Poster 1.7: Evidence Mapping of Environmental and Human Health Hazard Evidence for Phthalic Anhydride

Kellie Fay*, Francesca Branch*, Amelia Nguyen*, Amy Benson*, Dale Hoff†, Colleen Elonen†, Amanda Persad†, and Kris Thayer†
*U.S. EPA, OPPT; †U.S. EPA, ORD

www.epa.gov

Kellie Fay | Fay.Kellie@epa.gov | 218-576-5492

Introduction

Evidence Mapping of the Hazard Assessment Search and Screening Results: Specific Aims

- Conduct a comprehensive search and review of toxicity data in the open and gray literature with transparent standard operating procedures that meet requirements for systematic review protocols.
- Identify relevant studies in humans, plants and animals, including taxa relevant for environmental health evaluation.
- Use systematic review methods to identify and track studies pertinent to understanding potential human health and environmental health hazard as outlined in the Population, Exposure, Comparator, Outcome (PECO) criteria.
- Identify and track studies containing supplemental material that may be potentially relevant to an assessment.
- Provide interactive data visualizations that summarize both the screening results and extent and nature of the evidence that met the PECO criteria after full text screening.

Method overview

Identification

Chemical verification and development of search terms

Chemical verification process: The process for chemical verification followed that of the well-established approach for EPA' s ECOTOX Knowledgebase.

Search term development: Chemical name and CASRN, synonyms, tradenames, and other relevant forms such as isomers and related chemicals of interest (as requested) were identified from multiple sources. These sources included (among others): STN, Pesticide Action Network (PAN), EPA's Pesticide Fate Database (PFATE), EPA's Chemistry Dashboard.

Literature search: Searches relied on chemical name (including verified synonyms and trade names) and identifiers, as determined from chemical verification and were not subject to additional limitations.

Literature searches

Peer-review search: Queried search engines included:

Agricola	Science Direct
Current Contents	ToxNet
ProQuest	UNIFY
PubMed	Web of Science

Gray literature search: See Poster 1.3 for Gray Literature Decision Framework and sources searched. Hazard study data submitted under TSCA 4, 5, 8d, 8e and FYI were included.

Storage and deduplication in HERO: The search results were stored and deduplicated in the EPA's Environmental Research Online (HERO) database.

Evidence stream filter: Studies were imported into SWIFT-Review. The evidence stream filters identified the studies most likely to be applicable for hazard assessment.

Screening

PECO development

PECO statement: a framework for question formulation to explore the association of chemical exposure with health outcomes relevant for risk evaluation under TSCA.

Population Is the study about a population of concern?

Exposure Is there an exposures to a relevant forms of the substance?

Comparator Is there a reference population or control group that was less exposed or not exposed?

Outcome Is a hazardous effect of interest observed?

Title/Abstract screening against PECO criteria

Software: Studies filtered by evidence stream were imported into DistillerSR or SWIFT-Active Screener for title/abstract (TIAB) screening.

Calibration: Screeners jointly screened ~30 studies to identify points of confusion or chemical-specific considerations. The PECO may be modified, accordingly.

Screening/Tagging: Two independent reviewers screened each study and tagged as **Included** (PECO relevant), **Excluded** (not PECO relevant), **Unclear**, or **Supplemental** (potentially useful). Additional tags included **lines of evidence** (human health, animal - human health, animal - environmental, plant), **exclusion reason**, and **supplemental characterization** (*e.g.,* review, non-English, mechanistic). Screener conflicts were resolved at the inclusion level.

Full text screening against PECO criteria

PDF acquisition: Studies tagged at the TIAB levels as Included or Unclear moved forward to Full Text screening. PDFs of the full studies were acquired via HERO and linked to the DistillerSR software.

Screening/Tagging: All studies were screened by two independent reviewers. Studies were tagged as **Included** (PECO relevant), **Excluded** (not PECO relevant) or **Supplemental** (potentially useful). Additional study tags included **lines of evidence** (human health, animal –human health, animal – environmental, plant), **exclusion reason**, and **supplemental characterization** (*e.g.,* in vitro or mechanistic, review, non-English).

