United States Environmental Protection Agency

IRIS Today – An Update on Progress

Tina Bahadori, NCEA Director

EPA Science Advisory Board (SAB) Chemical Assessment Advisory Committee (CAAC)
September 27-28, 2017

New Leadership Structure in NCEA

- **In January 2017, EPA appointed new leadership to the National Center for Environmental Assessment and to its IRIS Program.**
  - With significant experience in the chemical industry, and formerly the Director of ORD's Chemical Safety for Sustainability National Research Program, the new NCEA Director brings knowledge of TSCA, innovative applications of computational toxicology, and exposure science.
  - As a recognized leader in systematic review, automation, and chemical evaluations, the new IRIS Program Director brings experience in early partner and stakeholder engagement and input, and demonstrated actions to increase capacity and transparency in assessments.
- **Improved responsiveness and accountability through Senior Leadership Team**
  - NCEA IO
  - Divisions
  - Integrating across the spectrum of human and ecological RA practices

- **Created in 1985 to foster consistency in the evaluation of chemical toxicity across the Agency.**
- **IRIS assessments contribute to decisions across EPA and other health agencies**
- **Toxicity values**
  - Noncancer: Reference Doses (RfDs) and Reference Concentrations (RfCs).
  - Cancer: Oral Slope Factors (OSFs) and Inhalation Unit Risks (IURs).
- **IRIS is the only federal program to provide toxicity values for both cancer and noncancer effects.**
- **IRIS assessments have no direct regulatory impact until they are combined with**
  - Extent of exposure to people, cost of cleanup, available technology, etc.
  - Regulatory options, which are the purview of EPA's program offices.

IRIS Addresses Agency Priorities and Mandates

IRIS

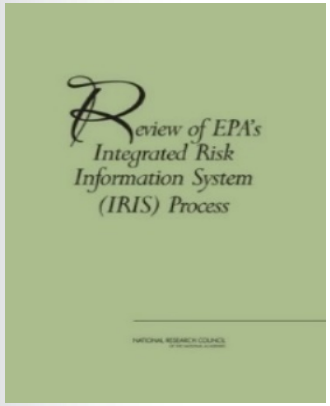
- Clean Air Act (CAA)
- Safe Drinking Water Act (SDWA)
- Food Quality Protection Act (FQPA)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
- Resource Conservation and Recovery Act (RCRA)
- Toxic Substances Control Act (TSCA)

Broad Input to Support

- Agency Strategic Goals
- Children's Health, Environmental Justice

National Academy of Sciences (2014) Overarching Statements

2014



"Overall, the committee finds that substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the recommendations in the NRC formaldehyde report. The NRC formaldehyde committee recognized that its suggested changes would take several years and an extensive effort by EPA staff to implement. Substantial progress, however, has been made in a short time, and the present committee's recommendations should be seen as building on the progress that EPA has already made." [p.9]

" . . . the IRIS program has moved forward steadily in planning for and implementing changes in each element of the assessment process. The committee is confident that there is an institutional commitment to completing the revisions of the process . . . Overall the committee expects that EPA will complete its planned revisions in a timely way and that the revisions will transform the IRIS Program." [p.135]

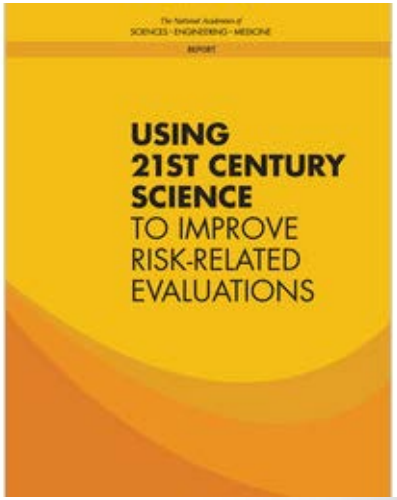
Previous Phased Improvements to the IRIS Program

- **Revising the structure of assessments to enhance the clarity and transparency of presentation:**
  - detailing the methods underlying each step of draft development (e.g., literature search strategy)
  - restructuring the document into separate hazard identification and dose-response chapters
  - replacing lengthy study summaries with synthesis text, supported by standardized tables and graphs
- **Implementing "IRIS Enhancements"**
  - an updated process for developing and reviewing assessments that increases public input and peer consultation at earlier stages of assessment development, and clarifies processes for considering new evidence and scientific issues
- **Establishing the SAB Chemical Assessment Advisory Committee (CAAC)**
  - 5 IRIS assessments completed CAAC review since 2014
- **Restructuring the IRIS program to create expertise-specific workgroups and improved assessment oversight**

How is IRIS Focusing?

- **Increase transparency and full implementation of systematic review**
  - implement using approaches that foster consistency across the IRIS program; many active and all new starts address ALL SR-related recommendations of 2014 NRC report
- **Modernize the IRIS Program**
  - through automation and machine learning to expedite systematic review, incorporation of emerging data types
- **Modularize product lines**
  - implement a portfolio of chemical evaluation products that optimize the application of the best available science and technology. These products will allow IRIS to remain flexible and responsive to clients within the EPA as well the diverse collection of stakeholders beyond EPA, including states, tribal nations, and other federal agencies.
- **Enhance accessibility**
  - provide outreach and training to make systematic review practices ubiquitous and more accessible; enhance data sharing through publicly available software platforms for assessments developed by EPA, other federal and state agencies, industry, academia and other third-parties.

Other IRIS Improvements



Next Generation IRIS

- IRIS in the 21st Century – implement recommendations of the NAS 2017 report, Using 21st Century Science to Improve Risk-Related Evaluations;
- Collaborate with EPA's National Center for Computational Toxicology (NCCT) to build expert-judgement case studies that inform assessment development and fill gaps in assessments, especially for data poor chemicals; inform where resources should be strategically invested to generate additional data.

Improved Management Practices

- Create efficiencies – engage other agencies to share common practices, data, and tools, and more efficiently leverage resources across the federal government.
- Improve timeliness and responsiveness – deploy program and project management tools to more effectively and efficiently utilize human resources to ensure timely delivery of products.

IRIS Multi-Year Agenda

Developing Agenda

- **Released to the public December 2015**
- **Survey EPA program and regional offices for their assessment needs**
- **Estimate the resources needed for each assessment by science discipline**
- **Discuss with senior EPA officials how to meet the most high-priority needs**
- **Allocation of IRIS resources based on the plan**
- **Evaluate annually for continued relevance**

Group	Chemicals
1	Manganese
	Mercury/methylmercury
	Nitrate/nitrite
	Perfluoroalkyl compounds
	Vanadium and compounds
2	Acetaldehyde
	Ammonia (oral)
	Cadmium and compounds
	Uranium
3	Di-(2-ethylhexyl) phthalate
	Dichlorobenzene isomers
	Methyl t-butyl ether (MTBE)
	Nickel and compounds
	Styrene

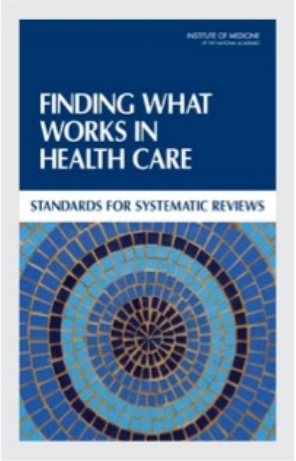
United States Environmental Protection Agency

Systematic Review and Implementation within the IRIS Program

Kris Thayer, NCEA IRIS Division Director

EPA Science Advisory Board (SAB) Chemical Assessment Advisory Committee (CAAC)
September 27-28, 2017

Systematic Review



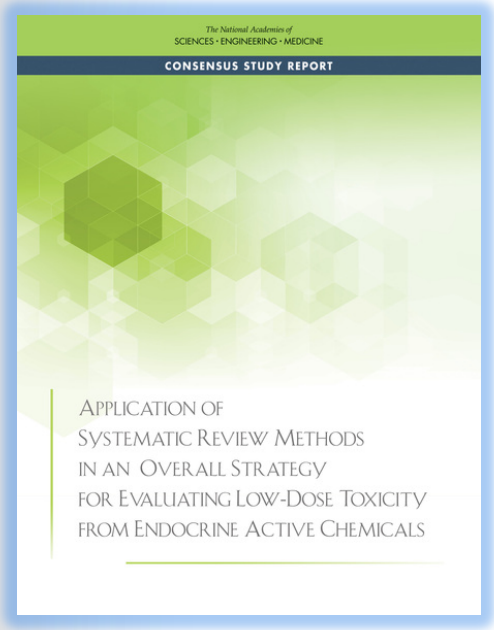
A structured and documented process for transparent literature review[1,2]

"… 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"

[1] Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act. EPA-HQ-OPPT-2016-0654. https://www.epa.gov/sites/production/files/2017-06/documents/prepubcopy_tsca_riskeval_final_rule_2017-06-22.pdf

[2] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

NAS (2017): Reflections and Lessons Learned from the Systematic Review



"….one disadvantage in conducting a systematic review is that it can be time and resource intensive, particularly for individuals that have not previously conducted a systematic review." [p.157]

"The committee discussed at length whether it could provide EPA with advice about when a systematic review should be performed but decided it could not be more specific because that decision will depend on the availability of data and resources, the anticipated actions, the time frame for decision making, and other factors." [p.157]

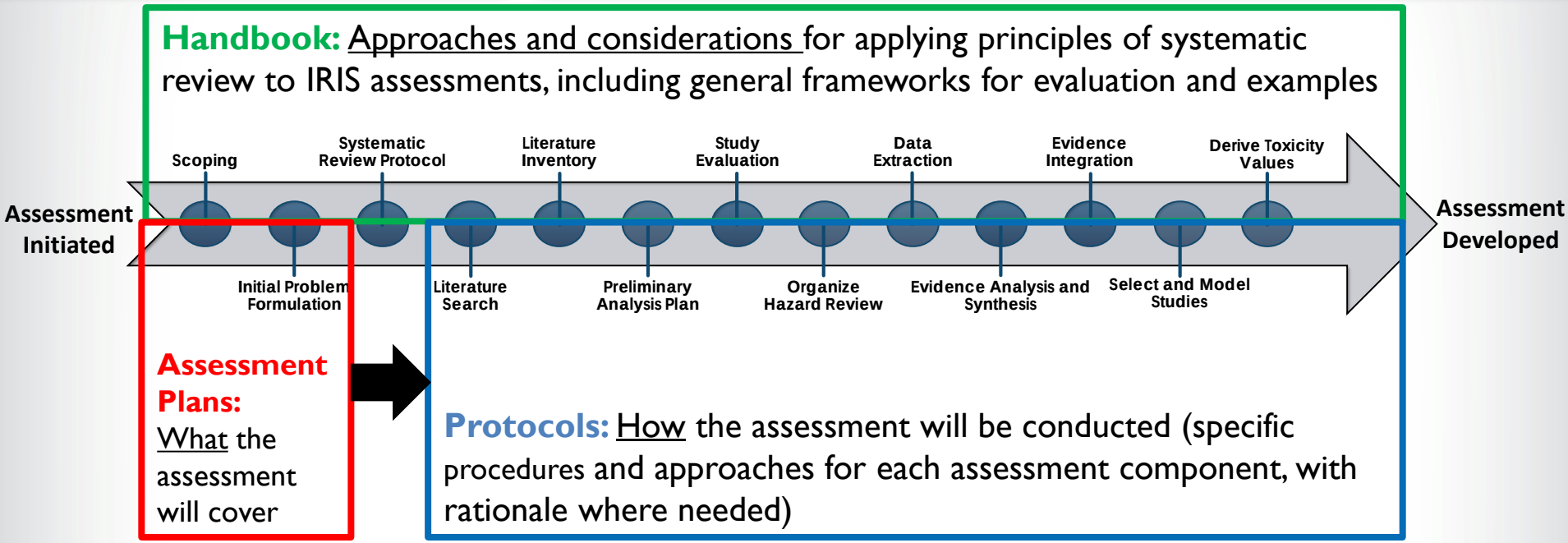
"The committee also recognized that it might be advantageous for EPA to build on existing systematic reviews that are published in the peer-reviewed literature." [p.157]

