EPA United States Environmental Protection Agency

Evidence mapping for use in human health and ecological chemical assessments

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Office of Research and Development
National Center for Environmental Assessment

Systematic Evidence Map (SEM)

- **SEMs are structured like research papers**
  - **Easily updated template format**
  - **Minimized narrative content (except for method text, which is template format)**
  - **Heavily visual with interactive graphics**
  - **Concise (~16 pages of main text, 35 pages total with references and appendices)**

General Process for Systematic Review

1. **Problem formulation and protocol development**
2. **Search for and select studies** for inclusion
3. **Extract data** from studies
4. **Assess quality and risk of bias** of individual studies
5. **Integrate evidence and develop conclusions**

Fit-for-purpose:
Decision-making needs can shape the SR (scoping and problem formulation)

ECOTOX Knowledgebase

Slide from Nichols and Lavoie, SETAC 2019.

General Process for Systematic Review

1. Problem formulation and protocol development
2. Search for and select studies for inclusion
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4. Assess quality and risk of bias of individual studies
5. Integrate evidence and develop conclusions

- Chemical verification and development of search terms
- Conduct Literature searches
- Identify and acquire potentially applicable studies
- Review Titles/Abstracts and full-text for relevance
- Extract and curate data from relevant studies

Literature Searching Methods

Search T

- Californ
- USEPA C
- Universi Base
- USEPA R
- Office o
- Food an
- PAN Pes
- Web "Sc

- Before t chemica sources

- Agricola
- Dissertation Ab
- ProQuest CSA
- PubMed (Natio
- Science Direct
- TOXNET
- Web of Science
- Unify (internal

  - Searches f additional

Other

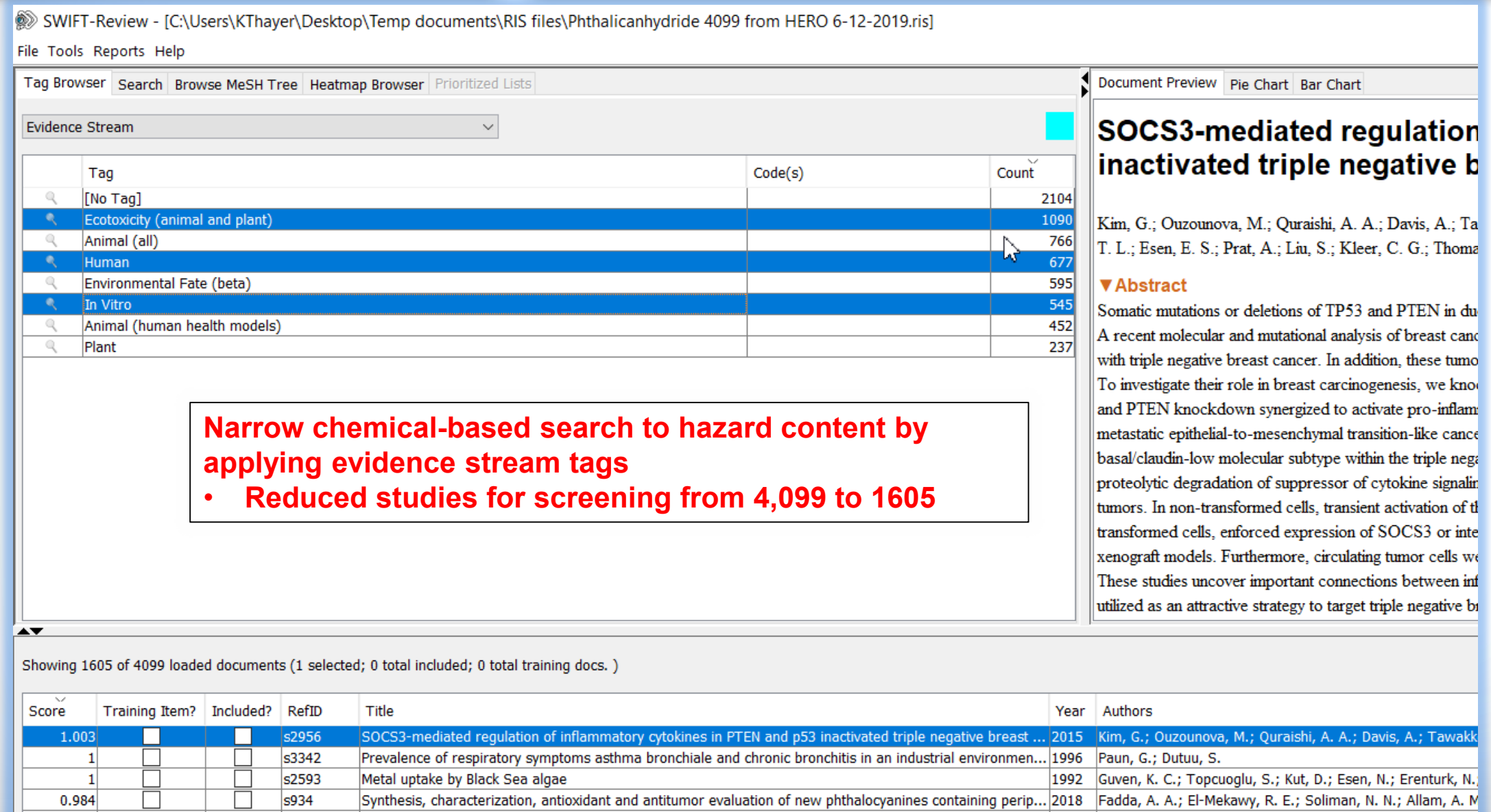
" Online Bioir

- Chemical Dashbo Pubchem Bioact
- National Toxicolo
- Comparative Tox
- Public Data from
- EPA Chemview d EPA under TSCA
- European Chemi
- EPA's High Produ
- The Organizatior Development (O High Production