Data Visualizations of Results

Literature inventory trees

Formating screening results for HAWC: A Python script was developed to convert full text screening results from DistillerSR to a format readable by the EPA's Health Assessment Workbench Collaborative (HAWC) to generate interactive literature inventory trees.

Literature Inventory Tree: The screening and tagging results are visualized in literature inventory trees that display the numbers of studies in each tagged category throughout screening process, providing transparent reference tracking.

Bibliographic linkages: Results in the Literature Inventory Tree are interactive with HERO and display bibliographic details.

Heat maps

Health Outcome filters: Studies included after full text screening were uploaded to SWIFT-Review. Pre-developed filters identify studies as likely to be relevant to health outcome categories based on keywords in the title, abstract and keywords as well as medical subject heading (MeSH) annotations. Each reference may align with multiple health outcomes.

Heat map generation: Tableau is used to create heat map visualizations of the results of the health outcome categorization for studies tagged to each line of evidence during full text screening. The data are visualized as a table with the number of studies matching each criteria with color gradation to reflect evidence abundance.

Bibliographic linkages: References in each heat map field are linked to HERO bibliographic information. Titles and Abstracts for all references in a given field are viewable.

Phthalic Anhydride example

Study Identification

Chemical verification for phthalic anhydride resulted in the following general search strategy based on chemical name, synonyms and identifiers:

"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 "Wiltrol P"

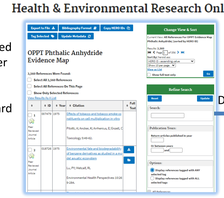
Literature searches: A total of 3,819 studies were returned from searching peer-reviewed sources. An additional 75 studies or datapoints were found in gray literature sources, which included TSCA submissions, previous assessments, databases, technical reports, and international resources.

Source: peer –reviewed	References
PubMed	385
Current Contents	1573
ProQuest CSA	555
Dissertation Abstracts	8
Science Direct	767
Agricola	119
TOXNET	780
UNIFY	17
Totals:	**3819**

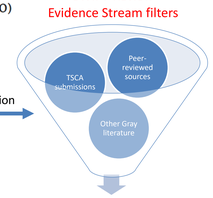
Source: gray	Studies
TSCA non-CBI	14
TSCA CBI	TBD
Other EPA sources (databases, previous assessments, etc)	25
Other US sources	26
International Resources	10
Totals:	**75**

Deduplication and Filtering for Hazard Studies

The references identified during the search process were entered into HERO, deduplicated, then imported into SWIFT-Review* to filter for general relevance to human health and environmental health hazard using likely to be more relevant to hazard assessment based on key words and MeSH annotations



Deduplication



1405 Studies for title/abstract hazard screening

**not all gray literature is amenable to filtering and screening using the approach described.*

PECO statement

P	**Human:** Any population and lifestage (e.g., occupational or general population, including children and other sensitive populations). **Animal**: Aquatic and terrestrial species (live, whole organism) from any lifestage (e.g., preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only). • Ecotoxicological models: invertebrates (e.g., insects, spiders, crustaceans, mollusks, and worms) and vertebrates (e.g., mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species.
E	**Relevant forms and isomers**: *(chemical name(s) and CASRN)* • Relevant isomer(s) (if any). Valid synonyms are available on the Comptox Chemical Dashboard **Human**: Any exposure to the chemical singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (i.e. urine, blood, semen, etc.). **Animal:** Any exposure to the chemical including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants**: Any exposure to the chemical including via water, soil, sediment.
C	**Human**: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of *(chemical name(s) and CASRN)*, or exposure to the chemical for shorter periods of time. **Animal and Plants**: A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement).
O	**Human**: All health outcomes (cancer and noncancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth.

