURE, and GOOGLE SCHOLAR. The main content area shows a 'Download' button with a count of 25. Below this is a table of synonyms with their quality ratings.

Synonym	Quality
Acrolein	Valid
Prop-2-enal	Valid
2-Propenal	Valid
107-02-8 Active CAS-RN	Valid
2-Propenal	Valid
2-Propen-1-al	Good
2-Propen-1-one	Good
acrilaldehydo	Good
Acroleina	Good
Acrylaldehyd	Good
Acrylaldehyde	Good
Acrylic aldehyde	Good
Allyl aldehyde	Good
Aqualin	Good

- **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**



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

- **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 inhibit and trigger apoptosis in glioma through the PI3K/AKT signaling pathway

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 recovery, and low blood-gas partition coefficient. However, 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, cell apoptosis assay, cell Transwell assays. Insulin-like growth factor-1 (IGF-1) and PI3K/AKT signaling pathway gene expression analysis, respectively. 5% sevoflurane significantly inhibited proliferation ability in both U251 and U87 cells. Sevoflurane promoted apoptosis. Sevoflurane inhibited IGF-1 and promoted the expression of apoptosis-related proteins in glioma cells. In addition, sevoflurane inhibited IGF-1 and promoted the expression of apoptosis-related proteins in glioma cells. This study clarifies that sevoflurane inhibits proliferation, invasion, and migration, and promotes apoptosis in glioma cells. These findings may be significant for the selection of anesthetic agents in glioma surgery to improve the prognosis.

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?	Revid	Title	Year	Authors	Journal
0.132	<input type="checkbox"/>	<input type="checkbox"/>	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.	Repr...
0.132	<input type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input type="checkbox"/>	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...

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 Frog" OR "Xenopus laevis" OR "Honey Bee" OR "Apis mellifera" OR "Northern Bobwhite" OR "Colinus virginianus" OR "Water Flea" OR "Ceriodaphnia dubia" OR "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

- **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

Reference Details

51 H. T. Wang, H. H. Tsou, C. H. Hu, J. H. Liu, C. J. Liu, C. H. Lee, T. Y. Liu. 2019. **Acrolein** is involved in the synergistic potential of cigarette smoking- and betel quid chewing-related human **oral** cancer. *Cancer Epidemiology Biomarkers and Prevention*. 2019. #volume#: #pages# https://heronet.epa.gov/heronet/index.cfm/reference/download/reference_id/5031091

Full Text Links
DOI.org

Reference Links

Reference Label(s):
Add Labels here

BACKGROUND: Cigarette smoking (CS) and betel quid (BQ) factors and have synergistic potential for the development of (OSCC) in Taiwan. The p53 mutation characteristics in OSCC similar to that of **acrolein**-induced DNA damage. **Acrolein** is a carcinogen that preferentially causes p53 mutations and inhibits DNA repair. We hypothesize that **acrolein** is associated with OSCC.

METHODS: A total of 97 OSCC patients and 230 healthy subjects with chewing histories were recruited. Slot blot analysis of Acr-dG adducts and **acrolein**-induced DNA damage in buccal DNA, LC-MS/MS and urinary Acr metabolites were performed.

RESULTS: Our results showed that the level of Acr-dG adducts in buccal cells was 1.4-fold higher in OSCC patients than in healthy subjects with CS and/or BQ chewing histories ($p < 0.001$). Additionally, in healthy subjects, CS and BQ chewing were associated with significantly higher levels of 3-HPMA, indicating that CS and BQ chewing promotes **acrolein** absorption. However, 3-HPMA levels in OSCC patients were significantly lower than those in healthy subjects, indicating impaired **acrolein** metabolism.

Reference Status

Show 10 entries

	References Added	Unreviewed	Some Reviews	Included	Excluded	Conflict	Fully Reviewed
Level 1 - Chloroprene Title & Abstract	182	0	0	17	165	0	182
Level 2 - Chloroprene Full Text		0	0	9	8	0	17

Any exposure to acrolein via **inhalation**. Studies involving exposure differentiated from shorter-term exposure durations.
Toxicity studies using other routes of administration s

C **Human**: A comparison or reference population exposed to lower
Animal: A concurrent control group exposed to vehicle-only treat



SWIFT Review + SWIFT Active Workflow

SWIFT-Review - [C:\Users\KThayer\Desktop\Temp documents\RIS files\Phthalcanhydride 4099 from HERO 6-12-2019.ris]

File Tools Reports Help

Tag Browser Search Browse MeSH Tree Heatmap Browser Prioritized Lists

Evidence Stream

Tag	Code(s)	Count
[No Tag]		2104
Ecotoxicity (animal and plant)		1090
Animal (all)		766
Human		577
Environmental Fate (Beta)		595
In Vitro		545
Animal (human health models)		452
Plant		237

Showing 1665 of 4099 loaded documents (1 selected; 0 total included; 0 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Authors
1.003			s3956	SOCS3-mediated regulation of inflammatory cytokines in PTEN and p53 inactivated triple negative breast...	2015	Kim, G.; Ouzounis...
1			s3342	Prevalence of respiratory symptoms asthma bronchiale and chronic bronchitis in an industrial environmen...	1996	Paun, G.; Dutau, S...
1			s2593	Metal uptake by Black Sea algae	1992	Gaven, K. C.; Topci...

Document Preview

File Chart Bar Chart

SOCS3-mediated regulation inactivated triple negative b

Kim, G.; Ouzounis...
T. L.; Ezen, E. S.

Abstract

Somatic mutations...
A recent molecular...
with triple negative...
To investigate thic...
and PTEN knocko...
metastatic: epithel...
basal/clinica-low...
proteolytic degrad...
tumors. In non-tr...
transformed cells...
xenograft models...
These studies us...
utilized as an attr...

Showing 6487 of 6487 loaded documents (6487 selected; 0 total included; 0 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Aut
0			s6412	Permeation Of Protective Garment Material By Liquid Halogenated Ethanes And A Polychlorinated Biphenyl...	8572	Wee
0			s4825	1,2-Dichloroethane - Health-based calculated occupational cancer risk values	5406	;
0			s4887	Ethylene dichloride	4676	Ano
0			s6253	In Vivo Genotoxicity And Acute Hepatotoxicity Of 1,2-Dichloroethane In Mice: Comparison Of Oral, Intrap...	4267	Sto
0			s5812	Mutagenicity Of Chloroacetaldehyde, A Possible Metabolic Product Of 1,2-Dichloroethane (Ethylene Dichloro...	3190	McC
0			s5893	Mutagenicity Of Chloroacetaldehyde, A Possible Metabolic Product Of 1,2-Dichloroethane (Ethylene Dichloro...	3190	McC
0			s5013	The toxicology of chemicals - 1. Carcinogenicity, Volu...	2983	Berf
0			s6270	The toxicology of chemicals - 2. Reproductive toxic...	2983	Sull
0			s4886	1,2-Dichloroethane	2920	Ano
0			s5568	Covalent Binding Of 1,2-Dihalohalkanes to DNA and S...	2839	Trsk
0			s5058	The mutagenicity and DNA-modifying effect of halo...	2576	Bren
0			s5057	The Mutagenicity and DNA-Modifying Effect of Halo...	2576	Bren
0			s5112	Chronic Inhalation Toxicity Study of 1,2-Dichloroeth...	2508	Chol
0			s5260	Chronic Inhalation Toxicity Study of 1,2-Dichloroeth...	2508	El-h
0			s5135	Derivatization of Ethylene Dibromide with Silica-Sup...	2366	Colg
0			s5818	Health Hazard Evaluation Report No. HETA-91-251-	2218	McM
0			s6125	Potential of Non-halocarbon Oxidants on Halocarb...	2192	Sans
0			s6430	The Carcinogenic Risk of Some Organic Vapors In...	2187	Wils
0			s4967	Microsome-mediated covalent binding of 1,2-dichloro...	2170	Bano
0			s5178	Toxicological evaluation of a number of substances that may pollute the workplace air	2100	Dam

“Right click” to move to SWIFT Active

SWIFT ActiveScreening

TSCA DECIS

Screen Reference

You have reached the predicted inclusion threshold and can stop screening.

Currently Screening Level 1 - Title & Abstract

3345136 Ground and surface water developmental toxicity at a municipal landfill: description and weather-related variation

From: M. K. ...; ...

Contaminated groundwater poses a significant health hazard and may also impact wildlife such as amphibians when it surfaces. Using RETAX (Rog Embryo Toxicity Assay-Kenopus), the developmental toxicity of ground and surface water samples near a closed municipal landfill at Norman, OK, were evaluated. The groundwater samples were taken from a network of wells in a shallow, unconfined aquifer downgradient from the landfill. Surface water samples were obtained from a pond and small stream adjacent to the landfill. Surface water samples from a reference site in a similar habitat were also analyzed. Groundwater samples were highly toxic in the area near the landfill, indicating a plume of toxicants. Surface water samples from the landfill site demonstrated elevated developmental toxicity. This toxicity was temporally variable and was significantly correlated with weather conditions during the 3 days prior to sampling. Mortality was negatively correlated with cumulative rain and relative humidity. Mortality was positively correlated with solar radiation and net radiation. No significant correlations were observed between mortality and weather parameters for days 4-7 preceding sampling.