APPENDIX B. LITERATURE SEARCH STRATEGIES

Agricola	Agricola 01: 1,2-BENZENE DICARBOXYLIC ACID ANHYDRIDE 1,2-Benzenedicarboxylic acid anhydride 1,2-Benzenedicarboxylic anhydride 1,3-Dihyd 1,3-Isober 1,3-Phthal 2-Benzofu Araldite H EINECS 2 HT 901 N Agricola Isobenzof NSC 1043 OP 392 o-phthalic ortho-phth Phthaland Phthalanh Phthalic a Phthalic a Phthalica N Agricola Retarder Retarder Retarder Retarder Rikacid P Sconoc 5 Sconoc 7 TGL 6525 UN 2214 Vulkalent N Agricola Vulkalent Wilrol P	May 1, 2019 Results: 119
ProQuest CSA	ALL("1,2-BENZENE DICARBOXYLIC ACID ANHYDRIDE" OR "1,2-Benzenedicarboxylic acid anhydride" OR "1,2-Benzenedicarboxylic anhydride" OR "1,3-Dihydro-1,3-dioxoisobenzofurane" OR "1,3-Isobenzofurandione" OR "1,3-Phthalandione" OR "2-Benzofuran-1,3-dione" OR "Araldite HT 901" OR "EINECS 201-607-5" OR "HT 901" OR "Isobenzofuran-1,3-dione" OR "NSC 10431" OR "OP 392" OR "o-phthalic acid anhydride" OR "ortho-phthalic acid anhydride" OR "Phthalandione" OR "Phthalanhydride" OR "Phthalic acid anhydride" OR "Phthalic anhydride" OR "Phthalicanhydride" OR "Retarder AK" OR "Retarder B-C" OR "Retarder ESEN" OR "Retarder PD" OR "Rikacid PA" OR "Sconoc 5" OR "Sconoc 7" OR "TGL 6525" OR "UN 2214" OR "Vulkalent B" OR "Vulkalent B/C" OR "Wilrol P") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	April 26, 2019 Results: 555
PubMed	"1,2-BENZENE DICARBOXYLIC ACID ANHYDRIDE" OR "1,2-Benzenedicarboxylic acid anhydride" OR "1,2-Benzenedicarboxylic anhydride" OR "1,3-Dihydro-1,3-dioxoisobenzofurane" OR "1,3-Isobenzofurandione" OR "1,3-Phthalandione" OR "2-Benzofuran-1,3-dione" OR "Araldite HT 901" OR "EINECS 201-607-5" OR "HT 901" OR "Isobenzofuran-1,3-dione" OR "NSC 10431" OR "OP 392" OR "o-phthalic acid anhydride" OR "ortho-phthalic acid anhydride" OR "Phthalandione" OR "Phthalanhydride" OR "Phthalic acid anhydride" OR "Phthalic anhydride" OR "Phthalicanhydride" OR "Retarder AK" OR "Retarder B-C" OR "Retarder ESEN" OR "Retarder PD" OR "Rikacid PA" OR "Sconoc 5" OR "Sconoc 7" OR "TGL 6525" OR "UN 2214" OR "Vulkalent B" OR "Vulkalent B/C" OR "Wilrol P"	May 5, 2019 Results: 385
Science Direct	Science Direct 01: "1,2-BENZENE DICARBOXYLIC ACID ANHYDRIDE" OR "1,2-Benzenedicarboxylic acid anhydride" OR "1,2-Benzenedicarboxylic anhydride" OR "1,3-Dihydro-1,3-dioxoisobenzofurane" OR "1,3-Isobenzofurandione" OR "1,3-Phthalandione" OR "2-Benzofuran-1,3-dione" OR "Araldite HT 901" OR "EINECS 201-607-5" N=7 Science Direct 02: "HT 901" OR "Isobenzofuran-1,3-dione" OR "NSC 10431" OR "OP 392" OR "o-phthalic acid anhydride" OR "ortho-phthalic acid anhydride" OR "Phthalandione" OR "Phthalanhydride" OR "Phthalic acid anhydride" N=19 Science Direct 03: "Phthalic anhydride" OR "Phthalicanhydride" OR "Retarder AK" OR "Retarder B-C" OR "Retarder ESEN" OR "Retarder PD" OR "Rikacid PA" OR "Sconoc 5" OR "Sconoc 7" N=741 Science Direct 04:	May 1, 2019 Results: 767

SWIFT Review to Identify Hazard Literature



SWIFT Review – Behind the Tags

Ecotoxicity (animal and plant)

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

Full search strategy is ~130 pages long

"Honey Bee" OR "Apis mellifera" OR "Bread Wheat" OR "Triticum aestivum" OR "Soybean" OR "Glycine max" OR "Northern Bobwhite Quail" 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

Sciome
Enabling Science via Analytical Informatics

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

~25,000 Scientific & common names from all species with toxicity data identified in ECOTOX Knowledgebase + Generic species habitat tags (e.g. AQUATIC,AVIAN TERRESTRIAL, BENTHIC)

POPULATION, exposures, comparators and outcomes (PECO) criteria

- ***Human*:** Any population and life stage

- ***Animal*:** Aquatic and terrestrial species (live, whole organism) of any life stage. Bacteria and viruses are not included

- ***Plants*:** Aquatic and terrestrial species (live), all plants including algal, moss, lichen and fungi species
  - Animal models further categorized as:
    - Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig
    - Ecotoxicological models: wild mammals (e.g. Peromyscus sp.), insects, spiders, crustaceans, fish, birds, mollusks, invertebrates, amphibians, worms and reptiles
      - NOTE: Identify and define how to categorize "cross-over species"
        - Laboratory strains of rats for Ecotoxicological models
        - Non-mammalian models for Human Health models (e.g. Zebrafish Embryo tests)

Population, EXPOSURES, comparators and outcomes (PECO) criteria.

- **Relevant forms of chemical:** Name, CASRNs, synonyms, isomers, trade names, product names, etc.
- ***Human***: Any exposure to the chemical
- ***Animal*:** Any exposure to chemical including via water, injection, diet and dermal
- ***Plants*:** Exposure to chemical via water or soil, with reported concentration and duration.
  - Studies involving exposures to mixtures will be included only if they also include exposure to chemical of interest alone
  - Chemical exposures for aquatic plants where only sediment concentrations are reported from field studies are excluded
  - laboratory-based sediment studies are retained

Population, exposures, COMPARATORS and OUTCOMES (PECO) criteria.