Supplemental Data

Mechanistic (including in vitro/in silico studies)
ADME/toxicokinetic
Mixture study (applies to experimental studies, not epidemiological studies)
Case study or case series (epidemiological reports)
Other assessments or records with no original data (e.g., reviews, editorials, commentaries)
Conference abstract
Non-english
*Used as known sensitizer

Screening Calibration and Chemical-Specific Tagging

* For phthalic anhydride, joint screening of studies and conflict resolution discussions identified a high percentage of studies which used phthalic anhydride as a known sensitizer. In these studies, phthalic anhydride was used to test toxicity or therapy of an unrelated substance. These studies were determined to not be of primary interest but were tracked as a supplemental category specific to phthalic anhydride.

Screening/Tagging

Screening at both the title/abstract and the full-text levels followed a similar process with two screeners independently tagging references in DistillerSR (*SWIFT-Active Screener was used for title/abstract screening for other TSCA substances undergoing risk evaluation*).

DistillerSR

Studies were tagged for:
PECO relevance: yes, no, supplemental, unclear (at TIAB level)

Record source, if not from a peer-reviewed database

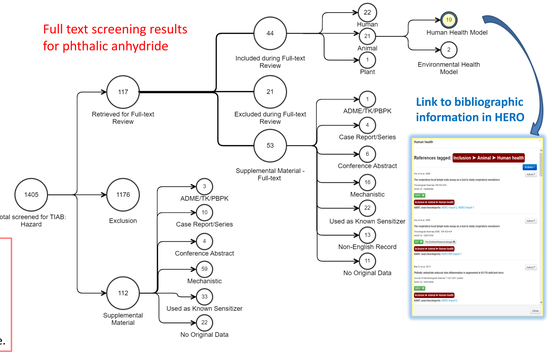
PECO-relevant studies were further tagged to an evidence stream:
Human (epidemiological)
Animal – Human Health
Animal – Environmental Health
Plant

Supplemental studies were further tagged to supplemental data categories.

Literature Inventory Tree

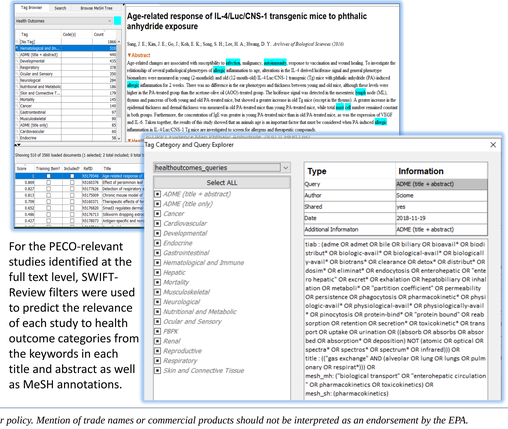
The literature inventory tree displays the number of references that were identified and how they were screened. For each branch of the tree, the number of identified references is linked to full bibliographic information as stored in HERO.

Full text screening results for phthalic anhydride



Link to bibliographic information in HERO

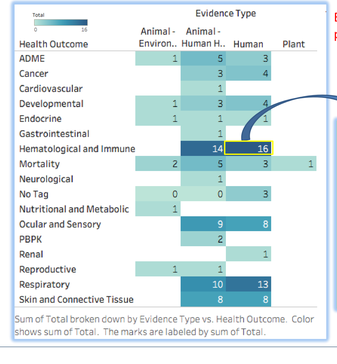
SWIFT-Review: Health Outcome Filter



For the PECO-relevant studies identified at the full text level, SWIFT-Review filters were used to predict the relevance of each study to health outcome categories from the keywords in each title and abstract as well as MeSH annotations.

Evidence Map/ Heat Map

Evidence type tagging and SWIFT-Review health outcome filter results are displayed in an interactive heat map for the PECO-relevant phthalic anhydride studies included after full text screening. Each field contains the number of studies matching both evidence type and health outcome criteria and is linked to full bibliographic information.



Evidence Map for phthalic anhydride

Link to bibliographic information in HERO

Links to titles and abstracts