

Evidence mapping for use in human health and ecological chemical assessments

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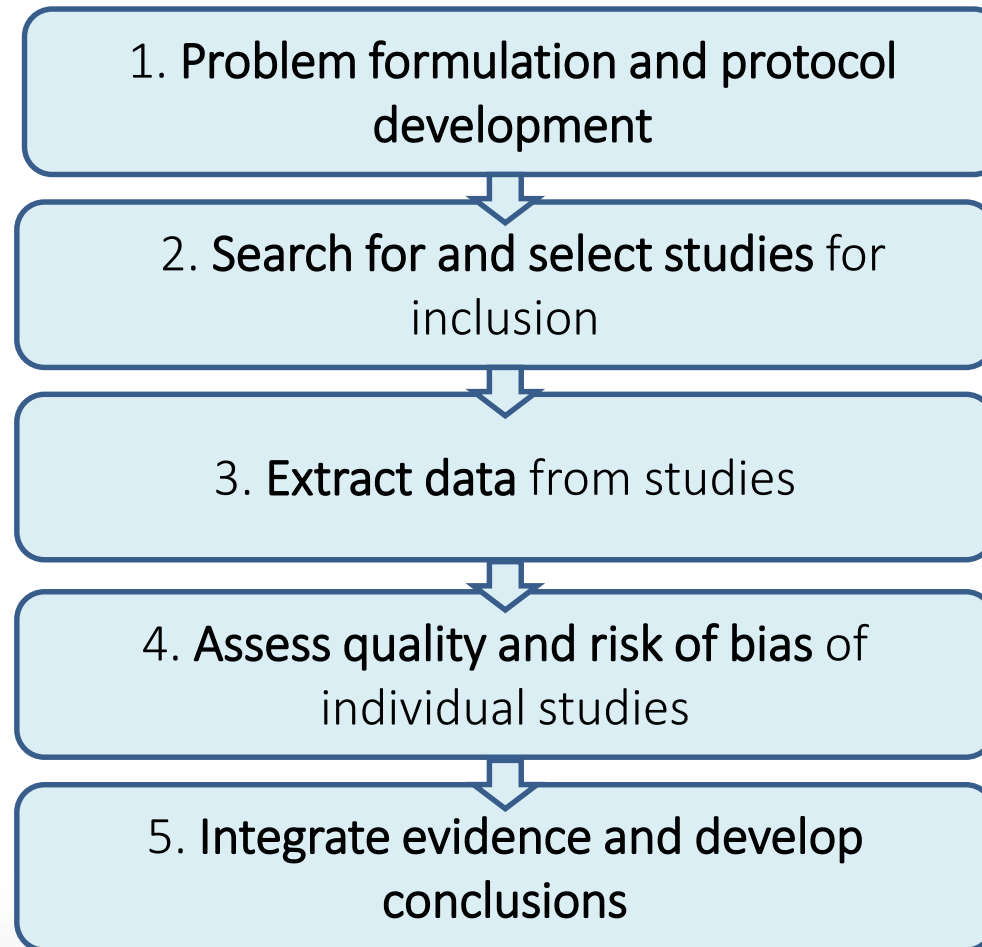
[‡] USEPA, Office of Research and Development, Center for Computational Toxicology and Exposure, Great Lakes Toxicology and Ecology Division, Duluth, MN



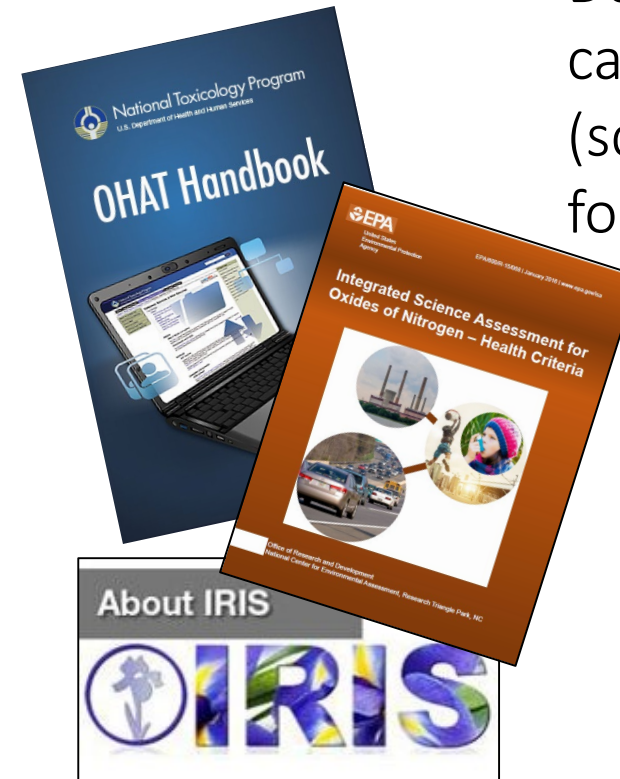
Systematic Evidence Map (SEM)

Headings	Pages	Results
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- **SEM**s 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)