- ***COMPARATORS***
- ***Human***: **A comparison or referent population exposed to lower/no measured chemical or for shorter periods of time.**
  - **Case series are considered to meet PECO criteria even if no referent group is presented.**
  - **Case reports describing findings in 1-3 people in any setting are tracked as "potentially relevant supplemental information.**
- ***Animal and Plants*: A concurrent control group exposed to vehicle-only treatment and/or untreated control**
- ***OUTCOMES***
  - ***Human***: All health outcomes (cancer and noncancer)
  - ***Animal and Plants*:** All biological effects

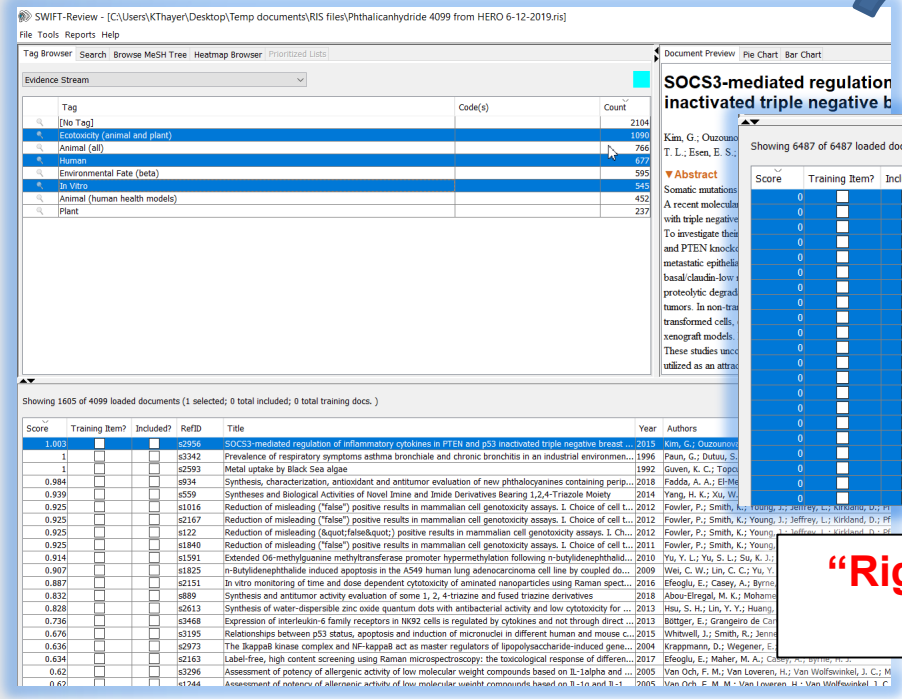
Categories of "Potentially Relevant Supplemental Material"

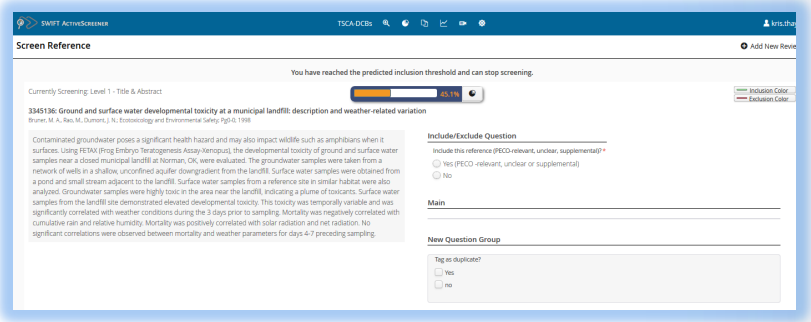
Category	Evidence
Mechanistic Studies	Studies reporting measurements that relate to a health outcome that inform the biological or chemical events associated with phenotypic effects in mammalian and non-mammalian models. Measurements are typically reported as *in vitro*, *ex vivo* and *in silico* studies.
ADME, PBPK, Toxicokinetic	Studies designed to capture information on the adsorption, distribution, metabolism and excretion, toxicokinetic or pharmacokinetic attributes of chemicals
Susceptible Populations	Studies that identify potentially susceptible subgroups: specific demographic, life stage or genotype
Mixture Studies	Mixture studies that are not PECO relevant because they do not have chemical of interest only data
Case Reports	Case reports ($n \leq 3$)
Non-English	Tracked as supplemental information for potential translation at a later time

Categories of "Potentially Relevant Supplemental Material"

Category	Evidence
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries
Conference Abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction
Chemical – Specific Considerations	After reviewing a reasonable representation of the abstracts/full-text often themes evolve that lead to conflict among screeners with variable interpretations. Therefore, chemical specific definitions can be added to bin these studies that may not be directly PECO relevant, but could contain useful information. Examples: 1.) Chemical of interest is used as a pretreatment sensitizing agent for other chemicals in a similar class to elicit an effect 2.) Chemical of interest is routinely used in a mixture as a synergist or antagonist to illicit the mechanism of action for a pesticide