Include/Exclude Question

Include this reference (PECO-relevant, under, supplemental) *

Yes (PECO - relevant, under or supplemental)

No

Main

New Question Group

Tag as duplicate?

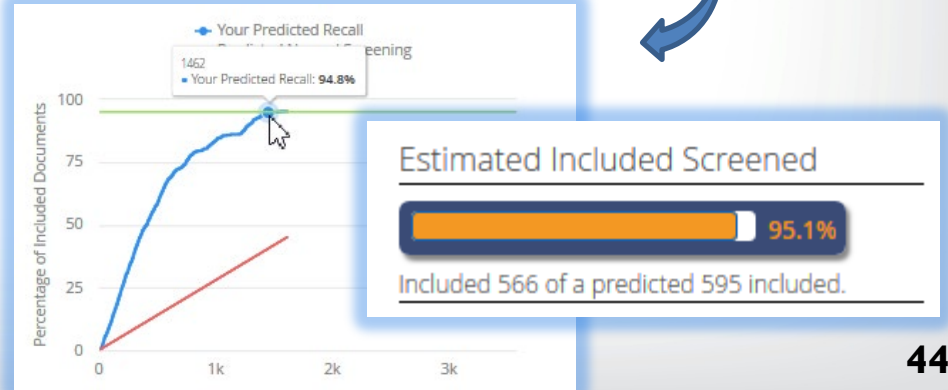
Yes

No

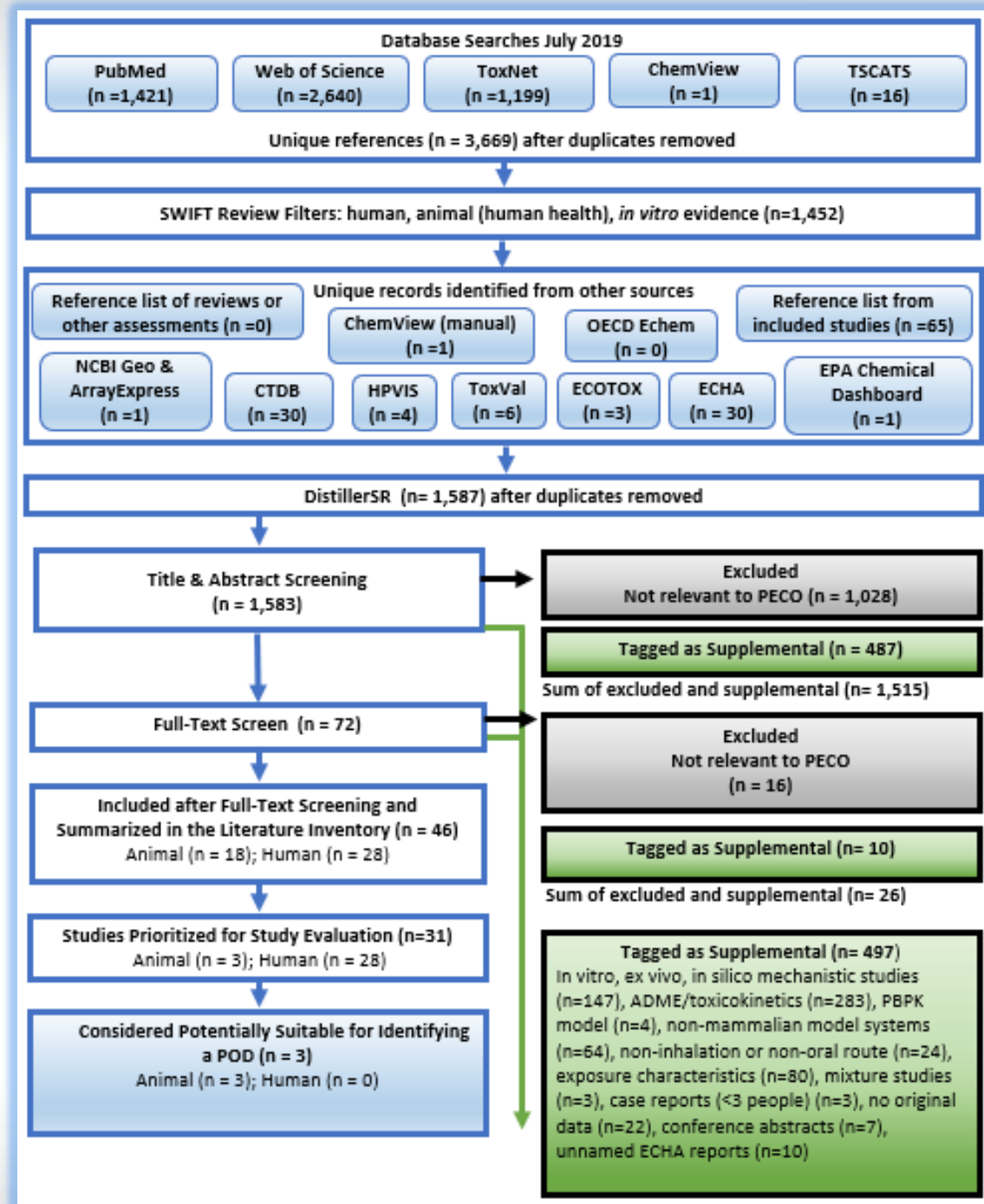
Machine-learning based screening

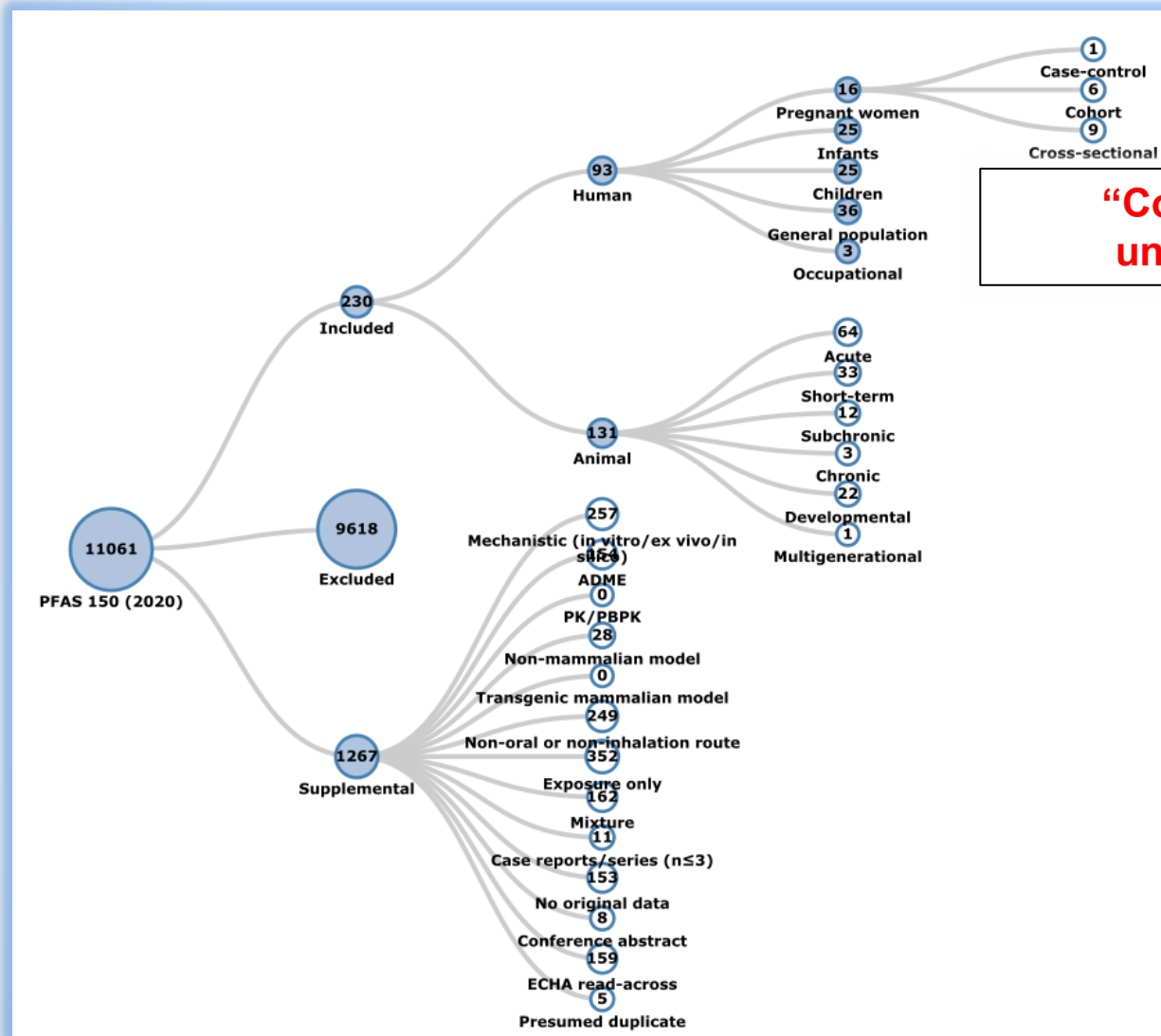
SWIFT Review to identify hazard records

- Only 45% of studies needed to be 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





“Control + click” to see underlying references

Cross-sectional

Wang Y, Rogan WJ, Chen PC, Lien GW, Chen HY, Tseng YC, Longnesder MP, Wang SL 2014
Association between maternal serum perfluoroalkyl substances during pregnancy and maternal and cord thyroid hormones: Taiwan maternal and infant cohort study
Environmental Health Perspectives 122:529-534.