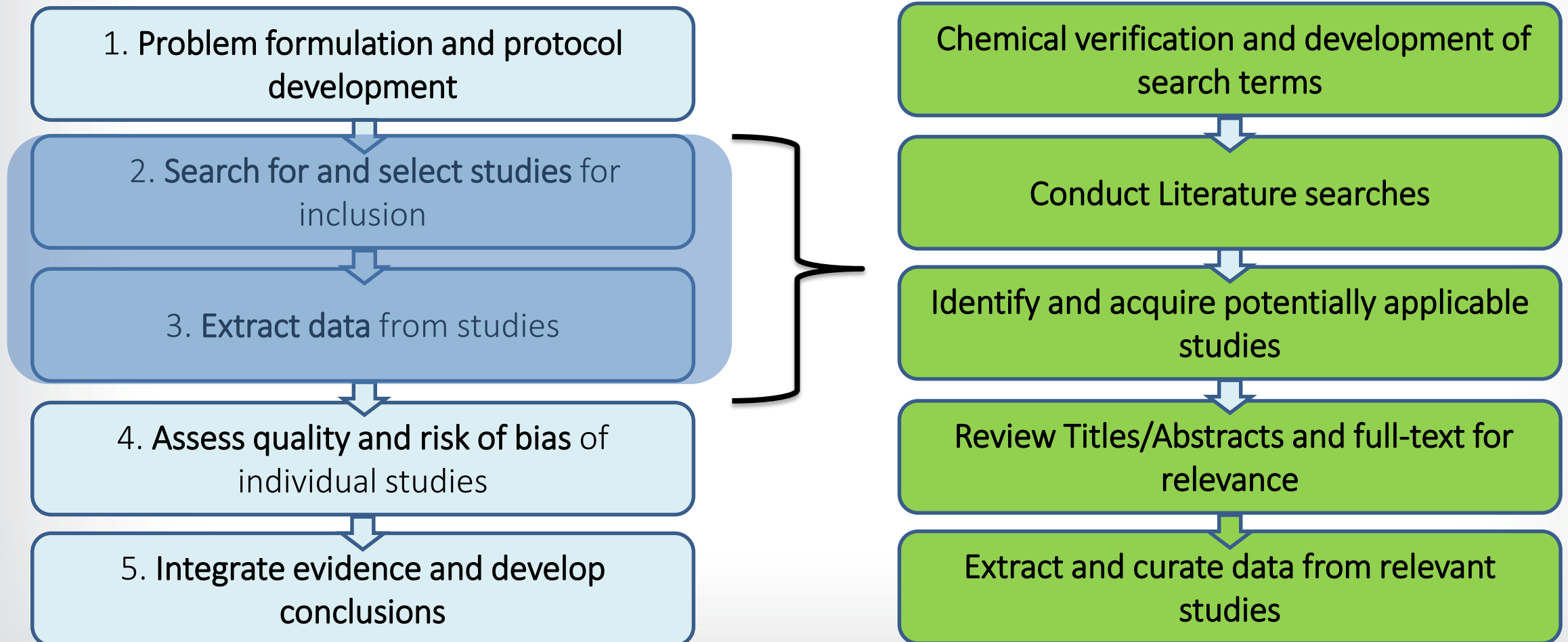


Fit-for-purpose:
Decision-making needs can shape the SR (scoping and problem formulation)



ECOTOX Knowledgebase

General Process for Systematic Review





Literature Searching Methods

Search

- California
- USEPA C
- University
- Base
- USEPA R
- Office o
- Food an
- PAN Pes
- Web "So
- Before t
- chemical
- sources

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

Other

"Online Bioin

- Chemical Dashbo
- Pubchem Bioact
- National Toxicolo
- Comparative Tox
- Public Data from
- EPA Chemview d
- EPA under TSCA
- European Chemi
- EPA's High Produ
- The Organization
- 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-Isobenzofuran-1,3-dione 1,3-Phthalandione 2-Benzofuran-1,3-dione Araldite HT 901 EINECS 201-607-5 HT 901 N=7 Agricola C Isobenzofuran-1,3-dione NSC 10431 OP 392 o-phthalic acid anhydride ortho-phthalic acid anhydride Phthalandione Phthalanhydride Phthalic anhydride Phthalic anhydride Phthalic anhydride Phthalic anhydride N=7 Agricola C Retarder AK Retarder B-C Retarder ESEN Retarder PD Rikacid PA Scopac 5 Scopac 7 TGL 6525 UN 2214 Vulcanat B/C Vulcanat B/C N=7 Agricola C Vulcanat B/C N=7	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-dioxoisobenzofuran" OR "1,3-Isobenzofuran-1,3-dione" 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 "Phthalic anhydride" OR "Retarder AK" OR "Retarder B-C" OR "Retarder ESEN" OR "Retarder PD" OR "Rikacid PA" OR "Scopac 5" OR "Scopac 7" OR "TGL 6525" OR "UN 2214" OR "Vulcanat B" OR "Vulcanat B/C" OR "Vulcanat 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-dioxoisobenzofuran" OR "1,3-Isobenzofuran-1,3-dione" 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 "Phthalic anhydride" OR "Retarder AK" OR "Retarder B-C" OR "Retarder ESEN" OR "Retarder PD" OR "Rikacid PA" OR "Scopac 5" OR "Scopac 7" OR "TGL 6525" OR "UN 2214" OR "Vulcanat B" OR "Vulcanat B/C" OR "Vulcanat 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-dioxoisobenzofuran" OR "1,3-Isobenzofuran-1,3-dione" 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 "Phthalic anhydride" OR "Retarder AK" OR "Retarder B-C" OR "Retarder ESEN" OR "Retarder PD" OR "Rikacid PA" OR "Scopac 5" OR "Scopac 7" N=741 Science Direct 04:	May 1, 2019 Results: 767