"The committee recognizes that the methods and role of systematic review and meta-analysis in toxicology are evolving rapidly and EPA will need to stay abreast of these developments, strive for transparency, and use appropriate methods to address its questions." [p.157]

Making Systematic Review (SR) Pragmatic and Feasible For IRIS

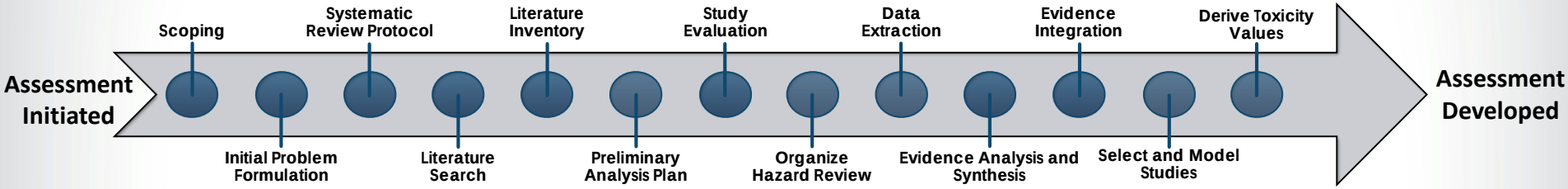
- Standard operating procedures (IRIS Handbook), templates (draft assessment plans, chemical-specific protocols), and regular training
- Solicit early feedback during scoping and problem formulation via assessment plans
- Utilize iterative protocols to ensure communication on included studies and focus on best-available and most-informative evidence as the assessment progresses
- Multiple assessment products ("modularity")
- Targeted focus, especially for evidencerich topics
  - Make better use of existing assessments as starting point
- Use of specialized SR software applications/automation and project management tools

Standard Operating Procedures (SOPs), Templates & Training



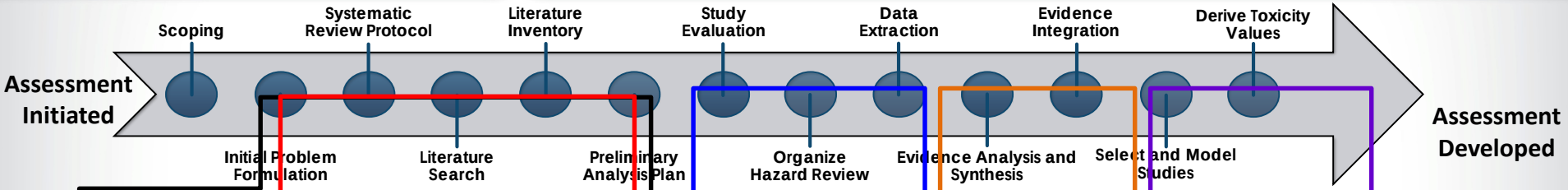
- **Promote consistency across the IRIS Program, which is implemented across staff in different Divisions and geographic regions**
- **Assemble systematic review support teams: One for handbook/template protocol and another to provide support to chemical assessment teams (e.g., screening, study evaluation, data extraction, use of specialized software, etc.)**
- **Provide regular training via skill-building seminars, focused discussions, and retreats**

IRIS Handbook



- Level of detail aimed for EPA staff and contractors, e.g., use of HERO
- Currently being updated to reflect agency input and evolving IRIS practices to implement SR
  - Anticipate public posting in 2018
- Evergreen to reflect future advances in implementing SR
- Chemical-specific protocols are stand-alone method description documents and do not rely on IRIS Handbook to convey methodology

Systematic Review Tools



HERO
Literature searching, storage and documentation (tagging)

SWIFT Review
Problem formulation

SWIFT Review DoCTOR
Machine learning for screening prioritization

Distiller SWIFT Active
Multiple reviewer reference screening and tracking (HERO-tagging)

HAWC DRAGON
Modules to track multiple reviewer study evaluations

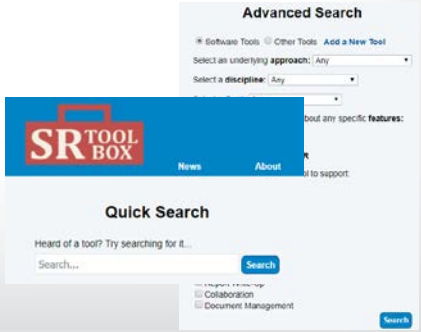
Extracted data storage

HAWC
Interactive graphical display, evidence profile tables

GRADEPro
Evidence profile table, evidence to decision making

METAXL, Metafor
Evaluation of heterogeneity or combined study results analysis

Database of SR software tools:
http://systematicreviewtools.com/



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IRIS Assessment Plans and their Role within the IRIS Process

Jason Fritz, Ph.D.
Associate Director for Science (acting)

Presentation Outline

- How the IRIS Assessment Plans (IAPs) fit into the 7-step IRIS process for developing human health assessments
- Refinement and increased transparency of systematic review materials, including scoping & problem formulation materials
- IAPs: what they are intended to be, and what they are not

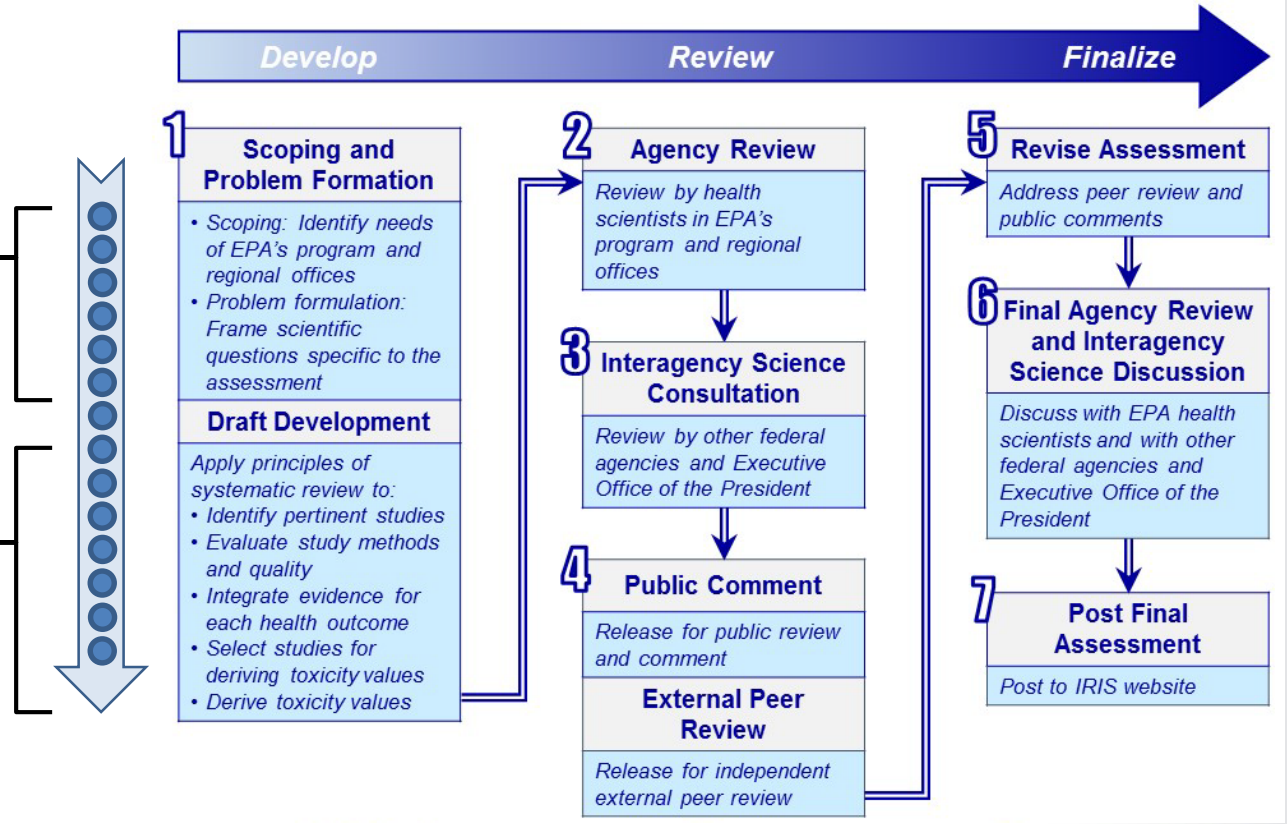
IRIS Assessment Plans in the 7-Step IRIS Process

IRIS Assessment Plans (IAPs)

- What the assessment will cover

Systematic Review Protocols

- How the assessment will be conducted

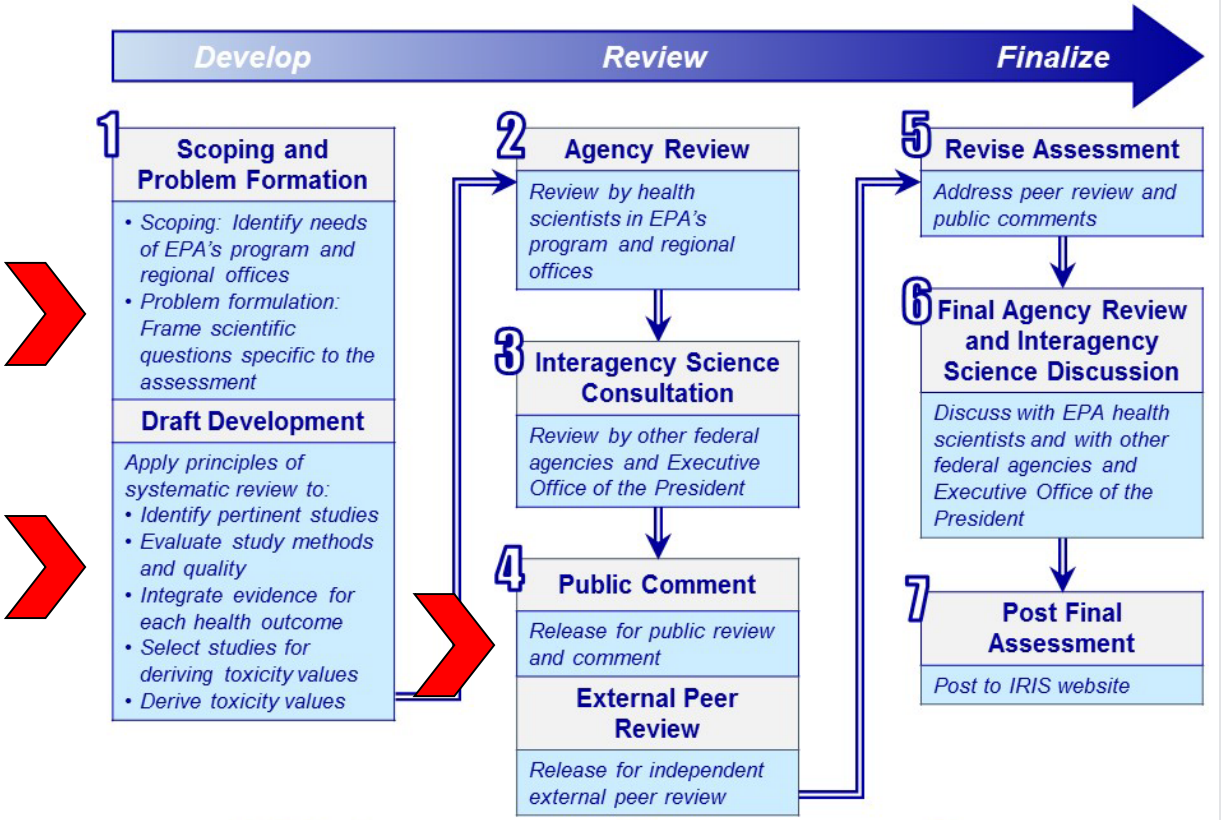


https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process

Transparency in the IRIS Assessment Process

Assessment materials will be made available for public comment at various stages in development