SWIFT Review + SWIFT Active Workflow



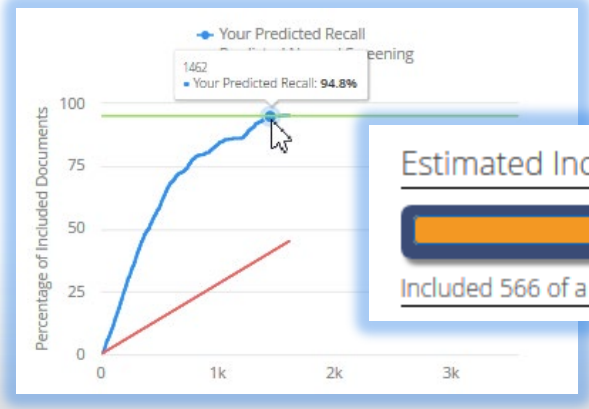


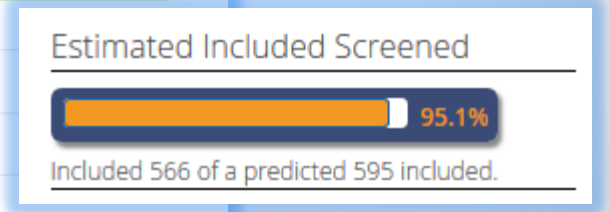
Machine-learning based screening

"Right click" to move to SWIFT Active

SWIFT Review to identify hazard records

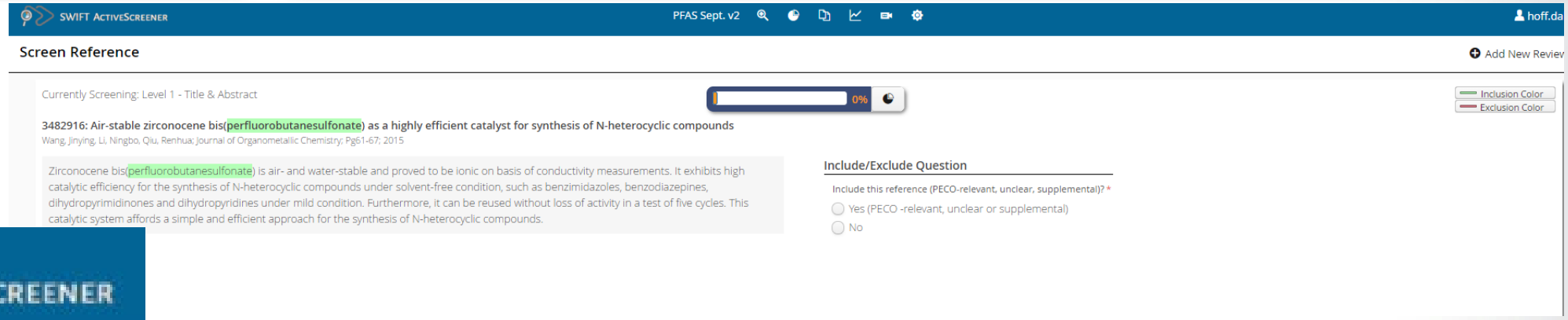
- **Only 45% of studies needed to screened**
- **Software tells screeners when they can stop**
- **Review of grey literature resources, reference list of included studies, references cited in other assessments, and public comment mitigate concern for missing "key" studies**