BACKGROUND: Perfluoroalkyl substances (PFASs) are synthetic compounds that are widely used in industry and are often detectable in humans. In pregnant rats and their pups, PFASs can interfere with thyroid hormone homeostasis. In humans, maternal thyroid hormones supply the fetus throughout pregnancy, and thyroid hormones play a critical role in fetal growth and neurodevelopment.

...on between maternal PFAS exposure and thyroid hormone status in pregnant women and neonates.

...sure and health in Taiwan, we measured serum concentrations of nine PFASs and four thyroid hormones for 285 pregnant women in their first trimester and 115 neonates. Associations between maternal PFASs and maternal and cord thyroid hormones were examined in...

...centrations were positively associated with maternal thyroid-stimulating hormone (TSH) levels. Pregnant women with higher levels of perfluorooctanoic acid (PFORDA), and perfluorododecanoic acid (PFDDDA) had lower free thyroxine (T4) and total T4 levels. For example, we estimated that maternal free T4 levels decreased 0.019 ng/dL (95% CI: -0.028, -0.009) with each nanogram per milliliter increase in maternal PFNA. Finally, maternal PFNA, PFUnDA, and PFDDDA levels were associated with lower cord total triiodothyronine (T3) and total T4 levels, and maternal perfluorodecanoic acid (PFDEA) was associated with lower cord total T3.

CONCLUSIONS: Our results suggest that exposure to some PFASs during pregnancy may interfere with thyroid hormone homeostasis in pregnant women and fetuses.

Included > Human > Pregnant women > Cross-sectional | Included > Human > Infants > Cohort | Chemicals > Perfluoroundecanoic acid

HAWC searches/imports: Auto-import at 2020-05-04 11:10:07

HERO HAWC

Jiang W, Zhang Y, Zhu L, Deng J 2014
Serum levels of perfluoroalkyl acids (PFAAs) with isomer analysis and their associations with medical parameters in Chinese pregnant women
Environment International 64:40-47.

Perfluoroalkyl acids (PFAAs) are a group of chemicals used for many applications and widely present in the environment and humans. In this study, serum levels of PFAAs and isomers of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) were analyzed in 141 Chinese pregnant women. Among all the samples, total PFOS (ΣPFOS, mean concentration 7.32ng/mL) was predominant, followed by ΣPFOA (mean 4.78ng/mL) and perfluorodecanoate (PFDA, mean 1.45ng/mL). On average, the proportion of linear PFOS (n-PFOS) was 66.7% of ΣPFOS, which was higher than the general population, implying that maternal women could excrete branched PFOS isomers to the fetus by transplacental transfer. Moreover, the proportion of n-PFOS decreased significantly with the increasing concentration of ΣPFOS in the serum samples (r=-0.342, p<0.001). The mean proportion of n-PFOA in the serum samples was 99.0%, which was much higher than the technical ECF (electrochemical fluorination) products (ca. 70%). The small proportion of branched isomers of PFOA suggests that there is still a source of ECF PFOA in China. Significant correlations (p<0.005) were observed between the concentrations of some PFAAs with certain...

Close

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: PFUnDA 86 Birth size 17

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														
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.

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 Laboratores (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-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

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



Study Evaluation & Evidence Analysis

- **Study evaluation tools available for epidemiology, animal toxicology, and in vitro studies, but pragmatic approaches need to be 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**

- **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**

1 **Template Systematic Evidence Map (SEM) Report Format and Methods Used for the US EPA**
2 **Integrated Risk Information System (IRIS) Program, Provisional Peer Reviewed Toxicity**
3 **Value (PPRTV) Program, and Other “Fit for Purpose” Analyses**
4

5
6 Kristina A. Thayer¹, Michelle Angrish¹, Xabier Arzuaga¹, Laura M. Carlson¹, Allen Davis¹, Laura
7 Dishaw¹, Ingrid Druwe¹, Catherine Gibbons¹, Barbara Glenn¹, Ryan Jones², J. Phillip Kaiser¹, Channa
8 Keshava¹, Nagalakshmi Keshava¹, Andrew Kraft¹, Lucina Lizarraga¹, Amanda Persad¹, Elizabeth G
9 Radke¹, Glenn Rice¹, Brittany Schulz³, Teresa Shannon¹, Andrew Shapiro², Shane Thacker²,
10 Suryanarayana Vulimiri¹, Antony J. Williams⁴, George Woodall¹, Erin Yost¹, Robyn Blain⁵, Katherine
11 Duke⁵, Ali Goldstone⁵, Pam Hartman⁵, Kevin Hobbie⁵, Brandall Ingle⁶, Courtney Lemeris⁵, Cynthia
12 Lin⁵, Alex Lindahl⁵, Kristen McKinley⁵, Parnian Soleymani⁵, Nicole Vetter⁵
13

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



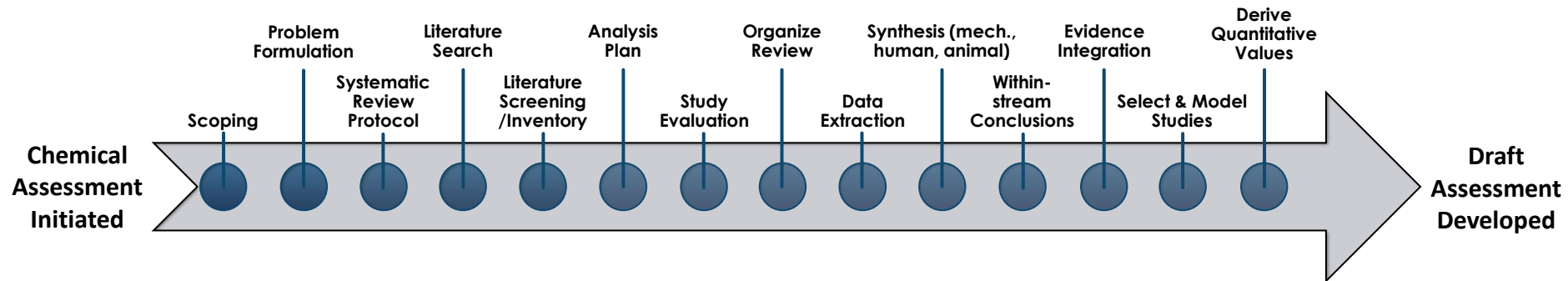
Questions?



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**



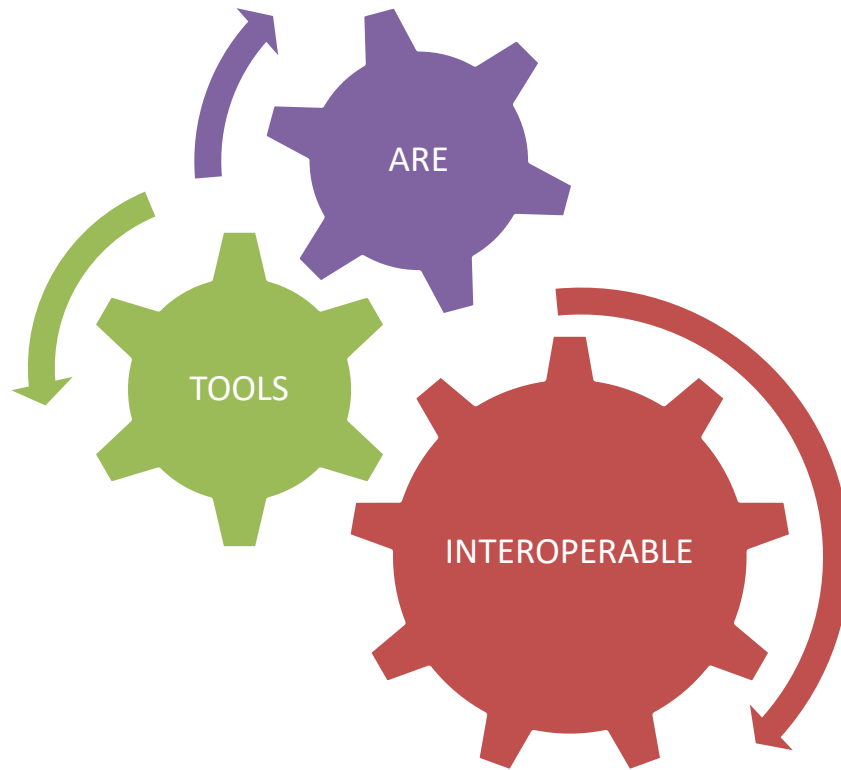
- **Develop problem formulation and scope of the systematic review**
- **Search journal databases (PubMed, WoS, Toxline, etc.) and grey literature using database specific search strings**
- **Use specialized SR software to:**
 - **focus on topics of interest**
 - **leverage machine-learning to rapidly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