SWIFT Review to Identify Hazard Literature

SWIFT-Review - [C:\Users\KThayer\Desktop\Temp documents\RIS files\Phthalicanhydride 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		677
Environmental Fate (beta)		595
In Vitro		545
Animal (human health models)		452
Plant		237

Narrow chemical-based search to hazard content by applying evidence stream tags

- Reduced studies for screening from 4,099 to 1605

Document Preview Pie Chart Bar Chart

SOCS3-mediated regulation of inflammatory cytokines in PTEN and p53 inactivated triple negative breast cancer

Kim, G.; Ouzounova, M.; Quraishi, A. A.; Davis, A.; Tawakkul, T. L.; Esen, E. S.; Prat, A.; Liu, S.; Kleer, C. G.; Thomas, S. A.

Abstract

Somatic mutations or deletions of TP53 and PTEN in ductal carcinoma in situ (DCIS) and triple negative breast cancer (TNBC) are associated with increased risk of progression to invasive disease. A recent molecular and mutational analysis of breast cancer with triple negative breast cancer. In addition, these tumors To investigate their role in breast carcinogenesis, we know and PTEN knockdown synergized to activate pro-inflammatory metastatic epithelial-to-mesenchymal transition-like cancer basal/claudin-low molecular subtype within the triple negative proteolytic degradation of suppressor of cytokine signaling tumors. In non-transformed cells, transient activation of the transformed cells, enforced expression of SOCS3 or interleukin xenograft models. Furthermore, circulating tumor cells were These studies uncover important connections between inflammation utilized as an attractive strategy to target triple negative breast

Showing 1605 of 4099 loaded documents (1 selected; 0 total included; 0 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Authors
1.003	<input type="checkbox"/>	<input type="checkbox"/>	s2956	SOCS3-mediated regulation of inflammatory cytokines in PTEN and p53 inactivated triple negative breast ...	2015	Kim, G.; Ouzounova, M.; Quraishi, A. A.; Davis, A.; Tawakkul, T. L.; Esen, E. S.; Prat, A.; Liu, S.; Kleer, C. G.; Thomas, S. A.
1	<input type="checkbox"/>	<input type="checkbox"/>	s3342	Prevalence of respiratory symptoms asthma bronchiale and chronic bronchitis in an industrial environmen...	1996	Paun, G.; Dutuu, S.
1	<input type="checkbox"/>	<input type="checkbox"/>	s2593	Metal uptake by Black Sea algae	1992	Guyen, K. C.; Topcuoglu, S.; Kut, D.; Esen, N.; Erenturk, N.
0.984	<input type="checkbox"/>	<input type="checkbox"/>	s934	Synthesis, characterization, antioxidant and antitumor evaluation of new phthalocyanines containing perip...	2018	Fadda, A. A.; El-Mekawy, R. E.; Soliman, N. N.; Allam, A. M.



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 "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

Full search strategy is ~130 pages long

~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 <i>in vitro</i> , <i>ex vivo</i> and <i>in silico</i> 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	<p>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.</p> <p><u>Examples:</u></p> <ol style="list-style-type: none">1.) Chemical of interest is used as a pretreatment sensitizing agent for other chemicals in a similar class to elicit an effect2.) 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