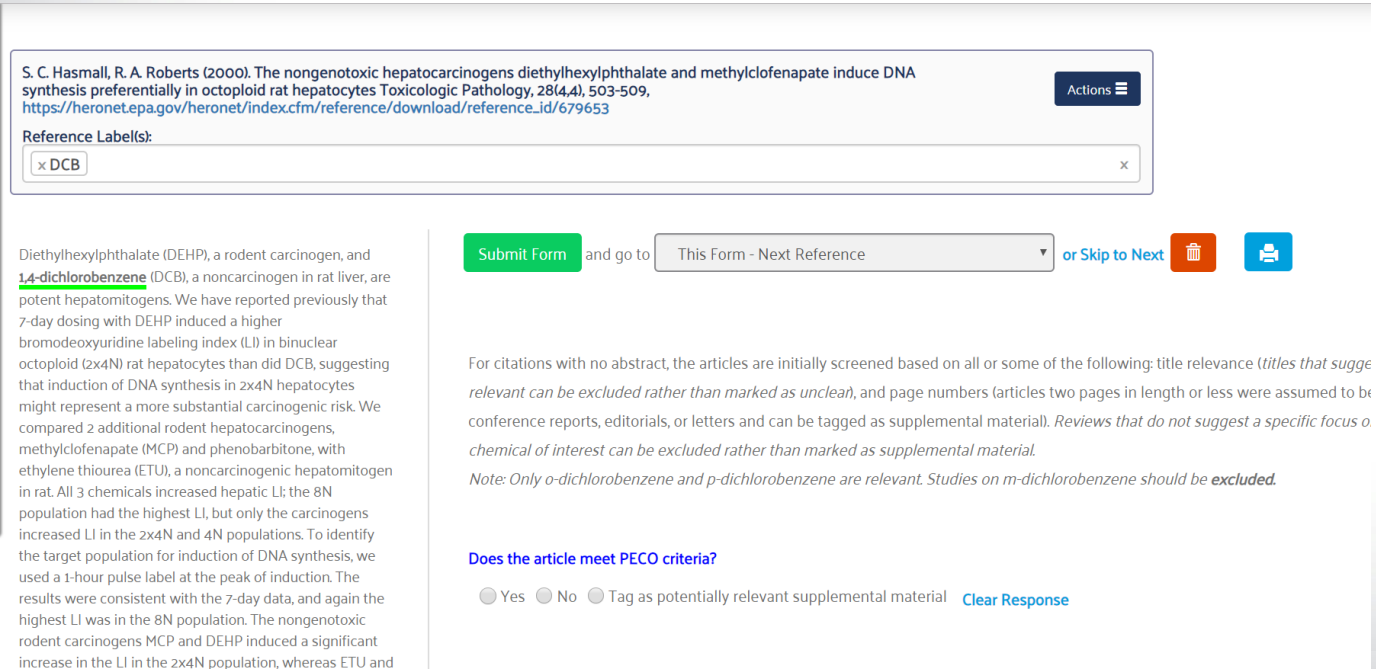


Using Swift Active Screener and DistillerSR for rapidly screening references

> 2000 References



SWIFT ACTIVESCREENER



DistillerSR

< 2000 References

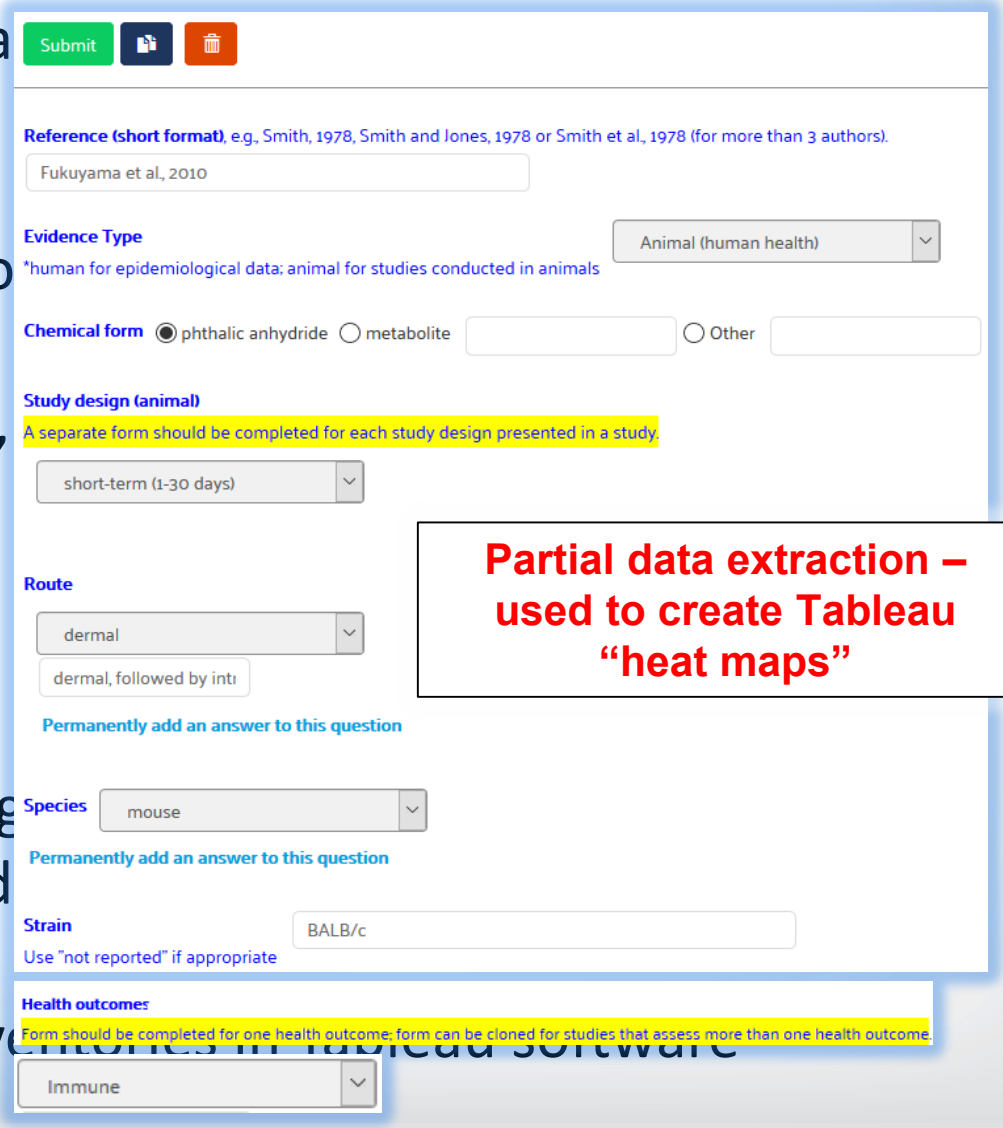
Summarizing Study Designs and Data Curation – Creating Literature Inventories

- Those references INCLUDED after TIAB screening a
  criteria using full text of the reference

- Data summarized for BOTH Human Health and Eco

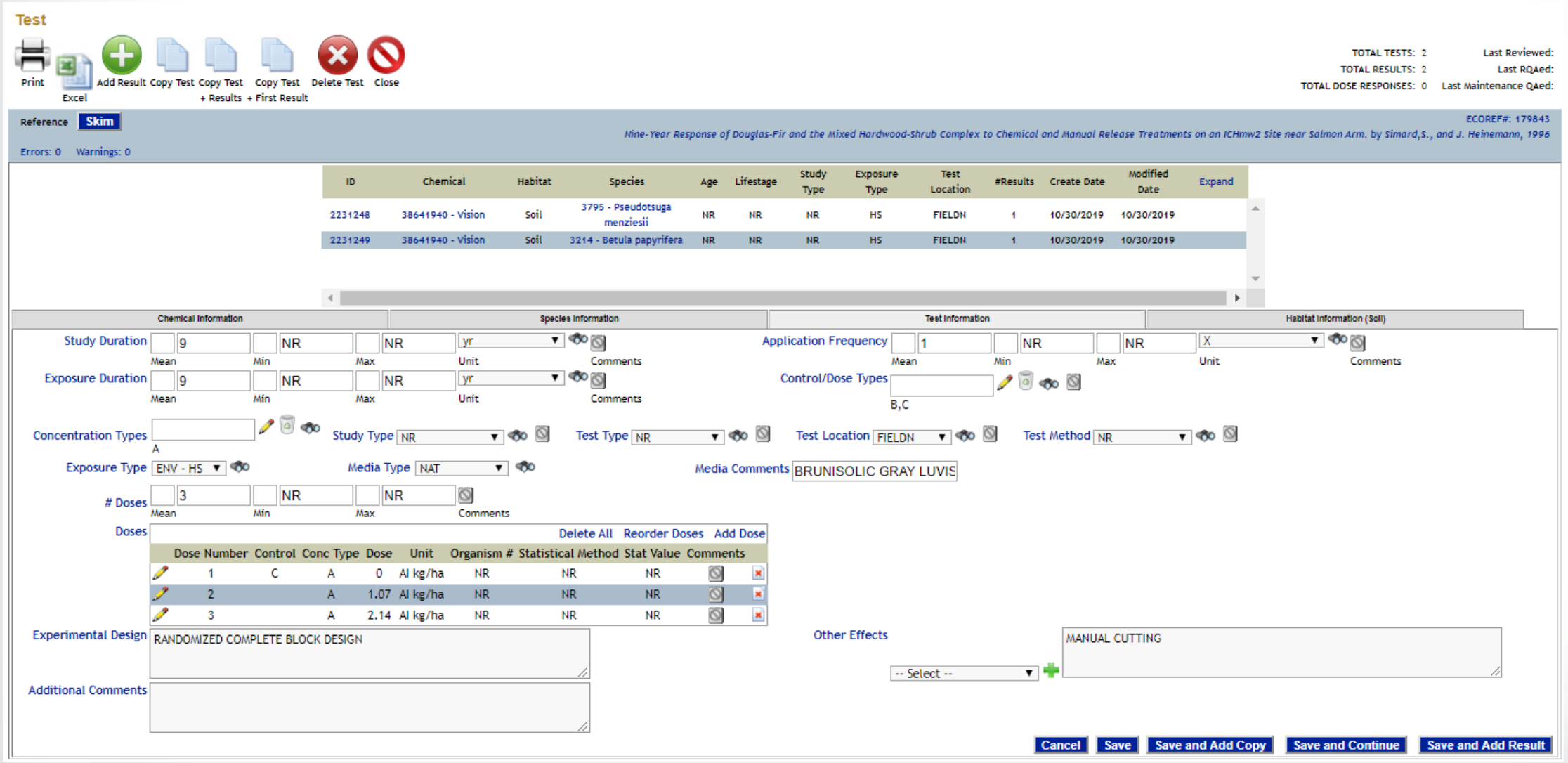
  - Study type: Acute, subchronic, developmental,
  - Exposure Route
  - Species
  - Health System or type of effect assessed
  - Take note of Cross-over species
    - Zebrafish binned into ECO or HH depending
    - Lab rodents binned into HH or ECO depend