Suite of Systematic Review Software Tools



 DistillerSR



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

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 Phillips¹, Kyle Miller¹, Arpit Tandon¹, Deepak Mav¹, Mihir R. Shah¹, Stephanie Holmgren², Katherine E. Pelch³, Vickie Walker², Andrew A. Rooney², Malcolm Macleod⁴, Ruchir R. Shah¹ and Kristina Thayer¹

SEARCH REFINEMENT

Discover important terms and phrases

TOPIC MODELING

Uncover hidden structure in your literature corpus

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

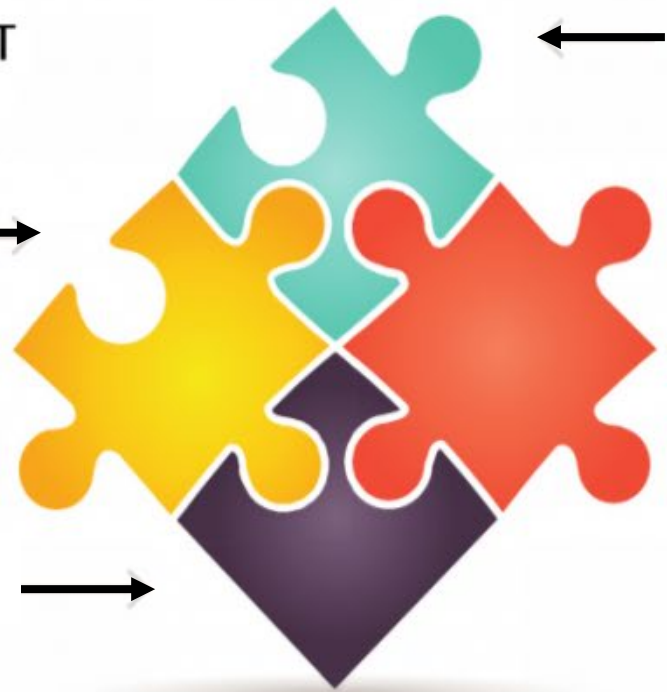
PROBLEM FORMULATION

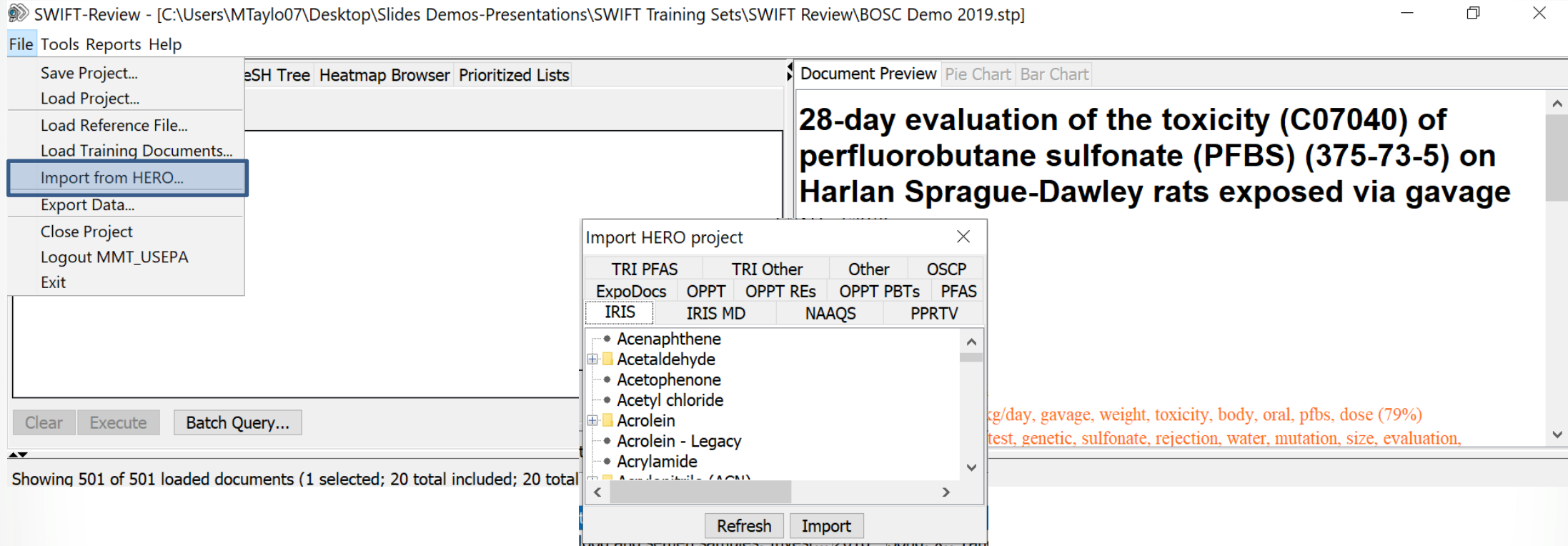
Identify interesting high impact research questions

LITERATURE PRIORITIZATION

Use machine learning to triage your reading list

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





The screenshot displays the SWIFT-Review application window. The title bar reads "SWIFT-Review - [C:\Users\MTaylo07\Desktop\Slides Demos-Presentations\SWIFT Training Sets\SWIFT Review\BOSC Demo 2019.stp]". The menu bar includes "File", "Tools", "Reports", and "Help". The "File" menu is open, with "Import from HERO..." highlighted. Below the menu, there are buttons for "Clear", "Execute", and "Batch Query...". The main workspace shows a document preview titled "28-day evaluation of the toxicity (C07040) of perfluorobutane sulfonate (PFBS) (375-73-5) on Harlan Sprague-Dawley rats exposed via gavage". A dialog box titled "Import HERO project" is open, showing a tree view of chemical categories: TRI PFAS, TRI Other, Other, OSCP, ExpoDocs, OPPT, OPPT RES, OPPT PBTs, PFAS, IRIS, IRIS MD, NAAQS, and PPRTV. The tree view is expanded to show a list of chemicals including Acenaphthene, Acetaldehyde, Acetophenone, Acetyl chloride, Acrolein, Acrolein - Legacy, and Acrylamide. The dialog box has "Refresh" and "Import" buttons at the bottom.

Import literature directly from HERO
Merge with existing project
Start a new project

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

Health Outcomes

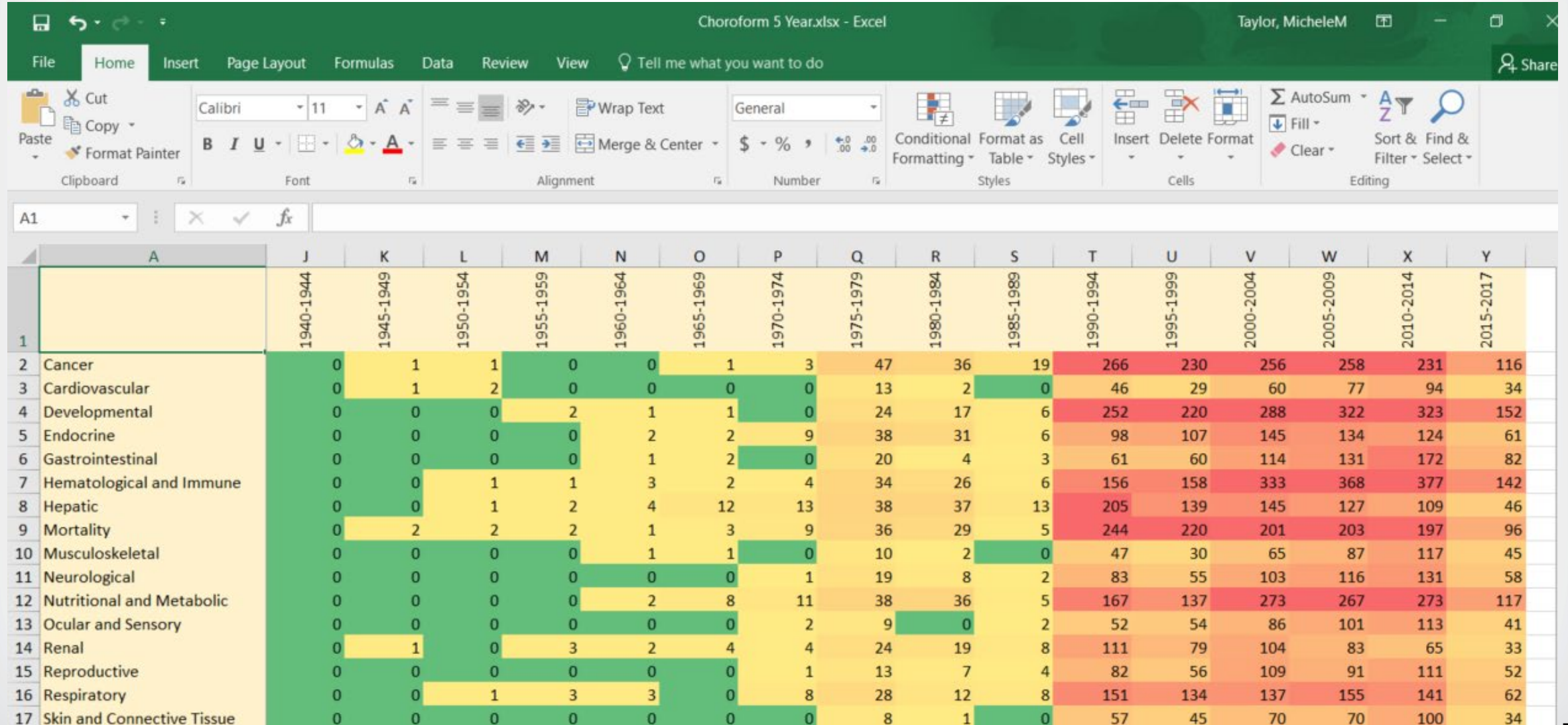
Health Outcome	Count
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Developmental	2117
Nutritional and Metabolic	1680
Mortality	1463
Endocrine	1293
Hepatic	1151
Respiratory	1051
Gastrointestinal	1032
Reproductive	824
Renal	713
Neurological	698
Skin and Connective Tissue	554