- **Early Step 1: IRIS Assessment Plans (IAPs)**
  - The federal docket for public comment is open for 30 days
- **Mid-Step 1: Systematic Review Protocols**
- **Step 4: Public Comment Assessment Draft**



IAPs Represent Continuous Refinement of Scoping/Problem Formulation Materials

07/2014 Ethylbenzene Scoping & Problem Formulation Document	09/2017 Ethylbenzene Assessment Plan Document
Introduction and background	Introduction and background
Production and use, human exposure pathways, environmental fate	Concise discussion to extent this information provides necessary context
Scoping ("Scope of the Assessment")	Scoping ("Scoping Summary")
[Not explicitly discussed]	Table of Agency Interest
Problem Formulation	Problem Formulation
Preliminary Literature Survey (conducted by manual review of studies retrieved)	Preliminary Literature Survey (conducted using various approaches, e.g. machine-learning, prior assessments)
Systematic Review Elements	Systematic Review Elements
[Not explicitly discussed]	Specific Aims
Hazard Questions for Systematic Review	Draft Populations, Exposures, Comparators, Outcomes (PECO)
[Not explicitly discussed]	Assessment Approach
Key Issues	Key Science Issues

What IAPs Are Intended to Be

IAPs are <u>what</u> will be covered in the assessment, including:

- **Summary of the assessment plan:**
  - Scoping and initial problem formulation determinations
  - Overall objectives and Specific aims
- **Presentation of draft PECO (Populations, Exposures, Comparators, and Outcomes)**
  - Outline what evidence will be considered most pertinent
- **Discussion of the fit-for-purpose approach:**
  - Address the need and decision context (e.g., targeted to outcome, route, and/or modular)
- **Identification of key areas of scientific complexity**

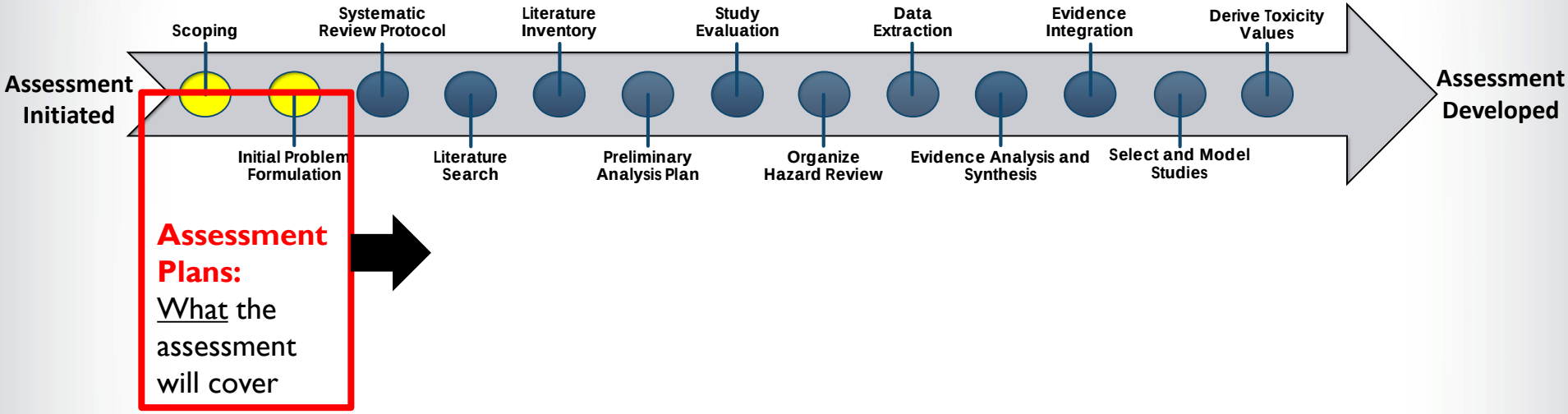
What IAPs Are Not Intended to Be

IAPs are not intended to be a discussion of how the work will be conducted.

Because they represent a very early step in the systematic review process, IAPs will not include detailed review of various topics, including:

- Agent use or production
- Agent properties, stability, biochemistry, metabolism, prevalence or fate
- Quality of identified literature
- Extensive discussion on hypothesized mechanisms or modes of human toxicity
- Strength or direction of reported hazard associations
- Other science issues

IAP Purpose



As the INITIAL step in problem formulation, IAPs summarize:

- Scoping and initial problem formulation conclusions
- Objectives and specific aims
- Draft PECO (Populations, Exposures, Comparators, and Outcomes)
- Identification of key areas of scientific complexity

Draft IAPs Presented as Case Studies

- **Chloroform**
  - RfD, cancer assessment and mode-of-action (MOA) (from 2001); IUR (from 1987)
  - Focusing on inhalation exposure – will attempt to derive a noncancer RfC based upon inhalation data, and conduct a cancer assessment
- **Nitrates/Nitrites (NO_3^-/NO_2^-)**
  - RfDs (from 1991, 1987)
  - Focusing on oral exposure – will attempt to derive separate noncancer RfDs for NO_3^- and NO_2^-, and conduct a cancer assessment
- **Ethylbenzene**
  - RfC and RfD (from 1991, 1987), cancer assessment (from 1988)
  - Modular approach – due to different levels-of-effort needed, may derive noncancer RfC, RfD, and a cancer assessment, separately and sequentially

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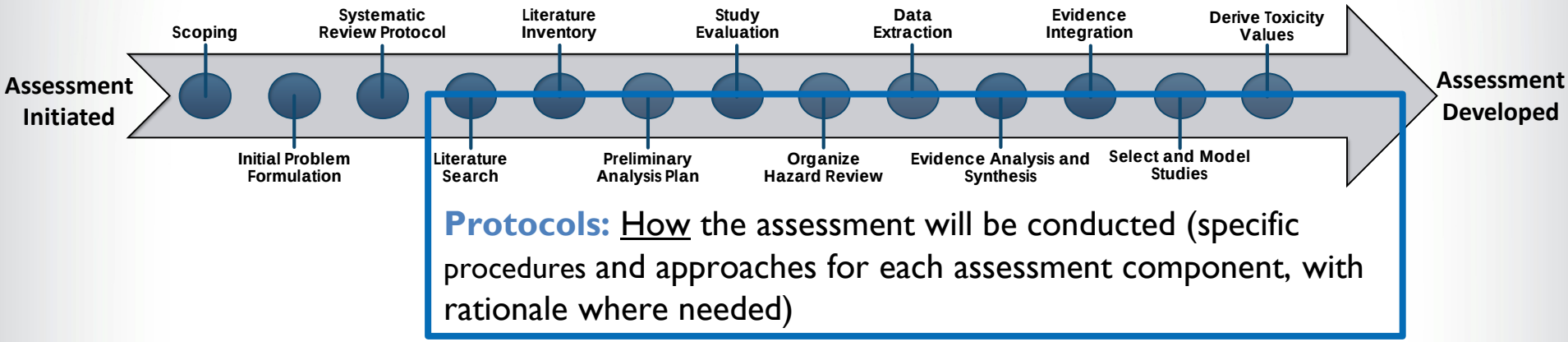
Protocols

Kris Thayer, NCEA IRIS Division Director

Protocol Release



- **Post protocol for public shortly after review of IAP**
- **Protocol captures changes made to IAP in response to public science meeting discussions**
- **Protocol is a separate document from draft assessment (supplemental material document, ~40-60 pages)**
- **Protocol is iterative to ensure the SR focuses on the best available and most informative evidence**
  - **Protocols include revision history to reflect updates**

Protocol: Literature Searching and Screening

basic practices

special topics

4. LITERATURE SEARCH AND SCREENING STRATEGIES

4.1. USE OF EXISTING ASSESSMENTS

Describe any use of existing assessments that serve as starting points for the literature search.

4.2. LITERATURE SEARCH STRATEGIES

Literature search strategies were developed using key terms and words relate
statement. Development of the search strategy for each topic area were conducted b
relevant search terms through (1) reviewing PubMed's Medical Subject Headings (M
relevant and appropriate terms, (2) extracting key terminology from relevant review
previously identified primary data studies that are known to be relevant to the topic
and
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4.3. UNPUBLISHED DATA

IRIS only includes publicly accessible, peer-reviewed information in its evaluations. However, it is possible that unpublished data directly relevant to the PECO statement may be identified during the course of the assessment. In this case, EPA is able to obtain external peer review if the owners of the data are willing to have the study details and results made publicly accessible. The peer review would include an evaluation of the study similar to that for peer review of a journal publication. The EPA would identify and select two to three scientists knowledgeable in scientific disciplines relevant to the topic as potential peer reviewers. Persons invited to serve as peer reviewers would be screened for conflict of interest (COI) prior to confirming their service. In most

4.4. SCREENING PROCESS

Studies that comply with the criteria specified in the PECO
inclusion while those that do not meet these criteria will be exclude
the exclusion criteria noted below will be applied. However, the refe
will be reviewed to identify PECO-relevant studies that may have been m
searching.

- Records that do not contain original data, such as reviews, editorials,
- Studies that have not been peer-reviewed (e.g., conference abstracts, theses/dissertations, working papers from research groups or committees, and white papers).
- [others decided by the assessment team]

Studies will be screened for inclusion using a structured form in [list the software application and URL to product site, e.g., DistillerSR (Evidence Partners;

4.4.1. Multiple publications of the same data

Multiple publications with overlapping data for the same study (e.g., publications reporting subgroups, additional outcomes or exposures outside the scope of an evaluation, or longer follow-up) can be identified by examining author affiliations, study designs, cohort name, enrollment criteria, and enrollment dates. If necessary, study authors will be contacted to clarify any uncertainty about the independence of two or more articles. IRIS will include all publications on the study, select one study to use as the primary, and consider the others as secondary publications with annotation as being related to the primary record during data abstraction. The primary study

Protocol: Defining Study Evaluation Ratings

6.1. STUDY EVALUATION OVERVIEW

The general approach (described in this section) of study evaluation for epidemiology and animal studies is the same, but the specifics of applying the approach differ and thus they are described separately in the following sections (Sections 6.2 and 6.3)

The evaluation will be conducted independently by at least two review for comparing and resolving differences. For studies that examine more than outcome, the evaluation process will be outcome or endpoint-specific, as the u vary for the different endpoints.