- These outputs are initially curated as literature inv



Partial data extraction – used to create Tableau "heat maps"

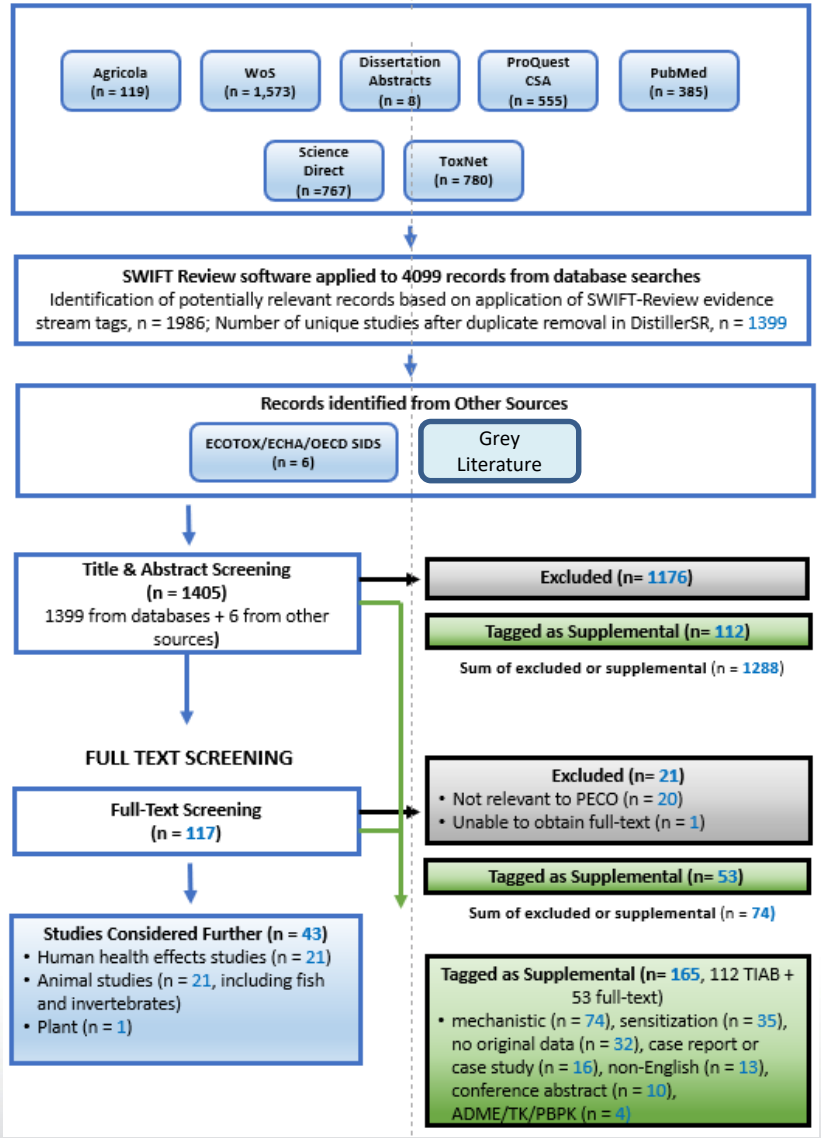
ECOTOX data curation in UNIFY and Knowledgebase - Post Evidence map



ECOTOX Knowledgebase curates up 250 fields from references meeting PECO Criteria

Literature Survey Study Flow

Used specialized-learning software
- **SWIFT Review "filters"**
- **SWIFT Review + SWIFT Active for other chemicals with > 2000 references**