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

File Tools Reports Help

Tag Browser Search Browse MeSH Tree Heatmap Browser Prioritized Lists

Evidence Stream

Tag	Code(s)	Count
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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
1.893			s2956	SOCS3-mediated regulation of inflammatory cytokines in PTEN and p53 inactivated triple negative breast...	2015	Kim, G.; Ouzounis, T. L.; Ezen, E. S.
1			s3342	Prevalence of respiratory symptoms asthma bronchiale and chronic bronchitis in an industrial environmen...	1996	Paun, G.; Dubau, S.
0.939			s2593	Metal uptake by Black Sea algae	1992	Gaven, K. C.; Topcu...
0.984			s934	Synthesis, characterization, antioxidant and antitumor evaluation of new phthalocyanines containing perip...	2018	Fadda, A. A.; El-M...
0.939			s559	Synthesis and Biological Activities of novel Imine and Imide Derivatives Bearing 1,2,4-Triazole Moiety	2014	Yang, H. K.; Xu, W.
0.925			s1016	Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell...	2012	Fowler, P.; Smith, K.; Young, J.; Jeffrey, L.; Kirkland, D.; P...
0.925			s2167	Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell...	2012	Fowler, P.; Smith, K.; Young, J.; Jeffrey, L.; Kirkland, D.; P...
0.925			s122	Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell...	2012	Fowler, P.; Smith, K.; Young, J.; Jeffrey, L.; Kirkland, D.; P...
0.925			s1840	Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell...	2011	Fowler, P.; Smith, K.; Young, J.; Jeffrey, L.; Kirkland, D.; P...
0.914			s1591	Extended O6-methylguanine methyltransferase promoter hypermethylation following n-butylidenephthalid...	2010	Yu, Y. L.; Yu, S. L.; Su, K. J.
0.907			s1825	n-Butylidenephthalide induced apoptosis in the A549 human lung adenocarcinoma cell line by coupled do...	2009	Wei, C. W.; Lin, C. C.; Yu, Y.
0.887			s2151	In vitro monitoring of time and dose dependent cytotoxicity of aminated nanoparticles using Raman spect...	2016	Efeoglu, E.; Casey, A.; Byrne...
0.832			s889	Synthesis and antitumor activity evaluation of some 1, 2, 4-triazine and fused triazine derivatives	2018	Abou-Elsaghe, M. K.; Moham...
0.828			s2613	Synthesis of water-dispersible zinc oxide quantum dots with antibacterial activity and low cytotoxicity for ...	2013	Hsu, S. H.; Lin, Y. Y.; Huang...
0.736			s3468	Expression of interleukin-6 family receptors in 1652 cells is regulated by cytokines and not through direct...	2013	Botzger, E.; Grangiers de Car...
0.676			s3195	Relationships between p53 status, apoptosis and induction of micronuclei in different human and mouse c...	2015	Whitwell, J.; Smith, R.; Jenn...
0.636			s2973	The IkappaB kinase complex and NF-kappaB act as master regulators of lipopolysaccharide-induced gene...	2004	Krappmann, D.; Wegener, E.
0.634			s2163	Label-free, high content screening using Raman microspectroscopy: the toxicological response of differen...	2017	Efeoglu, E.; Maher, M. A.; Casey, A.; Byrne, W. Z.
0.62			s3296	Assessment of potency of allergenic activity of low molecular weight compounds based on IL-1alpha and IL-1...	2005	Van Och, F. M.; Van Loveren, H.; Van Wolfswinkel, J. C.; M...
0.62			s1744	Assessment of potency of allergenic activity of low molecular weight compounds based on IL-1alpha and IL-1...	2005	Van Och, F. M.; Van Loveren, H.; Van Wolfswinkel, J. C.; M...

“Right click” to move to SWIFT Active

SOCS3-mediated regulation of inflammatory cytokines in PTEN and p53 inactivated triple negative breast

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	Stor
0			s5812	Mutagenicity Of Chloroacetaldehyde, A Possible Metabolic Product Of 1,2-Dichloroethane (Ethylene Dichloro...	3190	McC
0			s5813	Mutagenicity of chloroacetaldehyde, a possible metabolic product of 1,2-dichloroethane (ethylene dichloro...	3190	McC
0			s5863	Toxicity Studies of 1,2-Dichloroethane (Ethylene Dichloride) in F344 Rats, Sprague Dawley Rats, Osborn...	3122	Mor
0			s5013	The toxicology of chemicals - 1. Carcinogenicity. Volume 10. Chemicals of the scientific evidence	2883	Berl
0			s6270	The toxicology of chemicals - 2. Reproductive toxicology	2883	Sull
0			s4886	1,2-Dichloroethane	2920	Ano
0			s5568	Covalent Binding of 1,2-Dihalogenalkanes to DNA and S	2839	Insk
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	Chol
0			s5135	Derivatization of Ethylene Dibromide with Silica-Sup	2366	Col
0			s5818	Health Hazard Evaluation Report No. HETA-91-251-	2218	McM
0			s6125	Potential of Non-halocarbon Oxidants on Halocarb	2192	San
0			s6430	The Carcinogenic Risk of Some Organic Vapors In	2187	Wile
0			s4967	Microwave-mediated covalent binding of 1,2-dichloroethane to DNA and protein in the lung and liver of...	2170	Ban
0			s5178	Toxicological evaluation of a number of substances that may pollute the workplace air	2100	Dam

Select All
Shuffle
Remove Selected Reference(s)
Add/Remove Tag ...
Tag Search Results...
Compute Fingerprint for Selected...
Send to Active Screener...
Copy Selected
Export Document List...

SWIFT ActiveScreening

Screen Reference

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

Currently Screening Level 1 - Title & Abstract

3345186: Ground and surface water developmental toxicity at a municipal landfill: description and weather-related variation

Contaminated groundwater poses a significant health hazard and may also impact wildlife such as amphibians when it surfaces. Using RETAM (Rat Embryo Teratogenesis Assay-Micropump), 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 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, unclear, supplemental)?

☐ Yes (PECO-relevant, unclear or supplemental)
☐ No

Main

New Question Group

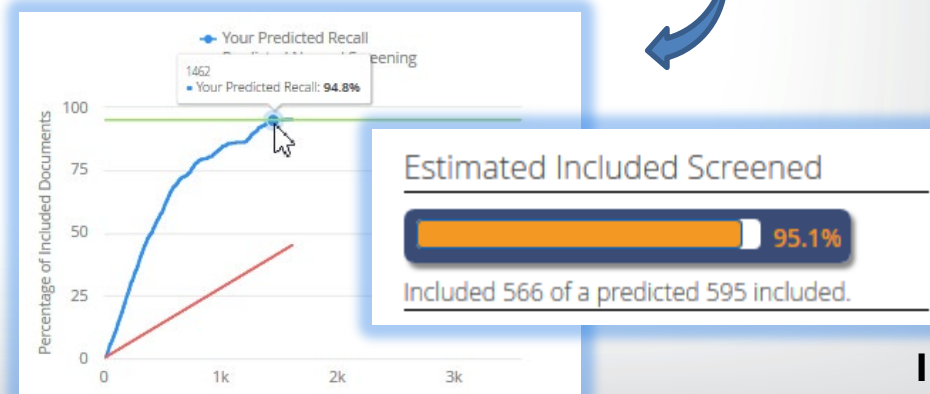
Tag as duplicate?