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	<input type="checkbox"/>	<input type="checkbox"/>	h1021972	Mutagenicity study of carbon tetrachloride and...	1998	Sasaki, T.; Suzuki, M.; Noda, K.; ...	Journal of Toxicological Sciences
0.95	<input type="checkbox"/>	<input type="checkbox"/>	h630464	Advances in research on carcinogenic and gen...	1993	Daniel, F. B.; Meier, J. R.; Deang...	Annali dell'Istituto superiore di sa...
0.95	<input type="checkbox"/>	<input type="checkbox"/>	h1024901	Cytosine attack by free radicals arising from br...	1993	Castro, G. D.; Castro, J. A.	Teratogenesis, Carcinogenesis, an...
0.95	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	h1010308	International Commission for Protection Again...	1992	Lohman, P. H. M.; Mendelsohn, M...	Mutation Research: Fundamental a...
0.95	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	h1024875	International Commission for Protection Again...	1992	Mendelsohn, M. I.; Moore, D. H.; ...	Mutation Research



Downloadable Data - Heatmaps



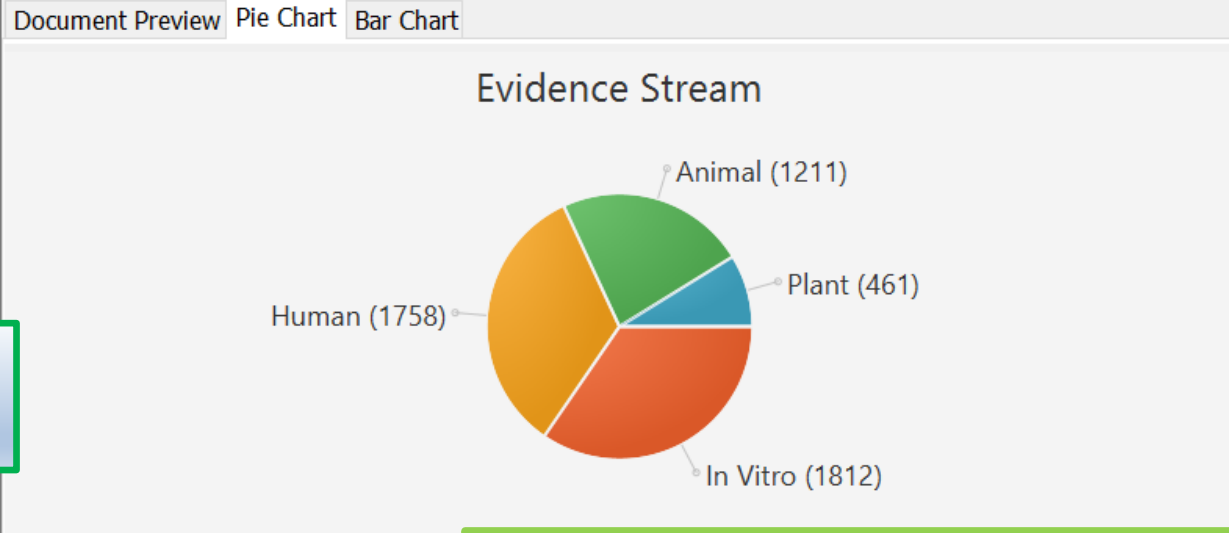
SWIFT-Review - [C:\Users\mtaylo07\Desktop\SWIFT Review\NAS Session 3.stp]

File Tools Reports Help

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

Evidence Stream

Tag	Count
In Vitro	1812
Human	1758
Animal	1211
Plant	461



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	<input type="checkbox"/>	<input type="checkbox"/>	h699241	The relationship between multiple myeloma a...	2010	Gold,
0.261	<input type="checkbox"/>	<input type="checkbox"/>	6759108	Epidemiological evidence of carcinogenicity of ...	1982	Cantor
0.243	<input type="checkbox"/>	<input type="checkbox"/>	h3719592	Toxic potentials of ten herbs commonly used f...	2015	Abuda
0.241	<input type="checkbox"/>	<input type="checkbox"/>	h3698164	Application of ultrasound-assisted emulsificati...	2014	Asgha
0.241	<input type="checkbox"/>	<input type="checkbox"/>	h1292499	Antioxidant, genotoxic and antigenotoxic activi...	2012	Chaabane, M.; Bouassery, M.; Bouassery, M.; Bouassery, M.; Bouassery, M.; Bouassery, M.; Bouassery, M.; Bouassery, M.; Bouassery, M.; Bouassery, M.
0.24	<input type="checkbox"/>	<input type="checkbox"/>	h1068198	Genotoxicity and toxicity assessment in urban ...	2006	Cardozo, T. R.; Rosa, D. P.; Feide...
0.24	<input type="checkbox"/>	<input type="checkbox"/>	h3698004	The use of endemic Iranian plant, Echium am...	2015	Uysal, H.; Kizilet, H.; Ayar, A.; Ta...
0.24	<input type="checkbox"/>	<input type="checkbox"/>	11518606	Classification of carcinogenic chemicals in the ...	2001	Greim, H.; Reuter, U
0.238	<input type="checkbox"/>	<input type="checkbox"/>	h1024786	In vitro protective effects of Terminalia arjuna ...	2002	Pasquini, R.; Scassellati-Sforzolini,...

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



Improved Ranking Model

- **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**



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

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

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^d, Ruchir R. Shah^a

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Instructions

P

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

Animat: Nonhuman mammalian animal species (whole organism) of any lifestyle (including pre-conception, 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."

Animat: 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

Screening References

+ Add New Review



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 potency 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

SWIFT ACTIVESCREENER Zebrafish ktsaioun

Manage References

Conflicted Level Filter Article Title and Author 8 References

Seed	Full Text	History	Abstract	Title	Current Level	Status
-				Using molecular signatures for identification of teratogenic compounds in the zebrafish embryo assay	Level 1 - Title & Abstract	Conflicted
-				Predictive modeling of developmental toxicity	Level 1 - Title & Abstract	Conflicted
-				From cutting edge describing the	Abstract	Conflicted
-				Development of a	Abstract	Conflicted
-				The classification of alternative approac	Abstract	Conflicted
-				DarT: The embryo	Abstract	Conflicted
-				Implementation of	Abstract	Conflicted
-				CFC1 as a candidat	Abstract	Conflicted

Reference Screening History

Edit	Level	Status	Created By	Modified By	Date Modified
	Level 1 - Title & Abstract	Included	ktsaioun	ktsaioun	08/10/2016 17:42
	Level 1 - Title & Abstract	Excluded	amaertens	amaertens	08/14/2016 22:54

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



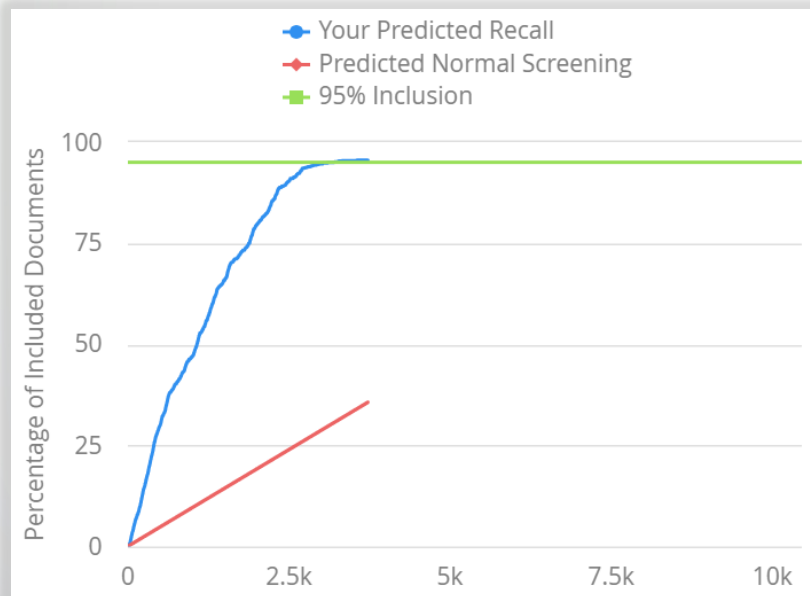
SWIFT-Active Screener Metrics

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



You have reached the predicted inclusion threshold and can stop screening.