4099 references identified

1399 references after De-Duplication and Swift-Review Filters

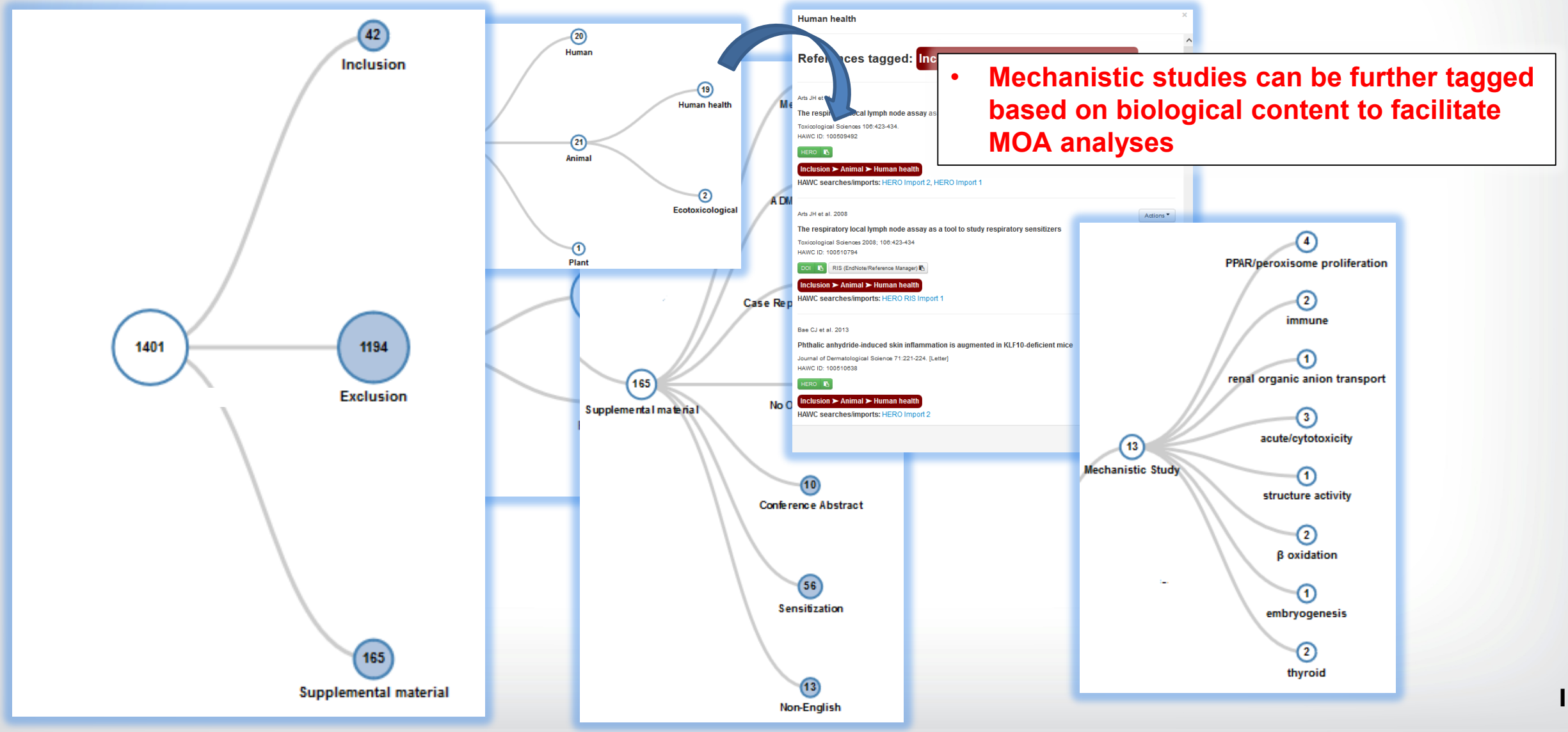
1405 after grey Literature

117 references after TIAB screening

Studies for full assessment (n=43)

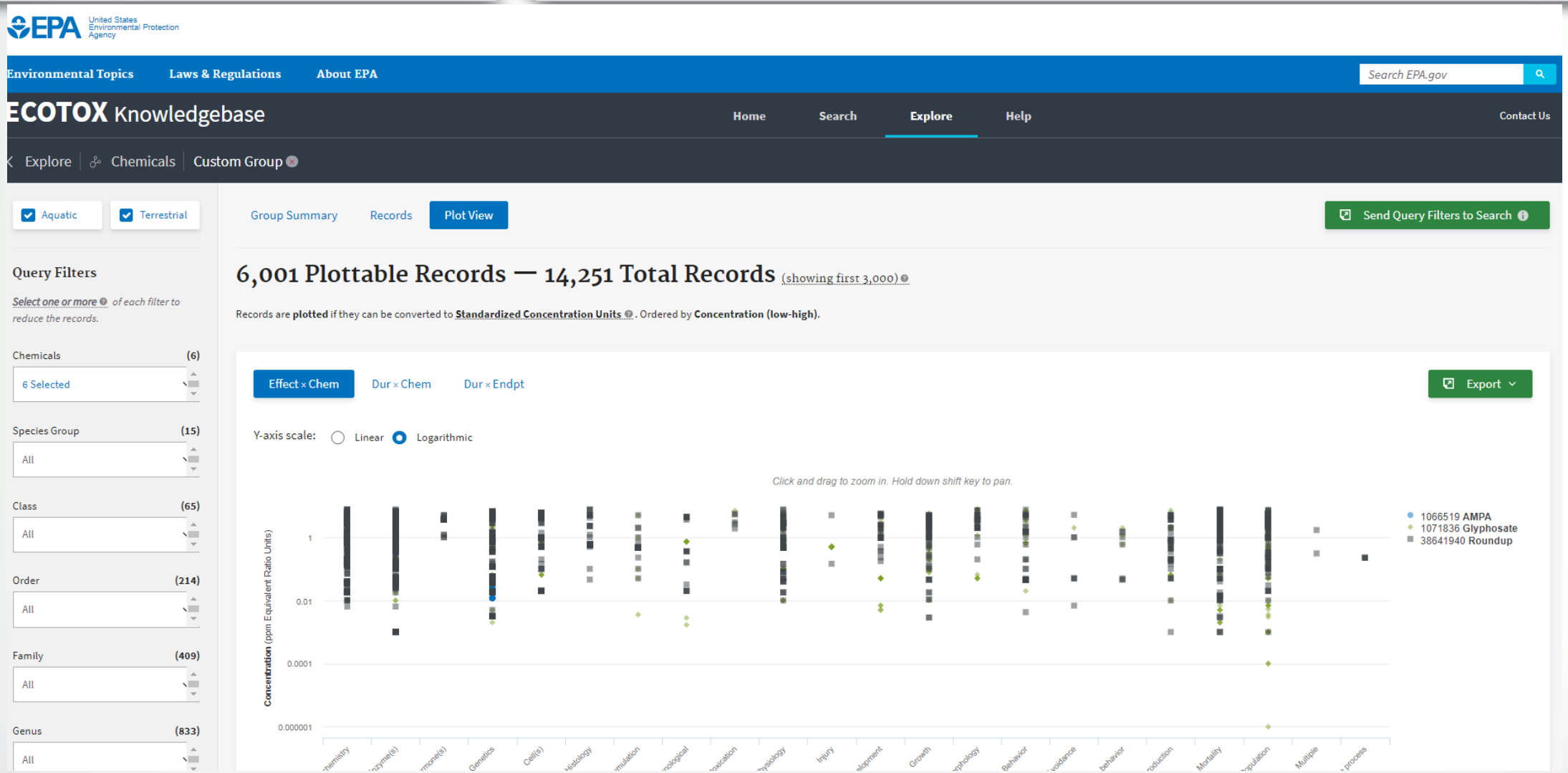
- Human Health Effect Studies (n = 21)
- Animal studies, including Fish and inverts (n=21)
- Plants (n=1)