☐ Yes
☐ No

Machine-learning based screening

SWIFT Review to identify hazard records

- Only 45% of studies needed to be screened
- 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 PFAS Sept. v2 hoff.da

Screen Reference Add New Review

Currently Screening: Level 1 - Title & Abstract 0%

3482916: Air-stable zirconocene bis(perfluorobutanesulfonate) as a highly efficient catalyst for synthesis of N-heterocyclic compounds
Wang, Jinying, Li, Ningbo, Qiu, Renhua; Journal of Organometallic Chemistry; Pg51-67; 2015

Zirconocene bis(perfluorobutanesulfonate) is air- and water-stable and proved to be ionic on basis of conductivity measurements. It exhibits high catalytic efficiency for the synthesis of N-heterocyclic compounds under solvent-free condition, such as benzimidazoles, benzodiazepines, dihydropyrimidinones and dihydropyridines under mild condition. Furthermore, it can be reused without loss of activity in a test of five cycles. This catalytic system affords a simple and efficient approach for the synthesis of N-heterocyclic compounds.

Include/Exclude Question
Include this reference (PECO-relevant, unclear, supplemental)?
☐ Yes (PECO -relevant, unclear or supplemental)
☐ No

Inclusion Color
Exclusion Color

S. C. Hasmall, R. A. Roberts (2000). The nongenotoxic hepatocarcinogens diethylhexylphthalate and methylclofenapate induce DNA synthesis preferentially in octoploid rat hepatocytes Toxicologic Pathology, 28(4,4), 503-509, https://heronet.epa.gov/heronet/index.cfm/reference/download/reference_id/679653

Reference Label(s):
x DCB x

Diethylhexylphthalate (DEHP), a rodent carcinogen, and 1,4-dichlorobenzene (DCB), a noncarcinogen in rat liver, are potent hepatomitogens. We have reported previously that 7-day dosing with DEHP induced a higher bromodeoxyuridine labeling index (LI) in binuclear octoploid (2x4N) rat hepatocytes than did DCB, suggesting that induction of DNA synthesis in 2x4N hepatocytes might represent a more substantial carcinogenic risk. We compared 2 additional rodent hepatocarcinogens, methylclofenapate (MCP) and phenobarbitone, with ethylene thiourea (ETU), a noncarcinogenic hepatomitogen in rat. All 3 chemicals increased hepatic LI; the 8N population had the highest LI, but only the carcinogens increased LI in the 2x4N and 4N populations. To identify the target population for induction of DNA synthesis, we used a 1-hour pulse label at the peak of induction. The results were consistent with the 7-day data, and again the highest LI was in the 8N population. The nongenotoxic rodent carcinogens MCP and DEHP induced a significant increase in the LI in the 2x4N population, whereas ETU and

Submit Form and go to This Form - Next Reference or Skip to Next

For citations with no abstract, the articles are initially screened based on all or some of the following: title relevance (titles that suggest relevant can be excluded rather than marked as unclear), and page numbers (articles two pages in length or less were assumed to be conference reports, editorials, or letters and can be tagged as supplemental material). Reviews that do not suggest a specific focus of chemical of interest can be excluded rather than marked as supplemental material.
Note: Only o-dichlorobenzene and p-dichlorobenzene are relevant. Studies on m-dichlorobenzene should be excluded.

Does the article meet PECO criteria?
☐ Yes ☐ No ☐ Tag as potentially relevant supplemental material Clear Response



< 2000 References



Summarizing Study Designs and Data Curation – Creating Literature Inventories

- Those references INCLUDED after TIAB screening and criteria using full text of the reference
- Data summarized for BOTH Human Health and Ecology
 - 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 depending
- These outputs are initially curated as literature inventories in Tableau software

The screenshot shows a web-based data entry form with the following sections:

- Submit**: Buttons for submitting, saving, and deleting.
- Reference (short format)**: A text input field containing "Fukuyama et al, 2010".
- Evidence Type**: A dropdown menu set to "Animal (human health)".
- Chemical form**: Radio buttons for "phthalic anhydride" (selected), "metabolite", and "Other".
- Study design (animal)**: A dropdown menu set to "short-term (1-30 days)".
- Route**: A dropdown menu set to "dermal".
- Species**: A dropdown menu set to "mouse".
- Strain**: A text input field containing "BALB/c".
- Health outcomes**: A dropdown menu set to "Immune".

Yellow highlights are present on the "Study design (animal)" and "Health outcomes" sections. A red text box on the right side of the form reads: "Partial data extraction – used to create Tableau ‘heat maps’".