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



Estimated Included Screened



Included 1088 of a predicted 1140 included.

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

- **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 separately, create new lines as needed.
 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.
 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.
 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.
 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 level Animal species, exposure, health outcomes
- Export to visualization tools (Tableau)



Full Text Screening

Ushijima, K., Sung, W., Tanaka, S., Kawakita, M., Mukai, Y., Tamura, K
functional health among residents of the Shiranui Sea communities

[LINK REFERENCE](#)

Quick Navigation

The objective of this study was to evaluate the effect of estimated historical methylmercury exposure on the functional health of residents living in the Shiranui Sea communities in Japan. Functional health was measured by self-reported activities of daily living (ADL). Study areas were categorized into high, medium and low methylmercury exposure areas according to their location or distance from the Shiranui Sea. We estimated the adjusted prevalence odds ratios of impaired ADL in relation to exposure using a logistic regression model. Compared with residents in the low-exposure area, residents in the high-exposure area were significantly associated with a higher prevalence odds ratio (OR) for impaired ADL after adjustment for confounding factors (adjusted ORs = 2.8, 95% CI: 1.3-6.2). These results showed strong dose-response relationships (p for trend = 0.0050). Our findings suggest that historical methylmercury exposure might cause functional impairment in later in life depending on the exposure level.

[SUBMIT FORM](#) and go to [Next](#)

Inclusion Criteria:
Studies will be included if, judged
-Epidemiological studies with c
-Errata, letters to editor, syster
For title only for recent articles
Foreign language abstracts, pl

Supporting information:
Includes human studies for DN
exposure, biomarkers or PBPP

Exclusion Criteria:
Studies in nonhuman species
Studies in humans without dos

1. **Do the title and abstract s data?**

- Yes, relevant, with dose
- No, not relevant
- Other Informative Studi
- Yes, relevant (identified
- No, not relevant (identif

DistillerSR

ASSESSMENT Reference

Review » Datarama Reports » References » Forms » Manage Levels » Users » Project »

My Tasks Project Progress

Level 2: Full text review after resolving conflicts

Category	Percentage
Included	25%
Conflicted	5%
Excluded	70%

Category	Percentage
Complete	100%
In Progress	0%
Not Started	0%



Download Data in Multiple Formats

Datarama

Report Settings

Advanced Options

Reference Criteria

Data Criteria

Reference Display Options

Saved Queries

Query History

Keys

Aggregate Reports

Basic Options

Report Format

View Online

Email the Report

Excel Spreadsheet

Export file name (optional)

Excel Spreadsheet (transposed)

Disagreements

Word Document

Bibliographic Format

PDF Document

Sort references by

CSV

Filter References

CSV (transposed)

RIS

JSON Online

Data to Display

▼ Level 1

▼ Level 2

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

	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7
Reporting Quality	++	++	+	++	++*	+	+
Allocation	+	+	NR	+	NR	+	+
Blinding	NR	NR	NR	NR	NR	NR	NR
Variable Control	+	++	++	++	++	++	++
Reporting/Attrition Bias	++	++	++	+	+	+	+
Exposure characterization	++	++	+	++	+	++	+
Study Design Applicability	++	++	++	++	+	++	++
Outcome Assessment	+	+	++*	++*	++	+	+
Results Presentation	++	++	++*	++*	+	++*	++*
Overall Confidence	++	++	++*	++*	++*	-	++

Reporting Quality

Reporting of information necessary for study evaluation

Good

Good. Critical and important information is provided for test species, strain, sex, age, exposure methods, experimental design, endpoint evaluations and the presentation of results. The authors report that this study was conducted according to OECD guidelines (Test 414: Prenatal Development Toxicity Study).

Selection/Performance

Allocation of animals to experimental groups?

Adequate

Adequate. Randomization was not explicitly reported, but the specific method of randomization used in the current study could not be inferred. However, the study was performed according to OECD guidelines which require that "mated animals should be assigned in an unbiased manner to the control and treatment groups" (See Test 414: Prenatal Development Toxicity Study).

Blinding of investigators, particularly during outcome assessment

Not reported

Not reported (Interpreted as adequate).

Number of fetuses/resorptions and implantations: Blinding for these outcome determinations was not reported (and assumed not conducted). However, compared to more subjectively measured outcomes, there is less concern for lack of blinding for these more objectively measured outcomes (i.e., counts of fetuses/resorptions/implantations).

Fetal evaluation for malformations: Blinding during initial evaluation of fetuses is typically not conducted as masked evaluation can make the task of separating treatment-related changes from normal developmental variation more difficult and may result in subtle developmental anomalies being overlooked. Fetal evaluations were conducted in accordance with regulatory test guideline recommendations, using standardized nomenclature. No subsequent steps to minimize the potential for observational bias were reported (e.g., conducting a secondary targeted blinded review, or an independent prospective or retrospective peer-review).

Body and organ weights: Blinding for these outcome determinations was not reported (and assumed not conducted). Potential concern for bias was mitigated because the endpoints were measured using automated/computer driven systems, standard laboratory kits, or relatively simple, objective measures.

Confounding/Variable Control

Control for variables across experimental groups

Adequate

Adequate. Based on the study report, husbandry practices were inferred to be the same in controls and treatment groups. The experimental conditions described provided no indication of concern for uncontrolled variables or different practices across groups. However, control and treated animals were allocated to treatment on different days (i.e., "The animals were allocated to the different groups on five consecutive days, viz. the 30-ppm group on two days and the remaining groups on one day each"). Instead, the investigators should have randomly distributed the dams across all groups each day rather than assigning only one group per day.

Reporting or Attrition

Reporting Quality

Reporting of information necessary for study evaluation

Overall

Good

Good. Critical and important information is provided for test species, strain, sex, age, exposure methods, experimental design, endpoint evaluations and the presentation of results. The authors report that this study was conducted according to OECD guidelines (Test 414: Prenatal Development Toxicity Study).

Study 2

Overall

Good

Good. Critical and important information is provided for test animal, exposure methods, experimental design, endpoints evaluation, and the presentation of results.

Study 3

Overall

Adequate

Adequate. Important information is provided for test species, strain, sex, age, exposure methods (including test article), experimental design, and endpoint evaluations. However, the results for organ weight and hematology were not reported.

Study 4

Overall

Good

Adequate. Critical and important information is provided for test animal, exposure methods, experimental design, endpoint evaluations, and qualitative or qualitative presentation of results.