Interactive Study Flows



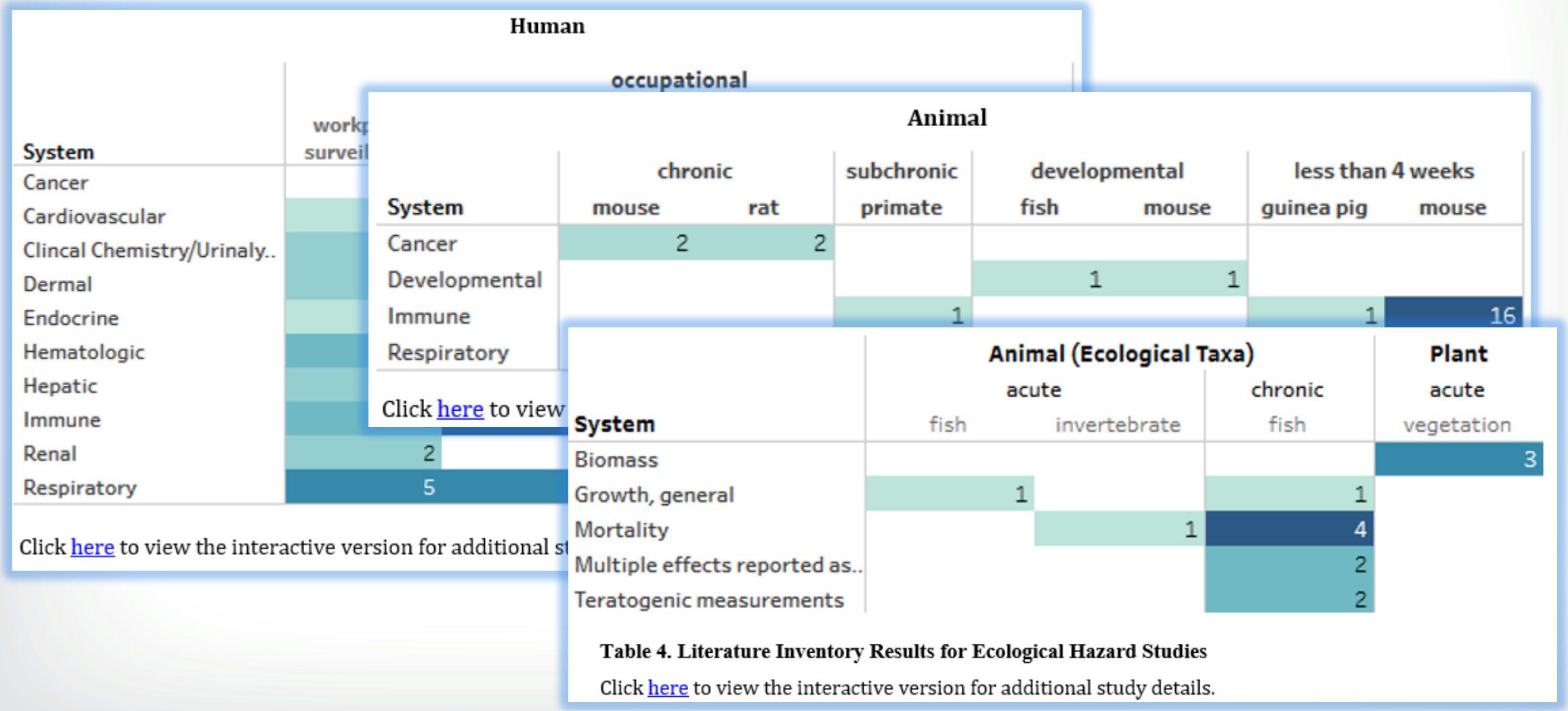
- **Mechanistic studies can be further tagged based on biological content to facilitate MOA analyses**

ECOTOX data visualization



ECOTOX Knowledgebase curates up 250 fields from references meeting PECO Criteria

Tableau Literature Inventory Heat Maps



Human

System	occupational
	workp surveil
Cancer	
Cardiovascular	
Clincal Chemistry/Urinaly..	
Dermal	
Endocrine	
Hematologic	
Hepatic	
Immune	
Renal	2
Respiratory	5

Click here to view the interactive version for additional st

Animal

System	chronic		subchronic	developmental		less than 4 weeks	
	mouse	rat	primate	fish	mouse	guinea pig	mouse
Cancer	2	2					
Developmental				1	1		
Immune			1			1	16
Respiratory							

Click here to view

Animal (Ecological Taxa) / **Plant**

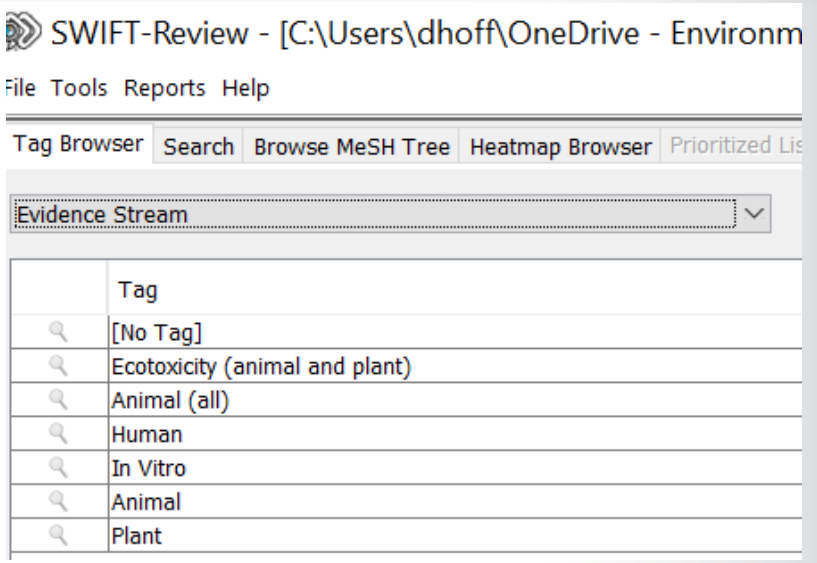
System	acute		chronic	acute
	fish	invertebrate	fish	vegetation
Biomass				3
Growth, general	1		1	
Mortality		1	4	
Multiple effects reported as..			2	
Teratogenic measurements			2	

Table 4. Literature Inventory Results for Ecological Hazard Studies

Click here to view the interactive version for additional study details.

Developmental achievements and lessons learned

- Calibrating and verifying data analytic/artificial intelligence tools
  - Developed & calibrated utilities in data analytic tools
  - Compared manual curation from ECOTOX protocols with evidence map process to validate results
    - Adjusted analytic tools to obtain 100% concurrence with manual curation results
  - Identified importance of pilot phase of screening to allow for chemical-specific considerations in the PECO



ECOTOX Knowledgebase = SWIFT ActiveScreener + DistillerSR

Developmental achievements and lessons learned

- Adjustment of literature search strategies to accommodate both human health and ecotoxicology
- Fit-for-purpose tool deployment; eg. Distiller <2000 TIAB refs, Swift Active >2000 refs)
- Training not onerous, but critical for software and HH vs. ECO discipline subtleties
- Need to use project management applications and tools to track progress in crowd sourcing environment of workflow
- HH/ECO TRANSLATION DICTIONARY: A lesson in parallel evolution!

DistillerSR

SWIFT ACTIVESCREENER

Evidence Mapping Support

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Marcy Card
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Stan Barone
Seema Schappelle
Yvette Selby-Mohamadu
Chantel Nicolas
Yousuf Ahmad