For each study[3] (specifically, an outcome or group of related outcomes study or in a sample within a study), in each domain, reviewers will reach a co **Good**, **Adequate**, **Poor**, or **Critically Deficient**. It is important to stress that t performed in the context of the study's utility for hazard identification of indiv While limitations specific to the usability of the study for dose-response analys (to inform those later decisions), they do not contribute to the study confidenc These terms are defined as follows:

- "Good" is intended to represent a judgment that there was appropriat relating to the domain, and any minor deficiencies that were noted wo to influence the study results.
- "Adequate" indicates a judgment that there were experimental limitati domain, but that those limitations are not likely to be severe or to have on the results.
- "Poor" denotes identified biases or deficiencies that are interpreted as substantial impact on the results or which prevent reliable interpretati findings.
- "Not reported" indicates that the information necessary to evaluate the was not available in the study. Generally, this term carries the same fu interpretation as "Poor" for the purposes of the study confidence classi on the number and severity of other limitations identified in the study, it may or may not be worth reaching out to the study authors for this information (see discussion below).
- "Critically Deficient" reflects a judgment that the experimental conduct relating to the domain question introduced a flaw so serious that the study should not be used without

Once the evaluation domains have been considered, the identified strengths and limitations will be combined to reach a study confidence classification of **High**, **Medium**, **Low**, or **Uninformative**. This classification will be based on the reviewer judgments across the evaluation domains, and will include consideration of the likely impact of the noted deficiencies in bias and sensitivity, or inadequate reporting, on the results. The classifications, which reflect a consensus judgment between reviewers, are defined as follows:

- **High Confidence:** No notable deficiencies or concerns were identified; the potential for bias is unlikely or minimal, and the study used sensitive methodology. In general, although classifications are not decided by "scoring", high confidence studies would reflect judgments of good across all or most evaluation domains.
- **Medium Confidence:** Possible deficiencies or concerns were noted, but the limitations are unlikely to be of a substantive degree. Generally, medium confidence studies will include adequate or good judgments across most domains, with the impact of any identified limitation not being judged as severe.
- **Low Confidence:** Deficiencies or concerns were noted, and the potential for substantive bias or inadequate sensitivity could have a significant impact on the study results or their interpretation. Typically, low confidence studies would have a poor evaluation for one or more domains (unless the impact of the particular limitations on the results is judged as unlikely to be severe).
- **Uninformative:** Serious flaw(s) make the study results unusable for informing hazard identification. Studies with critical deficiencies in any evaluation domain will almost always be classified as uninformative (see explanation above). Studies with multiple poor judgments across domains may also be considered uninformative, particularly when there is a robust database of studies on the outcome(s) of interest or when the impact of the limitations is viewed as severe.

Protocol: Study Evaluation (Epidemiology)

6.2. EPIDEMIOLOGY STUDY EVALUATION

Evaluation of epidemiology studies to assess bias and study sensitivity will be conducted for the following domains: exposure measures, outcome measures, participant selection, potential confounding, analysis, selection of reported results, and study sensitivity (**Table 2**)

Table 2. Domains of evaluation for epidemiology studies

Domain	Example information
Exposure measures	Source(s) of exposure (consumer products, occupational, an industrial accident) and sc exposure data, blinding to outcome, level of detail for job history data, when measure were taken, type of biomarker(s), assay information, reliability data from repeat meas studies, validation studies.
Outcome measures	Source of outcome (effect) measure, blinding to exposure status or level, how measured/classified, incident versus prevalent disease, evidence from validation studi prevalence (or distribution summary statistics for continuous measures).
Participant selection	Study design, where and when was the study conducted, and who was included? Recr process, exclusion and inclusion criteria, type of controls, total eligible, comparison bet participants and nonparticipants (or followed and not followed), final analysis group. D study include potential vulnerable/susceptible groups or lifestages?
Potential confounding	Background research on key confounders for specific populations or settings; participa characteristic data, by group; strategy/approach for consideration of potential confour strength of associations between exposure and potential confounders and between pc confounders and outcome; degree of exposure to the confounder in the population.
Analysis	Extent (and if applicable, treatment) of missing data for exposure, outcome, and confo approach to modeling, classification of exposure and outcome variables (continuous ve categorical), testing of assumptions, sample size for specific analyses, relevant sensitivi analyses.
Selective reporting	Are results presented with adequate detail for all of the endpoints of interest? Are res presented for the full sample as well as for specified subgroups? Were stratified analy modification) motivated by a specific hypothesis?
Sensitivity	What exposure range is spanned in this study? What are the ages of participants (e.g., young in studies of pubertal development)? What is the length of follow-up (for outco long latency periods)? Choice of referent group and the level of exposure contrast bet groups (i.e., the extent to which the "unexposed group" is truly unexposed, and the pr of exposure in the group designated as "exposed").

The principles and framework used for the evaluation of epidemiology studies are based c Cochrane Risk of Bias in Non-randomized Studies (ROBINS) of interventions (ROBINS-I) (al., 2016) but modified to address environmental and occupational exposures. The underl philosophy of ROBINS-I is to describes attributes of an "ideal" study with respect to each c evaluation domains (e.g., exposure measurement, outcome classification, etc.). Core and prompting questions are used to collect information to guide evaluation of each domain. In addition, expected

Table 3. Example question specification for evaluation of domains in epidemiology studies

Core question	Example prompting questions	Example follow-up questions
Exposure Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?	For all: • Does the exposure measure capture the major source(s) of variability in exposure among the participants, considering intensity, frequency, and duration of exposure? • Does the exposure measure reflect a relevant time window? If not, can the relationship between measures in this time and the relevant time window be estimated reliably? • Was the exposure measurement likely to be affected by a knowledge of the outcome or by the presence of the outcome (i.e., reverse causality)? For case-control studies of occupational exposures: • Is exposure based on a comprehensive job history describing tasks, setting, time period, and use of specific materials? For biomarkers of exposure, general population: • Is a standard assay used? What are the intra- and inter-assay coefficients of variation? Is the assay likely to be affected by contamination? Are values less than the limit of detection dealt with adequately? • What exposure time-period is reflected by the biomarker? If the half-life is short, what is the correlation between serial measurements of exposure?	Is the degree of exposure misclassification likely to vary by exposure level? If the correlation between exposure measurements is moderate, is there an adequate statistical approach to ameliorate variability in measurements? If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?
Outcome Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?	For all: • Is disease ascertainment likely to be affected by knowledge of, or presence of, exposure (e.g., consider access to health care, if based on self-reported history of diagnosis)? For case-control studies: • Is the non-diseased comparison group (e.g., controls in a case-control study) based on objective criteria with little or no likelihood of inclusion of people with the disease? For mortality measures: • How well does cause of death data reflect occurrence of the disease in an individual? How well do mortality data reflect incidence of the disease? For diagnosis of disease measures: • Is diagnosis based on standard clinical criteria? If based on self-report of diagnosis, what is the validity of this measure?	Is there a concern that any outcome misclassification is non-differential, differential, or both? What is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?

Protocol: Study Evaluation (Animal)

Table 4. General criteria to evaluate outcomes from animal toxicology studies

Domain	Metric	Criteria
Reporting Quality	Reporting of information necessary for study evaluation	Key information necessary for study evaluation (study would be deemed critically deficient if not reported[1]): • Species; test article desc endpoints investigated; Important information, which sh brackets contain secondary infor based on the needs of a given as information. • *Test animal* – strain; sex (e.g., housing, feed, mat procedures); age or bod • *Exposure methods* – test route of administration; volume, exposure cham verification methods]. • *Experimental design* – p during exposure and at evaluation(s) (e.g., laten • *Endpoint evaluations* – p were measured; proced and negative controls; [region of tissue/ organ (e.g., surgery, co-treatm • *Results presentation* – p were investigated; infor assessed; sample size; s maternal toxicity in deve in long-term bioassays). [1] Although such decisions should information is not reported, it is authors. However, for other miss confidence conclusions if it they out to study authors. *Note*: Studies adhering to GLP (g established by (inter)national age quality.
Selection or Performance Bias	Allocation of animals to experimental groups	Ideally, animal studies are rando chance of being assigned to any allocation procedures sufficiently or good, are studies indicating n exposure, for example according of randomization. The least prefe how groups were assigned.
	Blinding of investigators, particularly during outcome assessment	Good studies will conceal the tre the endpoint evaluations (and, in personnel and technicians). Conc outcome measures are more obj

Domain	Metric	Criteria
		weights) or measurement is automated using computer-driven systems (e.g., as is the case in many behavioral assessments).
Confounding/Variable Control	Control for variables across experimental groups	In a good study, outside of the (chemical) exposure of interest, all variables will be controlled for and consistent across expe additional variables, introduced intentionally mitigated by knowledge or inferences regard which the variable can influence the endpoi A very important example to consider is whe controlled to attribute the effects of exposu alone. Generally, well-conducted exposures exposures and will include experimental con confounding (e.g., use of a suitable vehicle c Other examples of variables that may be unc experimental groups include: protective or t exacerbate effects; diet composition; surgica
Reporting or Attrition Bias	Lack of selective data reporting and unaccounted for loss of animals	In a good study, information is reported on a comparisons for all animals, across treatmen Aspects to consider include whether all stud results (if not, are explanations, such as deat provided), and whether expected compariso from the analyses. In some studies, the outc (e.g., a suite of standard measures in a guide *Note*: This metric does not address whether considers statistical test methods.
Exposure Methods Sensitivity	Characterization of the exposure to the compound of interest	Consider whether there are notable issues th of the exposure levels, or of exposure to the on the chemical being assessed, this may inc stability and composition (e.g., purity; isome exposure generation and analytic verificatio tested levels and spacing between exposure methods); and details of exposure methods (gavage volume). In some cases, exposure bio treated animals can mitigate concerns regar on the validity of the biomarker for the chem *Note*: While this identifies uncertainties in d valid reason for exclusion from Hazard ID.
	Utility of the exposure design for the endpoint of interest	Based on the known or presumed biological evaluated, consider whether there are notab frequency, or duration of exposure. For exa will cover a greater proportion of the develo critical to the system of interest, while bette other chronic outcomes will be of longer du infrequently or sporadically, or, conversely, depending on the exposure level, can impact