ECOTOX data curation in UNIFY and Knowledgebase - Post Evidence map

Test

Print Excel Add Result Copy Test Copy Test Copy Test Delete Test Close

Reference **Skim** ECOREF#: 179843

Errors: 0 Warnings: 0

Nine-Year Response of Douglas-Fir and the Mixed Hardwood-Shrub Complex to Chemical and Manual Release Treatments on an ICHmw2 Site near Salmon Arm. by Simard, S., and J. Heinemann, 1996

ID	Chemical	Habitat	Species	Age	Lifestage	Study Type	Exposure Type	Test Location	#Results	Create Date	Modified Date	Expand
2231248	38641940 - Vision	Soil	3795 - Pseudotsuga menziesii	NR	NR	NR	HS	FIELDN	1	10/30/2019	10/30/2019	
2231249	38641940 - Vision	Soil	3214 - Betula papyrifera	NR	NR	NR	HS	FIELDN	1	10/30/2019	10/30/2019	

Chemical Information **Species Information** **Test Information** **Habitat Information (Soil)**

Study Duration: Mean 9, Min NR, Max NR, Unit YR, Comments

Exposure Duration: Mean 9, Min NR, Max NR, Unit YR, Comments

Concentration Types: A, Study Type: NR, Test Type: NR, Test Location: FIELDN, Test Method: NR

Exposure Type: ENV - HS, Media Type: NAT, Media Comments: BRUNISOLIC GRAY LUVIS

Doses: Mean 3, Min NR, Max NR, Comments

Doses

Dose Number	Control	Conc	Type	Dose	Unit	Organism #	Statistical Method	Stat Value	Comments
1	C	A	0	Al kg/ha	NR	NR	NR	NR	
2	A	1.07	Al kg/ha	NR	NR	NR	NR	NR	
3	A	2.14	Al kg/ha	NR	NR	NR	NR	NR	

Experimental Design: RANDOMIZED COMPLETE BLOCK DESIGN

Additional Comments:

Other Effects: -- Select --

MANUAL CUTTING

Cancel Save Save and Add Copy Save and Continue Save and Add Result



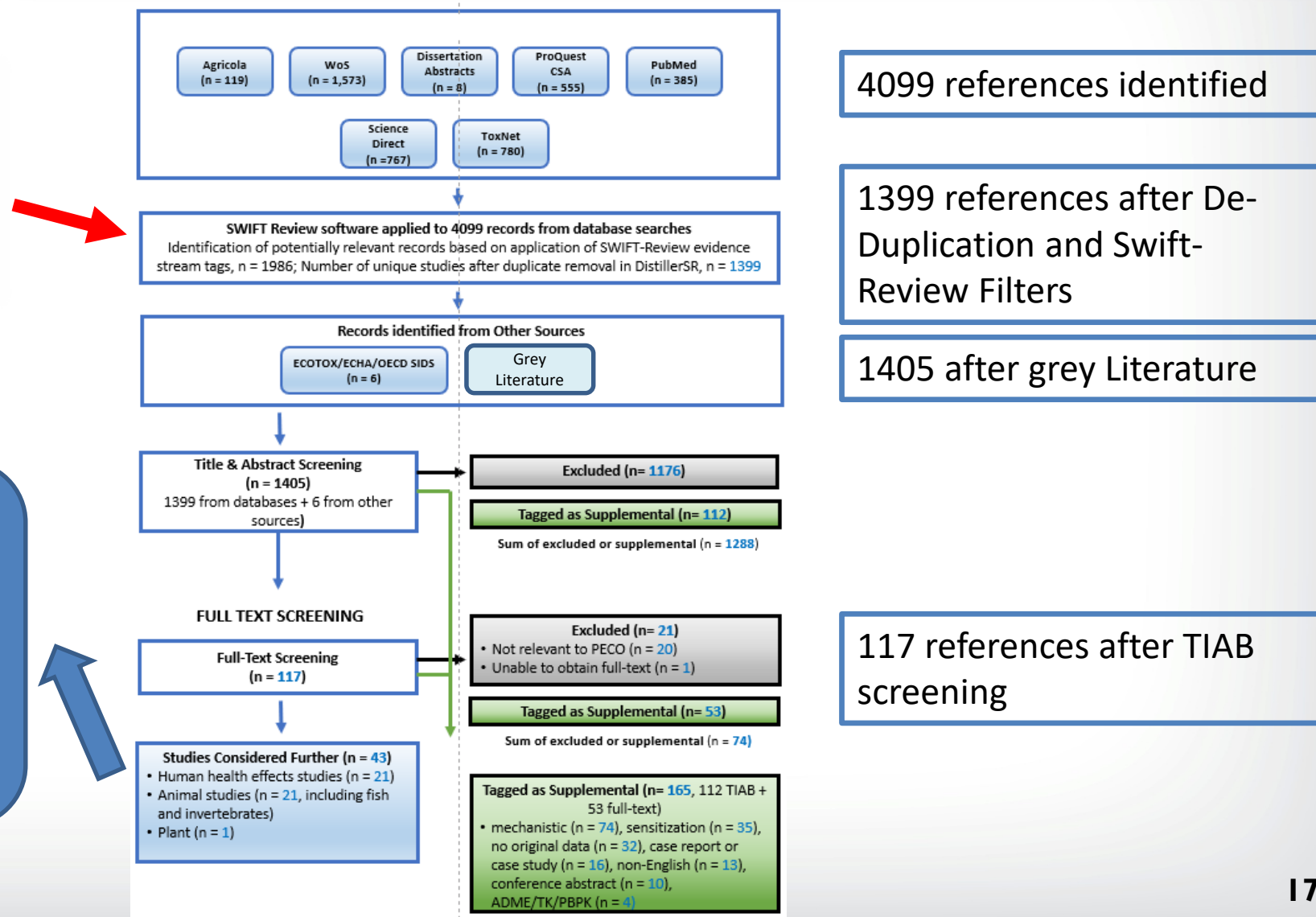
Literature Survey Study Flow

Used specialized-learning software

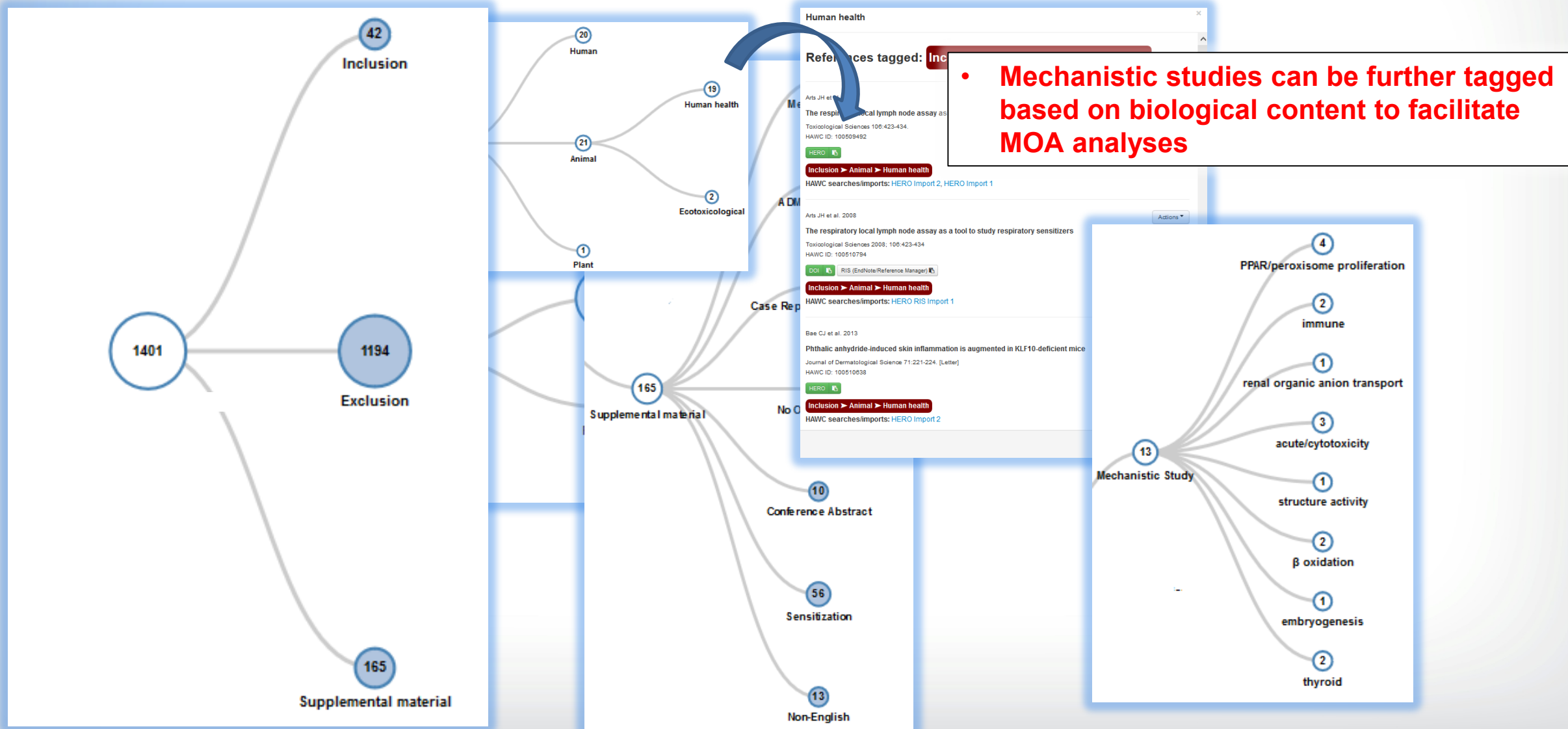
- **SWIFT Review “filters”**
- **SWIFT Review + SWIFT Active for other chemicals with > 2000 references**

Studies for full assessment (n=43)