Study 5

Overall

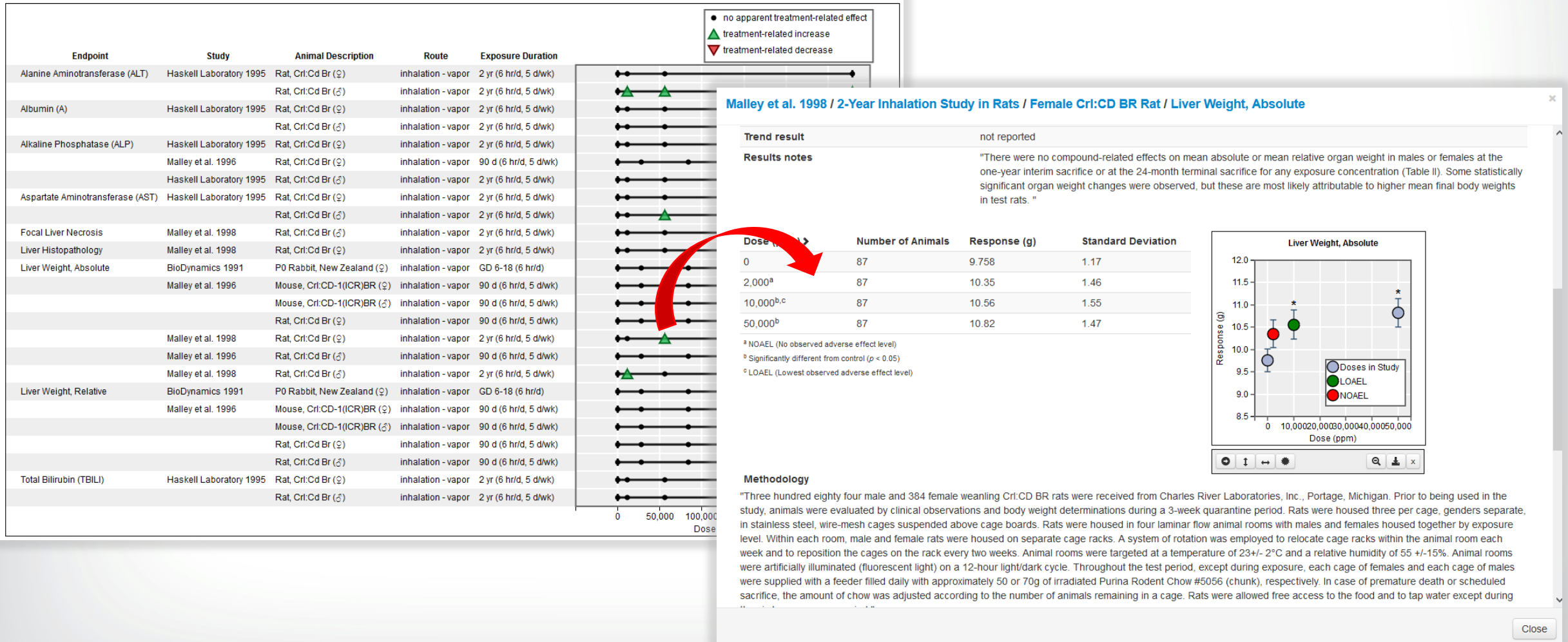
Good

Good. Information is provided for test animal, exposure methods, experimental design, endpoint evaluations, and presentation of results.

Study 6

Overall

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



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

Trend result not reported

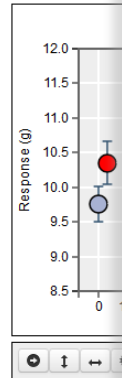
Results notes "There were no compound-related effects on mean absolute or mean relative organ weight in males or females at the one-year interim sacrifice or at the 24-month terminal sacrifice for any exposure concentration (Table I). Some significant organ weight changes were observed, but these are most prominent 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 Cri:CD BR rats were received from Charles River Laboratories, Inc., Portage, Michigan. Prior to being received, 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 with 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 and were artificially illuminated (fluorescent light) on a 12-hour light/dark cycle. Throughout the test period, except during exposures, rats were supplied with a feeder filled daily with approximately 50 or 70g of irradiated Purina Rodent Chow #5056 (chunk), resp. At the one-year interim sacrifice, the amount of chow was adjusted according to the number of animals remaining in a cage. Rats were allowed free access to water and food throughout the study."



Home / PFAS 150 (2020) / Malley et al. 1998 / 2-Year Inhalation Study in Rats / Female Cri: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

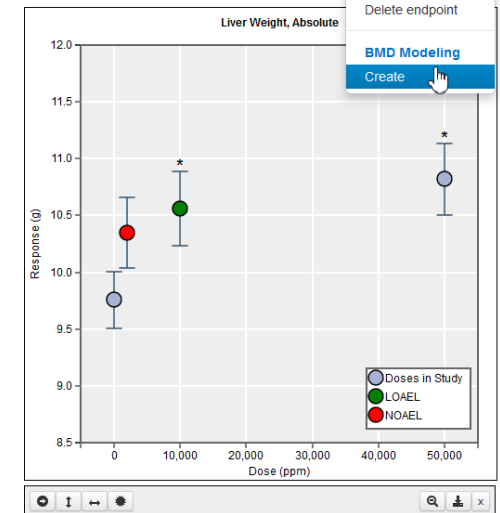
- Download datasets

Liver Weight, Absolute

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	increase from reference/control group
adversity direction	
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 I). Some significant organ weight changes were observed, but these are most prominent in test rats."

Plot

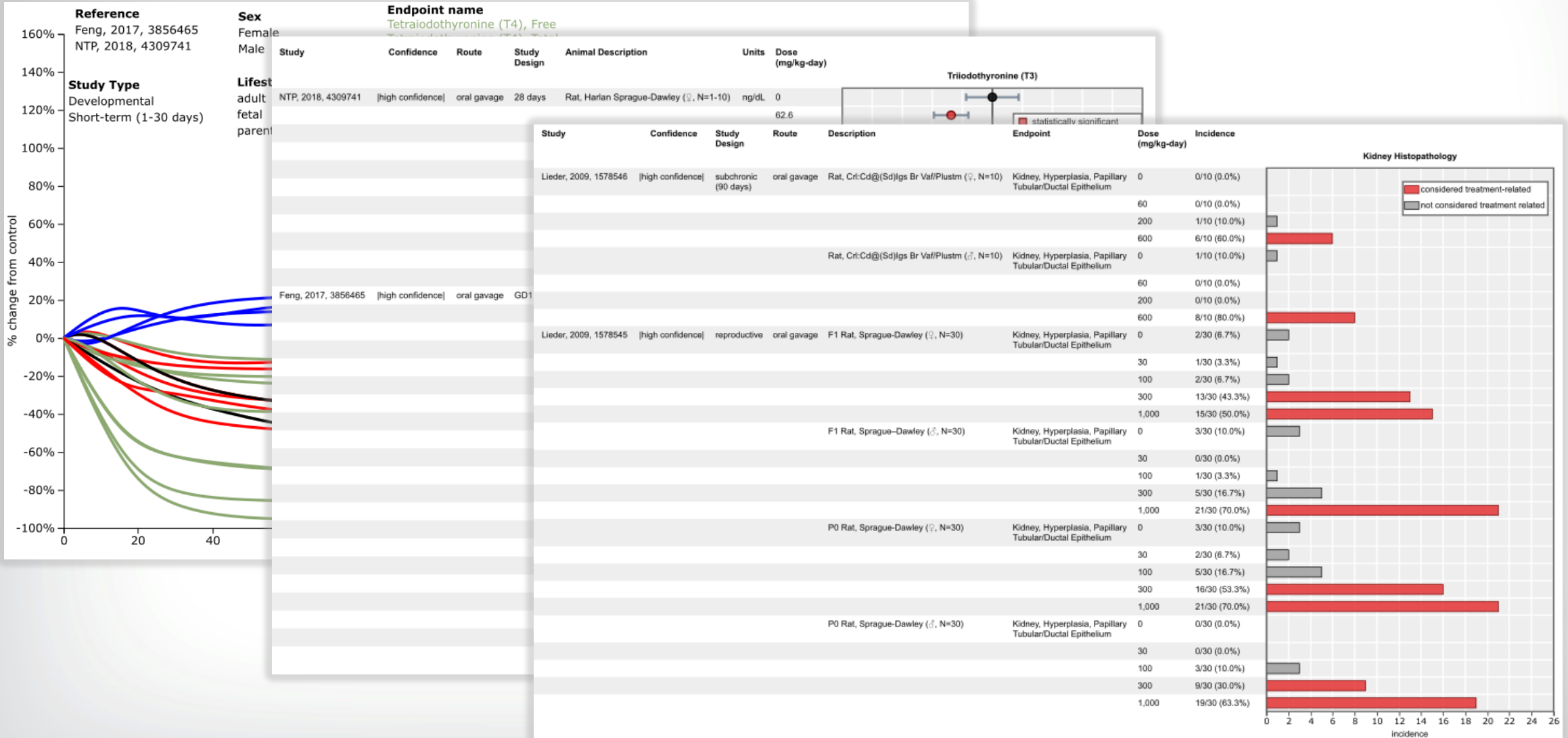


Methodology

"Three hundred eighty four male and 384 female weanling Cri:CD BR rats were received from Charles River Laboratories, Inc., Portage, Michigan. Prior to being received, 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 with 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 and were artificially illuminated (fluorescent light) on a 12-hour light/dark cycle. Throughout the test period, except during exposures, rats were supplied with a feeder filled daily with approximately 50 or 70g of irradiated Purina Rodent Chow #5056 (chunk), resp. At the one-year interim sacrifice, the amount of chow was adjusted according to the number of animals remaining in a cage. Rats were allowed free access to water and food throughout the study."