Domain	Metric	Criteria
Outcome Measures and Results Display	Sensitivity and specificity of the endpoint evaluations	Consider whether there are notable concerns about aspects of the procedures for, or the timing of, the endpoint evaluations. Based on the endpoint evaluation protocol used for the endpoints of interest, specific considerations will typically include: • Concerns regarding the sensitivity of the specific protocols for evaluating the endpoint of interest (i.e. assays can differ dramatically in terms of their ability to detect effects), and/or their timing (i.e. the age of animals at assessment can be critical to the appropriateness and sensitivity of the evaluation). This includes both overestimates or underestimates of the true effect, as well as a much higher (or lower) probability for detecting the effect(s) being assessed. • Concerns regarding the specificity and validity of the protocols. This includes the use of appropriate protocol controls to rule out non-specific effects, which can often be inferred from established guidelines or historical assay data. It may be considered useful for insensitive, complex, or novel protocols to include positive and/or negative controls. • Concerns regarding adequate sampling. This includes both the experimental unit (e.g., litter; animal) and endpoint (e.g., number of slides evaluated). This is typically inferred from historical knowledge of the assay or comparable assays. *Notes*: Human relevance of the endpoint is not addressed during study evaluation; for under sampling without blinding (e.g., sampling bias), this will typically lead to gross overestimates of effect; sample size is generally not a reason for exclusion.
	Usability and transparency of the presented data	Consider whether the results are analyzed or presented in a way that limits concerns regarding the reliability of the findings. Items that will typically be important to consider include: • Concern that the level of detail provided does not allow for an informed interpretation of the results (e.g., authors' conclusions without quantitative data; discussing neoplasms without distinguishing between benign and malignant tumors; not presenting variability). • Concern that the way in which the data were analyzed, compared, or presented is inappropriate or misleading. Examples include: failing to control for litter effects (e.g., when presenting pup data rather than the preferred litter data); pooling results from males and females or across lesion types; failing to address observed or presumed toxicity (e.g., in assessed animals; in dams) when exposure levels are known or expected to be highly toxic; incomplete presentation of the data (e.g., presenting continuous data as dichotomized); or non-preferred display of results (e.g., using a different readout than is expected for that assay). The evaluator should support how or why, and to what extent, this might mislead interpretations. *Notes:* Concerns regarding the statistical methods applied are not addressed during study evaluation, but should be flagged for review by a statistician. Missing information related to this metric should typically be requested from study authors.

Protocol: Evidence Synthesis and Integration

Table 8. Primary considerations for synthesizing the human and, separately, animal health effect evidence

Consideration	Description
Consistency	Repeated findings across different studies or experiments increase the evidence strength. When inconsistencies exist, the evalu "conflicting" or "differing" {U.S. *Stronger human evidence*: evid *Stronger animal evidence*: evid
Biological gradient (dose-response[b])	Increases in risk, or in the frequ concentration; duration) increa nonlinear) relationships. A lack strength, but this may be appro
Strength (effect magnitude) and precision	Given what is known about the particularly for rare or severe e grounds to dismiss an associati historical data, or bias to assess
Biological plausibility	Supporting mechanistic evidenc effects; changes in established evidence strength. While a lack strength, this can occur if findin *Human evidence*: studies in exp *Animal evidence*: studies in exp
Coherence[c]	Findings across the database th similarity in results for related e dose-dependent progression of Conversely, an observed lack of subsequently) with the effect o informed by the known biologic toxicokinetic/dynamic understa
Natural experiments	*Human evidence only*: Reductio Although rare, this can provide
Temporality	*Human evidence only*: The expo evaluation of exposure measur

[a]These ideas build upon the discussion for assess although there are some differences in the use

[b] While humans are "exposed" and not "dosed", used for convention, although it is acknowledge contexts.

[c] There is a clear overlap in the use of mechanisti or comparability of potentially coherent health information is synthesized separately and consi Section 10).

[d] Although it is not separately listed, Hill's consid association that supports causation) is indirectly of environmental health studies; however, this

Table 10. Framework for classification of strength of evidence from studies in humans

Extent of support for hazard	Within-stream strength of evidence conclusion	Description
Supports hazard	*Robust ... human evidence of an effect*	A set of *high* or *medium confidence* independent studies reporting an association between the exposure and the health outcome, with reasonable confidence that alternative explanations, including chance, bias, and confounding, are ruled out across studies. The set of studies is primarily consistent, and there are reasonable explanations when results differ; an exposure-response gradient is demonstrated; and the set of studies includes varied populations. Additional supporting evidence, such as associations with biologically-related endpoints in human studies but are not required. Selec explanation for results. In considered to be *robust*, ev finding of angiosarcoma, ar Mechanistic evidence from informing considerations su thus raising the level of cer described as *moderate*.
	Moderate ... human evidence of an effect	A smaller number of studies evidence), or with some het required for *robust*. There explanations, including char with related endpoints inclu cells, if available, may add s temporality, coherence, and studies that otherwise woul
Could support hazard or no hazard	*Slight ... human evidence of an effect*	One or more studies report where alternative explanati available, or considerable h understood. Strong biologi human cells may also be inc *confidence* study that is the generating vs. hypothesis-te serves primarily to encourag some support for an associa confidence required for mo
	Indeterminate ... human evidence of an effect	No studies available in hum not informative to the haza
Supports no hazard	*Compelling evidence of no effect ... in human studies*	Several *high confidence* stu of 1.0) ruling out alternative explanations including chance, bias, and confounding with reasonable confidence. Each of the studies should have used an optimal outcome and exposure assessment and adequate sample size (specifically for higher exposure groups and for sensitive populations). The set as a whole should include the full range of levels of exposures that human beings are known to encounter, an evaluation of an exposure-response gradient, and at-risk populations and lifestages, and should be mutually consistent in not showing any indication of effect at any level of exposure.

EPA's standardized hazard descriptors for cancer

Carcinogenic to humans: convincing epidemiologic evidence of a causal association; or strong human evidence of cancer or its key precursors, extensive animal evidence, identification of mode-of-action and its key precursors in animals, and strong evidence that they are anticipated in humans.

Likely to be carcinogenic to humans: evidence that demonstrates a potential hazard to humans. Examples include a plausible association in humans with supporting experimental evidence, multiple positive results in animals, a rare animal response, or a positive study strengthened by other lines of evidence.

Suggestive evidence of carcinogenic potential: evidence that raises a concern for humans. Examples include a positive result in the only study, or a single positive result in an extensive database.

Inadequate information to assess carcinogenic potential: no other descriptors apply. Examples include little or no pertinent information, *conflicting evidence*, or negative results not sufficiently robust for *not likely*.

Not likely to be carcinogenic to humans: convincing and extensive evidence to conclude that there is no basis for concern. Examples include no effects in well-conducted and well-designed studies in both sexes of multiple animal species (without data in animals or humans to suggest a potential for carcinogenicity), extensive evidence showing that carcinogenic effects only observed in animals arise through modes-of-action that do not operate in humans, or convincing evidence that effects are not likely by a particular exposure route or below a defined dose (in the latter situations, multiple descriptors might be applied for a single agent).

United States Environmental Protection Agency

Demonstrating Advances in Systematic Review

IRIS Systematic Review Workgroup

Office of Research and Development
NCEA, IRIS

IRIS Systematic Review Workgroup

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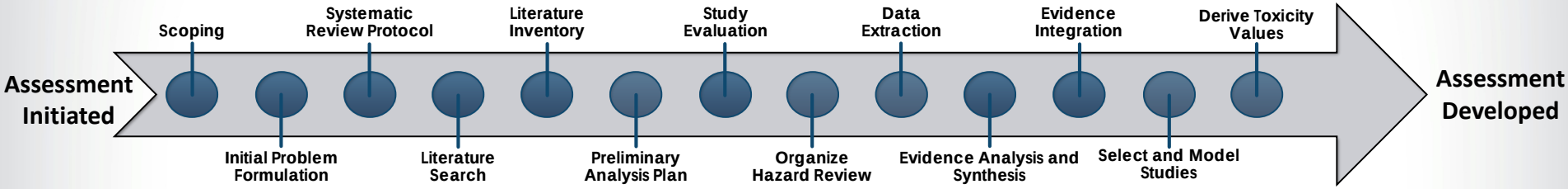

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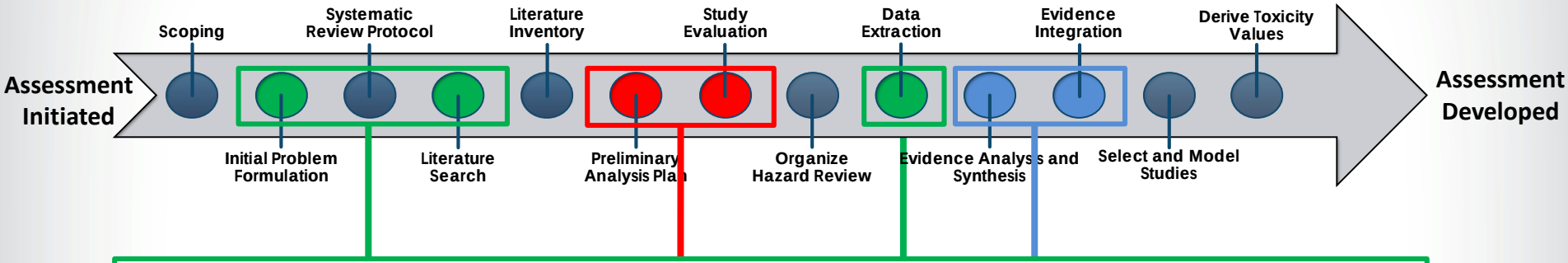
- **Many steps are being optimized through tools development**
- **Approaches and tools were developed based on extensive research within the field of systematic review (traditionally oriented around clinical medicine)**

Specific Examples of Advances



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- **Tools for Problem Formulation and Efficient Literature Screening**
- **Tools for Data Content Management**

2) Beth Radke and Xabier Arzuaga:

- **Evaluation of Individual Epidemiology and Animal Toxicology Studies**

3) Barbara Glenn and Andrew Kraft:

- **Synthesis and Integration of the Available Evidence**

United States Environmental Protection Agency

Demonstration of Tools for Problem Formulation and Efficient Literature Screening

Michele Taylor, Ph.D

Office of Research and Development
NCEA, IRIS

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- Freely available interactive workbench
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- Train the model with 10-20 include/10-20 exclude "seeds"
- Identifies data rich/data poor topics within the literature corpus
- Priority ranks documents for manual screening

SWIFT Review: Problem Formulation and Literature Screening

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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.

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SWIFT Review: Problem Formulation and Literature Screening

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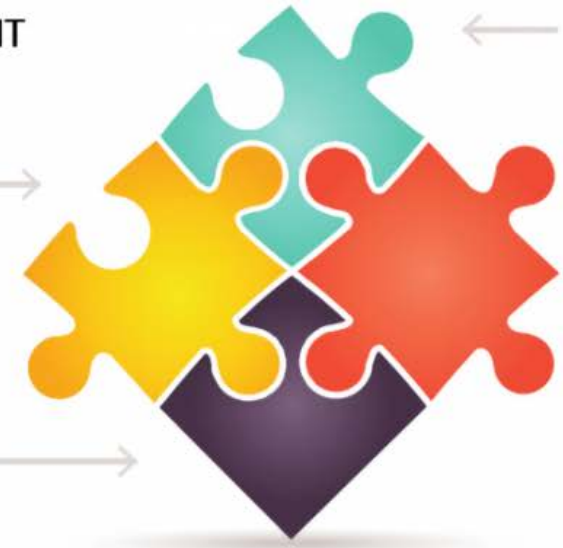
TOPIC MODELING
Uncover hidden structure in your literature corpus.