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

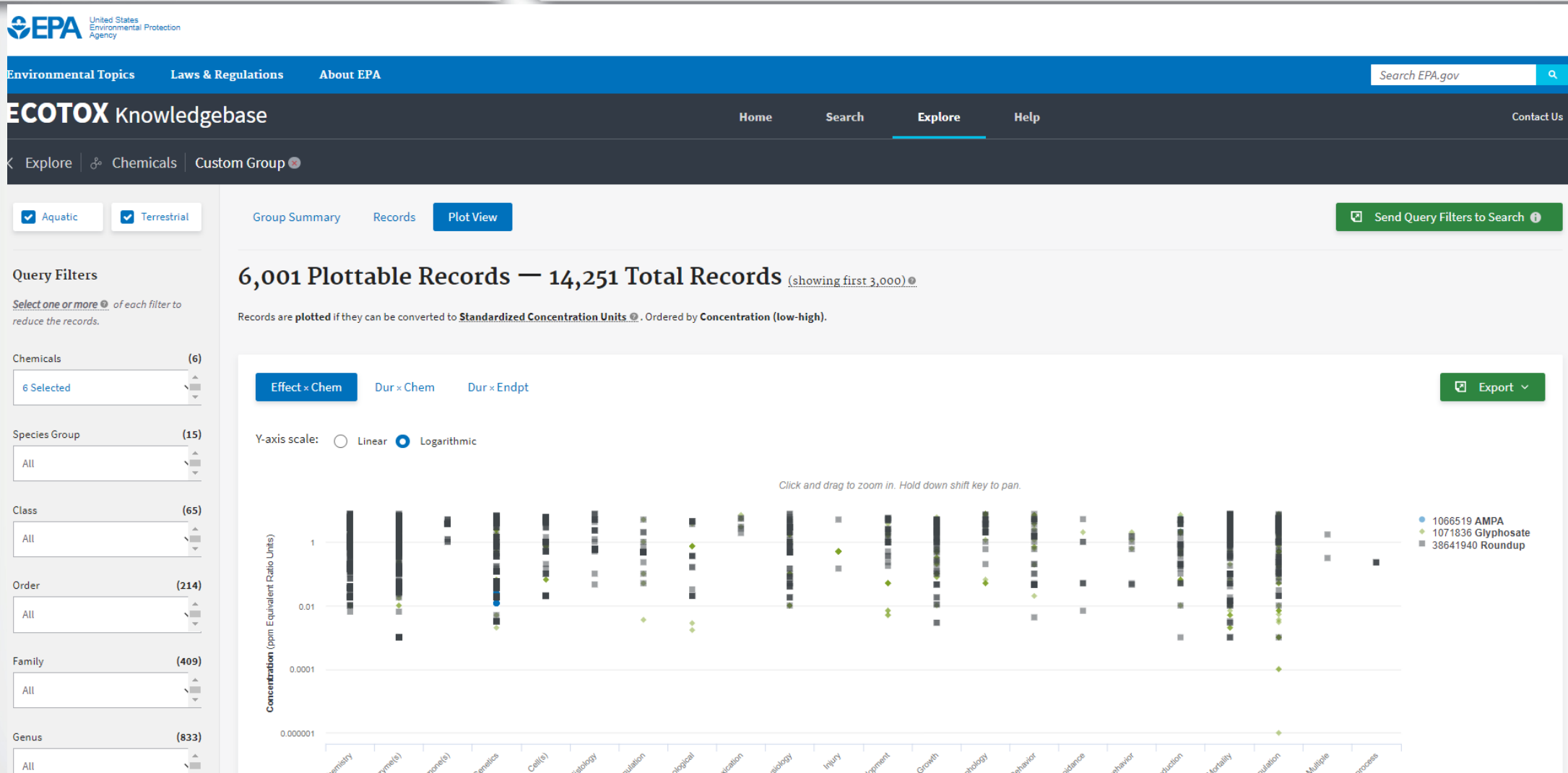


Interactive Study Flows





ECOTOX data visualization



ECOTOX Knowledgebase curates up 250 fields from references meeting PECO Criteria



Tableau Literature Inventory Heat Maps

Human

occupational

System	workplace surveillance
Cancer	
Cardiovascular	
Clinical Chemistry/Urinalysis	
Dermal	
Endocrine	
Hematologic	
Hepatic	
Immune	
Renal	2
Respiratory	5

System

Cancer
Developmental
Immune
Respiratory

Click [here](#) to view the interactive version for additional study details.

Click [here](#) to view the interactive version for additional study details.

Animal

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

Animal (Ecological Taxa)

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

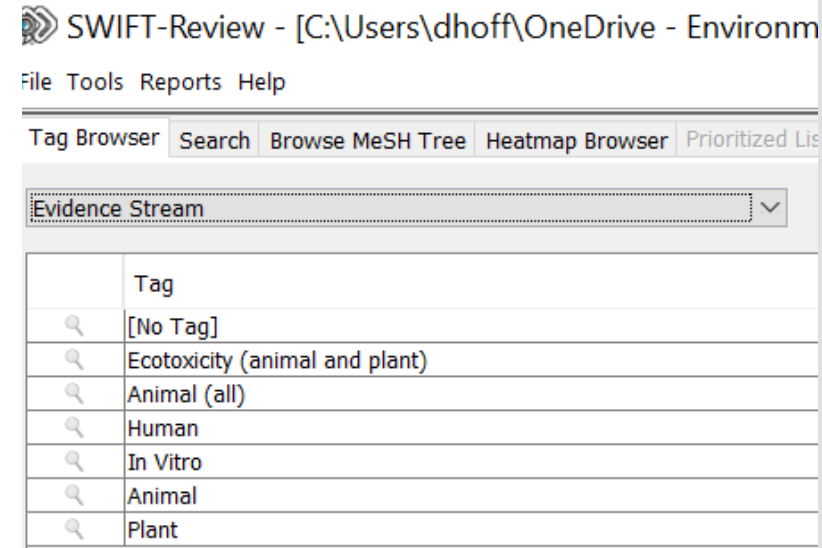
Table 4. Literature Inventory Results for Ecological Hazard Studies

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



$$\text{ECOTOX Knowledgebase} = \text{SWIFT ACTIVESCREENER} + \text{DistillerSR}$$



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**





Evidence Mapping Support

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