Looking at Patterns Across Studies





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 (e.g., 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

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

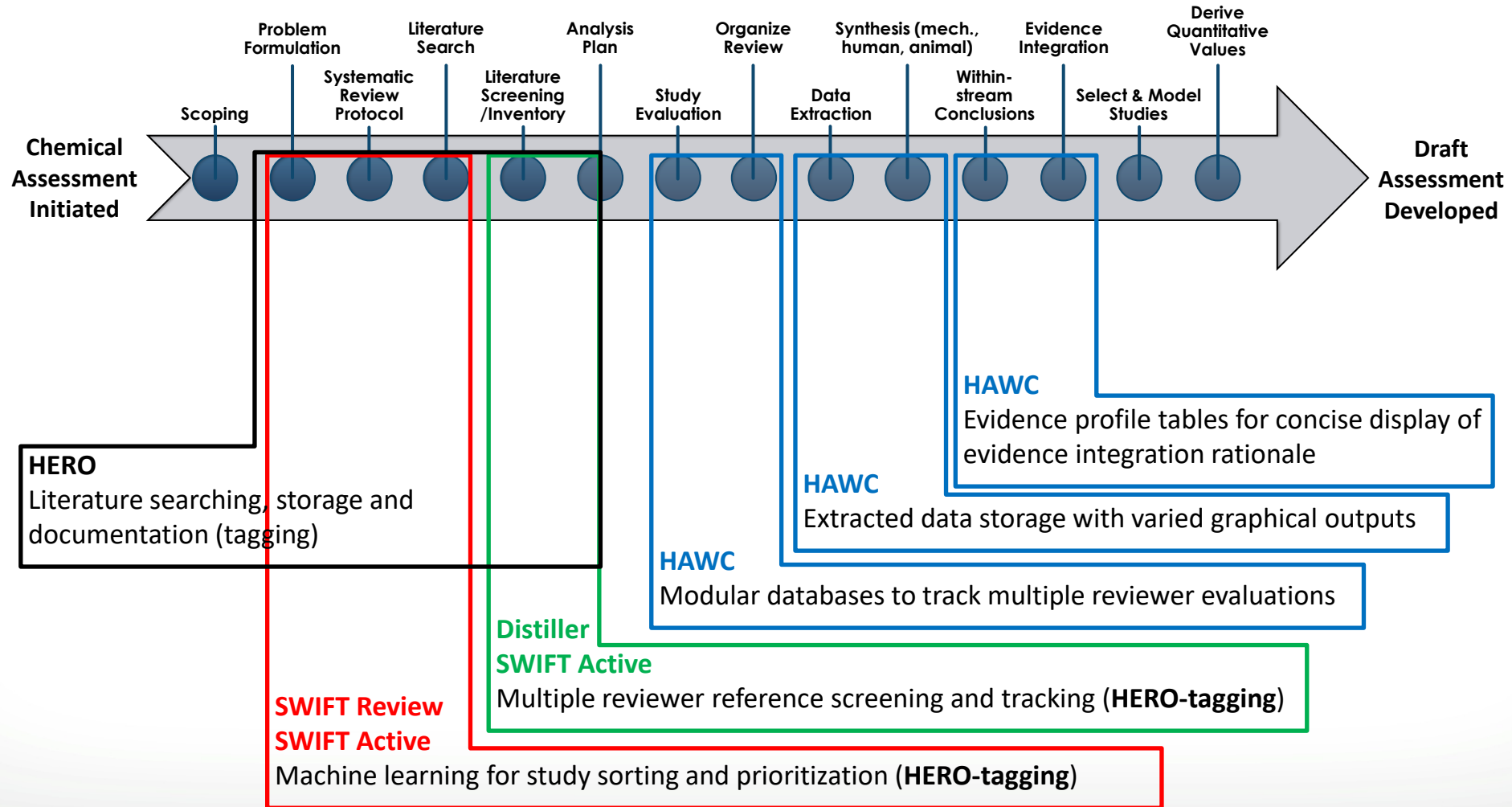
- **Animal bioassay data**

Complete export

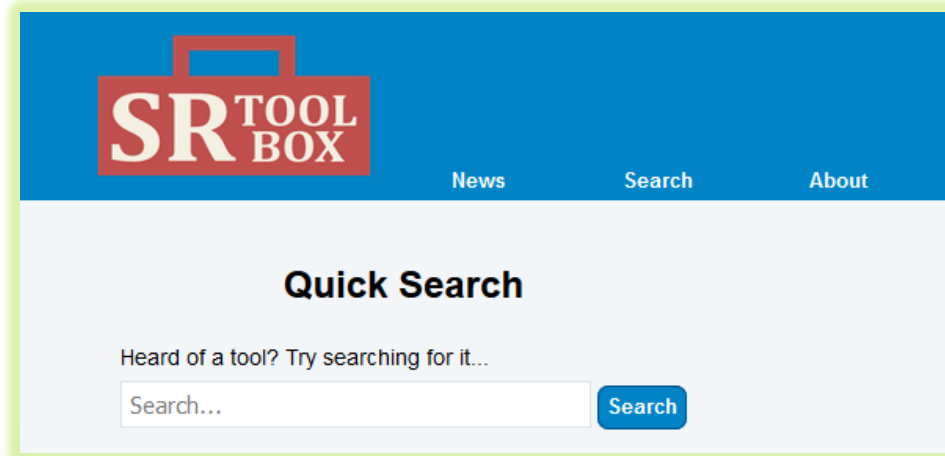
Endpoint summary

Microsoft Excel spreadsheet

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

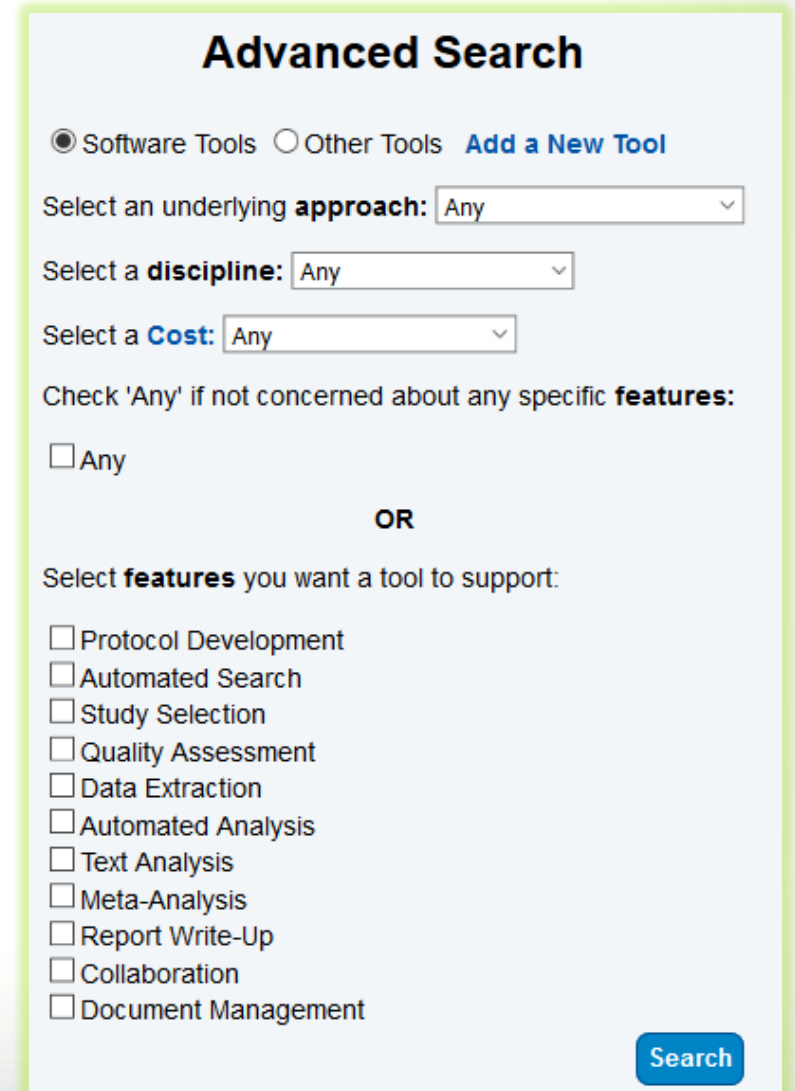


- Rapidly-growing field
- Machine-learning methods for screening (fairly mature)
- Topic modeling for clustering (fairly mature)
- Electronic extraction from full-text (developing rapidly)
- Text analytics for automated evidence mapping (in development)



The screenshot shows the SR Tool Box website. At the top is a blue header with the SR Tool Box logo on the left and navigation links for 'News', 'Search', and 'About' on the right. Below the header is a 'Quick Search' section with a text input field containing 'Search...' and a blue 'Search' button. Above the input field is the text 'Heard of a tool? Try searching for it...'.

<http://systematicreviewtools.com/>



The screenshot shows the 'Advanced Search' interface. It features a title 'Advanced Search' and two radio buttons: 'Software Tools' (selected) and 'Other Tools', with a link 'Add a New Tool'. Below are three dropdown menus for 'approach', 'discipline', and 'Cost', all set to 'Any'. A checkbox 'Any' is present with the instruction 'Check 'Any' if not concerned about any specific features:'. An 'OR' separator follows. A list of features with checkboxes includes: Protocol Development, Automated Search, Study Selection, Quality Assessment, Data Extraction, Automated Analysis, Text Analysis, Meta-Analysis, Report Write-Up, Collaboration, and Document Management. A blue 'Search' button is at the bottom right.



QUESTIONS??