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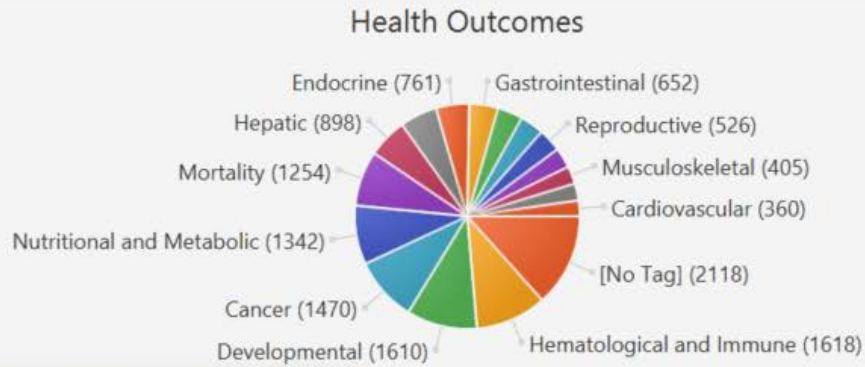

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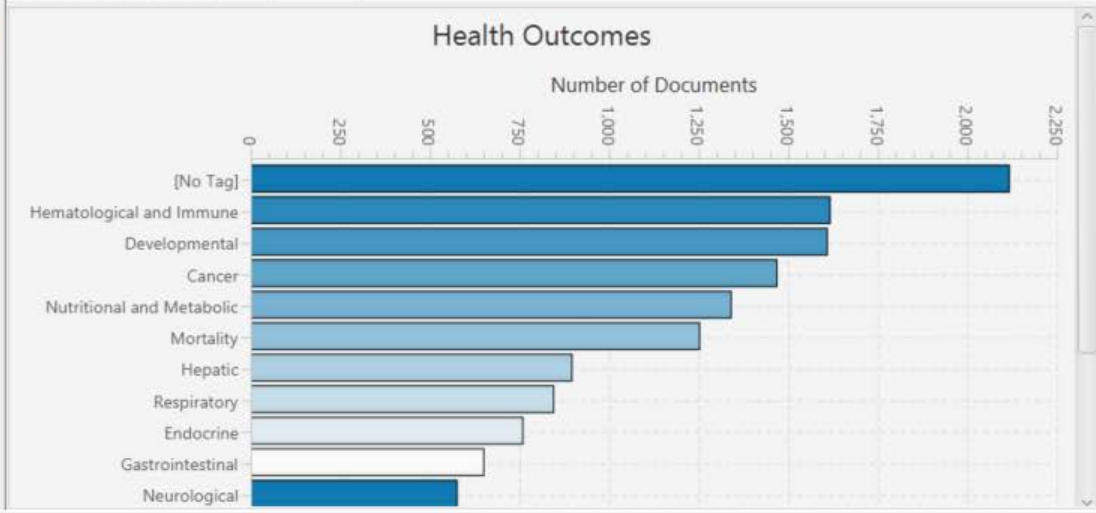

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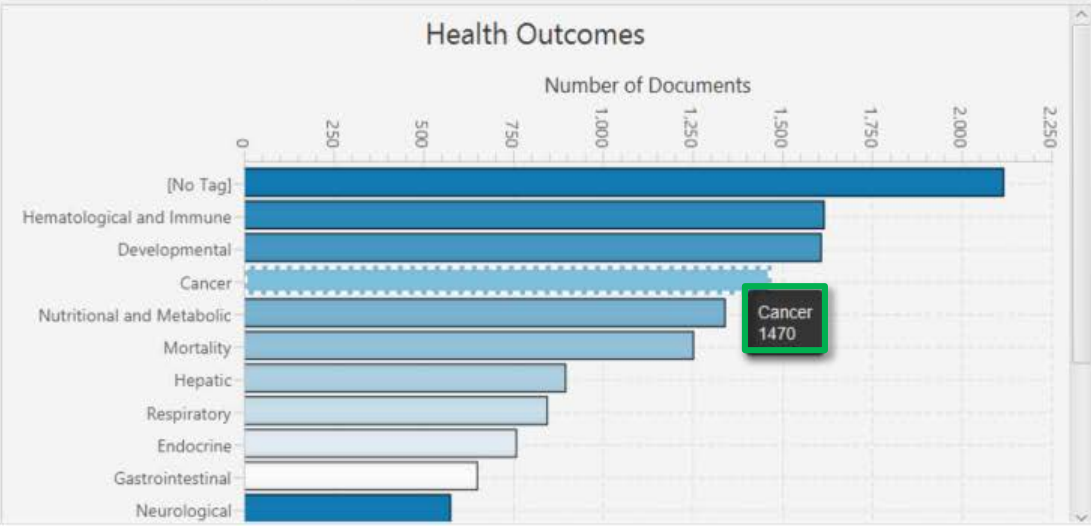

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0.238	☐	☐	h1010095	A combined COMPACT and HazardExpert study ...	1998	Lewis D, F. V.; Ioannides, C.; Parke, ...	Human & Experimental Toxicology
0.238	☐	☐	h1066172	Antimutagenic and anticarcinogenic potentials of...	1998	Kusamran, W. R.; Tepsuwan, A.; Ku...	Mutation Research
0.238	☐	☐	h1023694	Chloroform-induced cytolethality in freshly isolat...	1998	Ammann, P.; Laethem, C. L.; Kedder...	Toxicology and Applied Pharmacology
0.238	☐	☐	h1010509	Chromosome aberration assays in genetic toxico...	1998	Ishidate, M.; Miura, K. F.; Sofuni, T.	Mutation Research
0.238	☐	☐	h1022403	In vitro studies on non-genotoxic carcinogens: r...	1998	Stenius, U.; Ståhl, A.; Högberg, J.	Toxicology In Vitro
0.238	☐	☐	h1023662	Occurrence of toxicity and cell proliferation after...	1998	Miyagawa, M.; Katsuta, O.; Chida, T....	Journal of Toxicological Sciences
0.238	☐	☐	h1022373	DIMETHYLNITROSAMINE AND CHLOROFORM I...	1997	Butterworth, B.; Sprankle, C.; Templi...	
0.238	☐	☐	h730581	Glutathione S-transferase-mediated mutagenicity...	1997	Pegram, R. A.; Andersen, M. E.; War...	Toxicology and Applied Pharmacology
0.238	☐	☐	h1023715	Potency grading in carcinogen classification	1997	Sanner, T.; Dybing, E.; Kroese, D.; R...	Molecular Carcinogenesis
0.238	☐	☐	h1022593	ROLE OF CELL REPLICATION IN THE HEPATO...	1997	Lake, B. G.	
0.238	☐	☐	h1024035	A 90-day chloroform inhalation study in F-344 r...	1996	Templin, M. V.; Larson, J. L.; Butter...	Fundamental and Applied Toxicology
0.238	☐	☐	h1022774	Assessment of health risk associated with THM i...	1995	Ambroise, D.; Blech, M. F.; Di Majo, ...	
0.238	☐	☐	h1069047	METABOLISM AND COMETABOLISM OF HALOG...	1995	Jain, M. K.; Criddle, C. S.	
0.238	☐	☐	h1022778	THE NEED FOR TOXICOLOGICAL STUDIES ON ...	1995	Nigam, S. K.	Indian journal of industrial medicine

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Health Outcomes

Tag	Code(s)	Count
[No Tag]		2118
Hematological and Immune		1618
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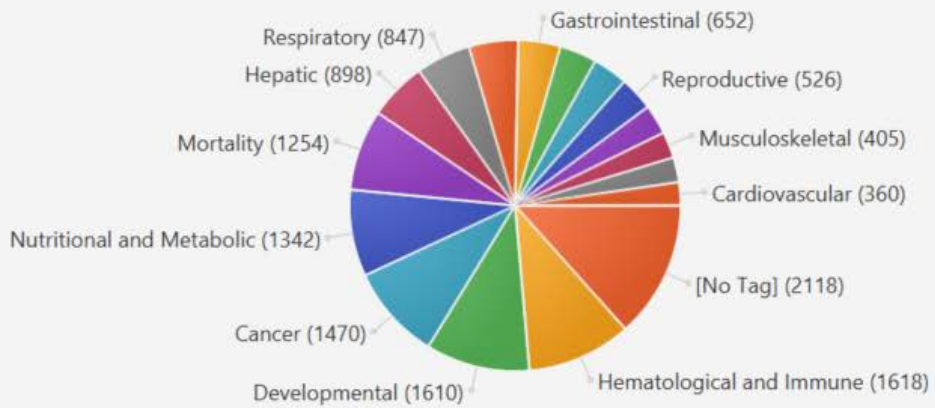

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Score	Training Item?	Included?	RefID	Title	Year	Authors	Journal
0			h3719964	(1) H qNMR Quantification of Annonaceous Acet...	2017	Bonneau, N.; Cynober, T.; Jullian, J....	
0			h3718321	A continuous flow synthesis and derivatization o...	2017	Baumann, M.; Baxendale, I. R.	Bioorganic & Medicinal Chemistry
0			h3720104	Activity of Pericampylus glaucus and periglaucin...	2017	Shipton, F. N.; Khoo, T. J.; Hossan, ...	Journal of Ethnopharmacology
0			h3696444	Airways and vascular smooth muscles relaxant a...	2017	Alam, F.; Saqib, Q. N. U.,s; Shah, A....	Pakistan Journal of Pharmaceutical S...
0			h3718324	Ameliorative potential of Alstonia scholaris (Linn...	2017	Singh, H.; Arora, R.; Arora, S.; Sing...	BMC Complementary and Alternative...
0			h3696443	Antibacterial activities of Diospyros blancoi, Pho...	2017	Tahir, L.; Aslam, A.; Ahmed, S.	Pakistan Journal of Pharmaceutical S...
0			h3696441	Antidiabetic activity and histopathological analys...	2017	Khan, I.; Ahmad, W.; Karim, N.; Ah...	Medicinal Chemistry Research
0			h3720138	Antidiabetic effects of Brucea javanica seeds in t...	2017	Ablat, A.; Halabi, M. F.; Mohamad, J...	BMC Complementary and Alternative...
0			h3696446	Anti-mitragynine monoclonal antibody-based EL...	2017	Limsuwanchote, S.; Putalun, W.; Kea...	Forensic Toxicology
0			h3719935	Antioxidant and antiproliferative effects of differ...	2017	Basu, T.; Panja, S.; Ghate, N. B.; Ch...	Cytotechnology
0			h3720106	Azithromycin assay in drug formulations: Valida...	2017	Bouklouze, A.; Kharbach, M.; Cherra...	Annales Pharmaceutiques Francaises
0			h3696360	Chloroform ingestion causing severe gastrointes...	2017	Jayaweera, D.; Islam, S.; Gunja, N.; ...	Clinical Toxicology
0			h3719963	Cholinesterase inhibitory, anti-amyloidogenic an...	2017	Sheeja Malar, D.; Beema Shafreen, R...	Pharmaceutical Biology
0			h3718323	Composition profiles, levels, distributions and ec...	2017	Niu, Z.; Li, X.; Zhang, Y.	Marine Pollution Bulletin
0			h3593309	Compound-Specific Chlorine Isotope Analysis of...	2017	Heckel, B.; Rodríguez-Fernández, D.;...	Analytical Chemistry
0			h3720080	Development and evaluation of naproxen sodiu...	2017	Patwardhan, S. K.; Patil, M. J.; Socka...	
0			h3671764	Disinfection by-product exposures and the risk o...	2017	Wright, J. M.; Evans, A.; Kaufman, J....	Environmental Health Perspectives
0			h3719591	DNA extraction from benthic Cyanobacteria: co...	2017	Gaget, V.; Keulen, A.; Lau, M.; Moni...	Journal of Applied Microbiology
0			h3718322	Enhancing silymarin fractionation using the cond...	2017	Brace, E. C.; Engelberth, A. S.	Journal of Chromatography A
0			h3696442	Enzyme inhibitory, Antifungal, Antibacterial and ...	2017	Riaz, T.; Abbasi, M. A.; Aziz-ur-Reh...	Pakistan Journal of Pharmaceutical S...
0			h3696357	Evaluating genomic DNA extraction methods fro...	2017	Koshy, L.; Anju, A. L.; Harikrishnan, ...	Molecular Biology Reports
0			h3720259	Evaluation of the antidiarrheal activity of the leaf...	2017	Sisay, M.; Engidawork, E.; Shibeshi, ...	BMC Complementary and Alternative...

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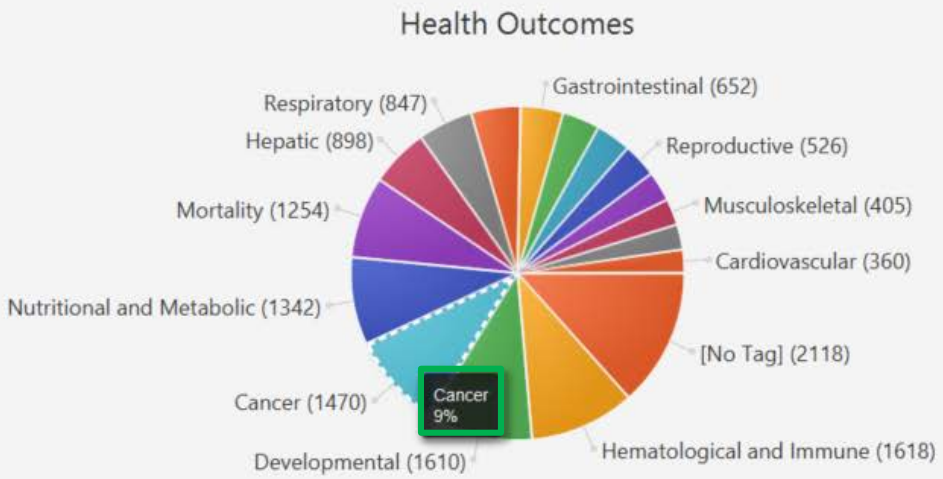

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Score	Training Item?	Included?	RefID	Title	Year	Authors	Journal
0.95	☐	☐	h1022338	Identification of genotoxic compounds in drinkin...	1998	Le Curieux, F.; Erb, F.; Marzin, D.	
0.95	☐	☐	h1021972	Mutagenicity study of carbon tetrachloride and c...	1998	Sasaki, T.; Suzuki, M.; Noda, K.; No...	Journal of Toxicological Sciences
0.95	☐	☐	h630464	Advances in research on carcinogenic and genot...	1993	Daniel, F. B.; Meier, , J. R.; Deangelo...	Annali dell'Istituto superiore di sanità
0.95	☐	☐	h1024901	Cytosine attack by free radicals arising from bro...	1993	Castro, G. D.; Castro, J. A.	Teratogenesis, Carcinogenesis, and ...
0.95	☐	☐	h1010308	International Commission for Protection Against...	1992	Lohman, P. H. M.; Mendelsohn, M. L....	Mutation Research: Fundamental and...
0.95	☐	☐	h1024875	International Commission for Protection Against...	1992	Mendelsohn, M. L.; Moore, D. H.; Lo...	Mutation Research
0.95	☐	☐	h1024972	Rational approach to the quantification of genot...	1992	Benigni, R.	Environmental and Molecular Mutage...
0.95	☐	☐	h194881	An association between mutagenicity of the Ara ...	1991	Roldán-Arjona, T.; García-Pedrajas, ...	Mutagenesis
0.95	☐	☐	h1023024	Volatile Organohalogen Compounds from the Bl...	1991	Rosenberg, C.; Nylund, L.; Aalto, T.;...	Chemosphere
0.95	☐	☐	h1021433	The toxicology of chemicals - 1. Carcinogenicity,...	1990	Berlin, A.; Draper, M.; Krug, E.; Roi, ...	
0.95	☐	☐	h10072	Bacterial mutagenicity studies on chloroform in ...	1982	Van Abbe, N. J.; Green, T. J.; Jones,...	Food and Chemical Toxicology
0.95	☐	☐	h10063	Detection of genotoxic carcinogens in the in vivo...	1982	Mirsalis, J. C.; Tyson, C. K.; Butterw...	Environmental and Molecular Mutage...
0.48	☑	☑	h3719968	Podophyllum hexandrum ameliorates endosulfa...	2017	Dar, S. A.; Yousuf, A. R.; Balkhi, M. ...	Pharmaceutical Biology
0.48	☐	☐	h3585628	Mutagenicity and genotoxicity of drinking water i...	2015	Abda, A.; Benouareth, D. E.; Tabet, ...	Environmental Monitoring and Asses...
0.48	☐	☐	h3698004	The use of endemic Iranian plant, Echium amoe...	2015	Uysal, H.; Kızılet, H.; Ayar, A.; Taher...	Toxicology and Industrial Health
0.48	☐	☐	h3719592	Toxic potentials of ten herbs commonly used for...	2015	Abudayyak, M.; Özdemir Nath, E.; Ö...	Turkish Journal of Medical Sciences
0.48	☐	☐	h3698164	Application of ultrasound-assisted emulsification...	2014	Asghari, A.; Fazl-Karimi, H.; Barfi, B....	Human & Experimental Toxicology
0.48	☐	☐	h1292499	Antioxidant, genotoxic and antigenotoxic activiti...	2012	Chaabane, F.; Boubaker, J.; Loussaif,...	BMC Complementary and Alternative...
0.475	☐	☐	h1068198	Genotoxicity and toxicity assessment in urban hy...	2006	Cardozo, T. R.; Rosa, D. P.; Feiden, ...	Mutation Research
0.475	☐	☐	h1024786	In vitro protective effects of Terminalia arjuna b...	2002	Pasquini, R.; Scassellati-Sforzolini, G....	Journal of Environmental Pathology, ...
0.475	☐	☐	h1066151	Antigenotoxic properties of Terminalia arjuna ba...	1999	Scassellati-Sforzolini, G.; Villarini, L. ...	Journal of Environmental Pathology, ...
0.475	☐	☐	h657377	Use of the SOS chromotest, the Ames-fluctuatio...	1995	Le Curieux, F.; Gauthier, L.; Erb, F.; ...	Mutagenesis

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

Health Outcomes

Add Level
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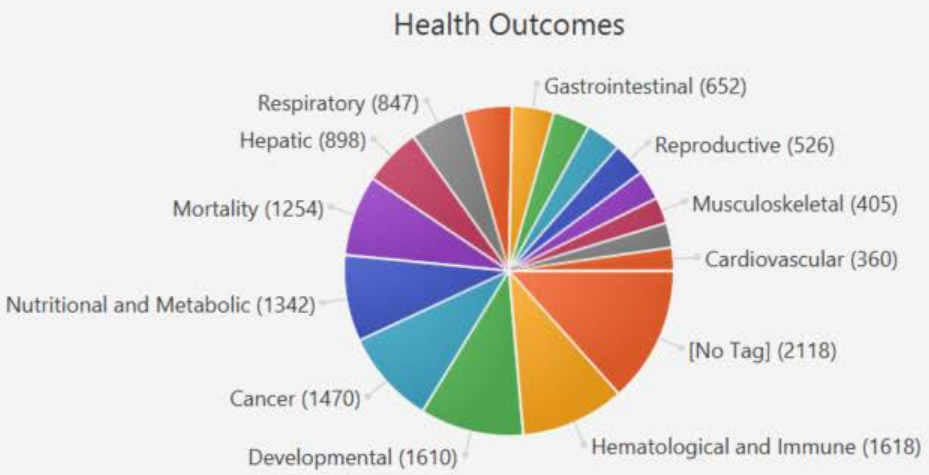

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0.238	☐	☐	h1066919	An improved method for determination of ethyl ...	2001	Woo, I. S.; Kim, I. H.; Yun, U. J.; Ch...	Journal of Industrial Microbiology an...
0.238	☐	☐	h1069305	Modulation of gap junction plaques containing C...	2001	Mally, A.; Cowles, C.; Chipman, J. K.	Toxicology
0.238	☐	☐	h1068110	Mutagens that are not carcinogens: faulty theory...	2001	Zeiger, E.	Mutation Research
0.238	☐	☐	h1065850	Supplementary guidance for conducting health ri...	2000	U.S. EPA,	
0.238	☐	☐	h658806	Exposição humana a trialometanos presentes e...	1999	Tominaga, M. Y.; Midio, A. F.	Revista de Saude Publica
0.238	☐	☐	h1023686	Absence of PhIP adducts, p53 and Apc mutation...	1998	Shen, C. L.; Purewal, M.; San Francis...	Nutrition and Cancer
0.238	☐	☐	h1067968	A combined COMPACT and HazardExpert study ...	1998	Lewis, D. F. V.; Ioannides, C.; Parke,...	Human & Experimental Toxicology
0.238	☐	☐	h1010095	A combined COMPACT and HazardExpert study ...	1998	Lewis D, F. V.; Ioannides, C.; Parke, ...	Human & Experimental Toxicology
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0.238	☐	☐	h1023662	Occurrence of toxicity and cell proliferation after...	1998	Miyagawa, M.; Katsuta, O.; Chida, T....	Journal of Toxicological Sciences
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0.238	☐	☐	h1022593	ROLE OF CELL REPLICATION IN THE HEPATO...	1997	Lake, B. G.	
0.238	☐	☐	h1024035	A 90-day chloroform inhalation study in F-344 r...	1996	Templin, M. V.; Larson, J. L.; Butter...	Fundamental and Applied Toxicology
0.238	☐	☐	h1022774	Assessment of health risk associated with THM i...	1995	Ambroise, D.; Blech, M. F.; Di Majo, ...	
0.238	☐	☐	h1069047	METABOLISM AND COMETABOLISM OF HALOG...	1995	Jain, M. K.; Criddle, C. S.	
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Evidence Stream

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Animal	2211

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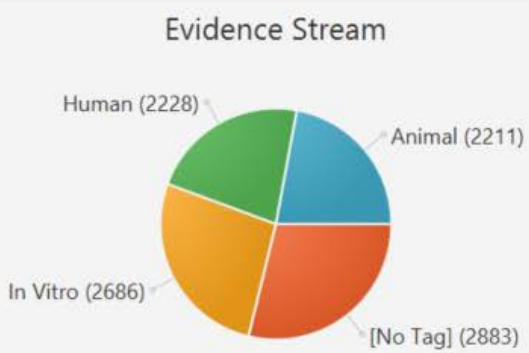

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0	☐	☐	h3696357	Evaluating genomic DNA extraction methods fro...	2017	Koshy, L.; Anju, A. L.; Harikrishnan, ...	Molecular Biology Reports
0	☐	☐	h3696443	Antibacterial activities of Diospyros blancoi, Pho...	2017	Tahir, L.; Aslam, A.; Ahmed, S.	Pakistan Journal of Pharmaceutical S...
0	☐	☐	h3720106	Azithromycin assay in drug formulations: Valida...	2017	Bouklouze, A.; Kharbach, M.; Cherra...	Annales Pharmaceutiques Francaises
0	☐	☐	h3718321	A continuous flow synthesis and derivatization o...	2017	Baumann, M.; Baxendale, I. R.	Bioorganic & Medicinal Chemistry
0	☐	☐	h3696440	Potential Health Benefits and Metabolomics of C...	2017	Ahamad, S. R.; Raish, M.; Ahmad, A...	Biological Trace Element Research
0	☐	☐	h3696441	Antidiabetic activity and histopathological analys...	2017	Khan, I.; Ahmad, W.; Karim, N.; Ah...	Medicinal Chemistry Research
0	☐	☐	h3696442	Enzyme inhibitory, Antifungal, Antibacterial and ...	2017	Riaz, T.; Abbasi, M. A.; Aziz-ur-Reh...	Pakistan Journal of Pharmaceutical S...
0	☐	☐	h3719802	New xanthones and cytotoxic constituents from ...	2017	Mohamed, G. A.; Al-Abd, A. M.; El-...	Journal of Ethnopharmacology
0	☐	☐	h3719961	Molecularly imprinted phloroglucinol-formaldehy...	2017	Liang, S.; Yan, H.; Cao, J.; Han, Y.; ...	Analytica Chimica Acta
0	☐	☐	h3719678	In vivo antimalarial activity of crude extracts and...	2017	Fentahun, S.; Makonnen, E.; Awas, ...	BMC Complementary and Alternative...
0	☐	☐	h3718319	Quantitative Analysis of Volatile Impurities in Di...	2017	Liu, C.; Zhang, Y.; Wang, H.; Wang, ...	International Journal of Analytical Ch...
0	☐	☐	h3718323	Composition profiles, levels, distributions and ec...	2017	Niu, Z.; Li, X.; Zhang, Y.	Marine Pollution Bulletin
0	☐	☐	h3593309	Compound-Specific Chlorine Isotope Analysis of...	2017	Heckel, B.; Rodríguez-Fernández, D.;...	Analytical Chemistry
0	☐	☐	h3696447	Securigenin glycosides as hypoglycemic principl...	2017	Tofighi, Z.; Moradi-Afrapoli, F.; Ebra...	Journal of Natural Medicines
0	☐	☐	h3719812	Live and heat-killed Lactobacillus spp. interfere ...	2017	Ciandrini, E.; Campana, R.; Baffone, ...	Archives of Oral Biology
0	☐	☐	h3719964	(1) H qNMR Quantification of Annonaceous Acet...	2017	Bonneau, N.; Cynober, T.; Jullian, J....	
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0	☐	☐	h3720181	Formation of Haloacetonitriles, Haloacetamides, ...	2017	Nihemaiti, M.; Le Roux, J.; Hoppe-Jo...	Environmental Science and Technology
0	☐	☐	h3720261	Refined experimental annotation reveals conserv...	2017	Wang, P. H.; Tang, S.; Nemr, K.; Flic...	ISME Journal: Multidisciplinary Journ...
0	☐	☐	h3718320	Predicting reactivity of model DOM compounds t...	2017	de Vera, G. A.; Gernjak, W.; Radjen...	Water Research
0	☐	☐	h3719968	Podophyllum hexandrum ameliorates endosulfa...	2017	Dar, S. A.; Yousuf, A. R.; Balkhi, M. ...	Pharmaceutical Biology
0	☐	☐	h3719707	Modulation of the lipid profile and insulin levels ...	2017	Achi, N. K.; Ohaeri, O. C.; Ijeh, I. I.;...	Biomedicine & Pharmacotherapy
0	☐	☐	h3720259	Evaluation of the antidiarrheal activity of the leaf...	2017	Sisay, M.; Engidawork, E.; Shibeshi, ...	BMC Complementary and Alternative...

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

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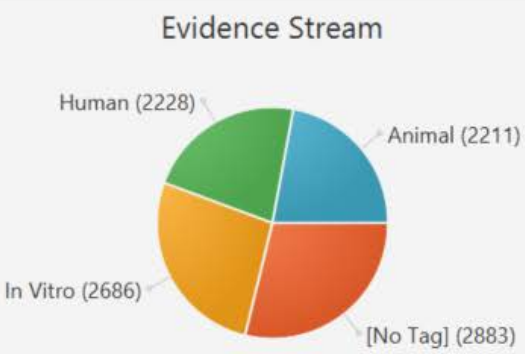

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0	☑	☐	h3719964	(1) H qNMR Quantification of Annonaceous Acet...	2017	Bonneau, N.; Cynober, T.; Jullian, J....	
0	☐	☐	h3720104	Activity of Pericampylus glaucus and periglaucin...	2017	Shipton, F. N.; Khoo, T. J.; Hossan, ...	Journal of Ethnopharmacology
0	☐	☐	h3720181	Formation of Haloacetonitriles, Haloacetamides, ...	2017	Nihemaiti, M.; Le Roux, J.; Hoppe-Jo...	Environmental Science and Technology
0	☐	☐	h3720261	Refined experimental annotation reveals conserv...	2017	Wang, P. H.; Tang, S.; Nemr, K.; Flic...	ISME Journal: Multidisciplinary Journ...
0	☐	☐	h3718320	Predicting reactivity of model DOM compounds t...	2017	de Vera, G. A.; Gernjak, W.; Radjen...	Water Research
0	☑	☐	h3719968	Podophyllum hexandrum ameliorates endosulfa...	2017	Dar, S. A.; Yousuf, A. R.; Balkhi, M. ...	Pharmaceutical Biology
0	☐	☐	h3719707	Modulation of the lipid profile and insulin levels ...	2017	Achi, N. K.; Ohaeri, O. C.; Ijeh, I. I.;...	Biomedicine & Pharmacotherapy

Priority Ranking Improves Literature Screening Efficiency

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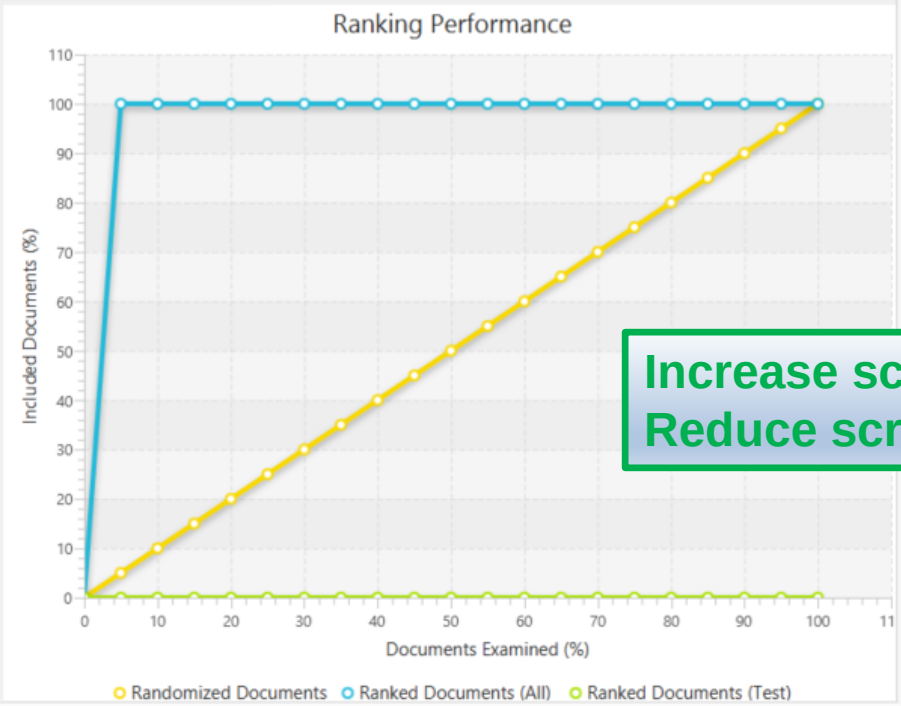
File Tools Reports Help

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

Sep 25, 2017 1:29:04 PM



Document Preview | Pie Chart | Bar Chart

Chloroform

IARC,. *(1999)*

▼Abstract

Exposure data. Occupational exposure to chloroform may occur during its production and use as a solvent and chemical intermediate. The general population may be exposed as a result of its presence in chlorinated drinking-water, ambient air and some foods. Human carcinogenicity data. Two cohort studies of cancer and drinking-water quality were carried out in the United States. One conducted in Maryland showed excess mortality from cancers of the liver and breast in association with water chlorination, while that conducted in Iowa showed increased risks for cancers of the colon and lung ater. Eight case-control ing-water in the United consistency in the risk ke. Significant increasing trends in the risk for bladder cancer were seen in two studies. The study in Colorado showed increasing risk with years of exposure to chlorinated water; the study in Iowa showed increasing risk with lifetime intake of trihalomethanes (from drinking-water), but only in men and not in women. Seven case-control studies addressed the risk for cancers of the large bowel in association with consumption of chlorinated water. In two of these studies, lifetime exposure to trihalomethanes was assessed. Two studies showed significant associations with rectal cancer. Overall, however, the results were inconsistent with regard to the subsite of the large bowel and sex,

Increase screening efficiency
Reduce screening burden on average 50%

Showing 7701 of 7701 loaded documents (1 selected; 20 total included; 40 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Authors	Journal
0.906	☑	☑	h1068322	Chloroform	1991	Meldrum, M.	
0.903	☑	☑	h1065954	Chloroform	1999	IARC,	
0.903	☑	☑	h1022997	Chloroform	1994	IPCS,	

Interactive Displays Reveal Patterns of Available Evidence

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

Choose Row/Columns...

	Cancer	Cardiovascular	Developmental	Endocrine	Gastrointestinal	Hematological and Immune	Hepatic	Mortality	Musculoskeletal	Neurological	Nutritional and Metabolic	Ocular and Sensory
Animal	5	179	545	454	310	781	658	617	211	234	609	168
Human	736	169	674	253	269	717	291	488	156	212	380	152
In Vitro	819	172	701	410	371	869	515	544	235	226	706	189

Document Preview | Pie Chart | Bar Chart

Reversible inhibition of intercellular communication among cardiac myocytes by halogenated hydrocarbons

Toraason, M.; Breitenstein, M. J.; Wey, H. E.. *Toxicological Sciences (1992)*

▼Abstract

National Institute for Occupational Safety and Health.

▼Health Outcomes

Cardiovascular (100%)

Showing 169 of 7701 loaded documents (1 selected; 17 total included; 33 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Authors	Journal
1	☐	☐	h3719051	Francis Sibson (1814-1876): the unsung hero of...	2012	Osiro, S.; Downs, E.; Grater, J.; Lou...	World Journal of Surgery
0.911	☐	☐	h3072364	Cytotoxic, thrombolytic, membrane stabilizing a...	2015	Abu Sufian, M.,d; Haque, M. R.	Bangladesh Journal of Pharmacology
0.882	☐	☐	h1067777	A TREK-1-like potassium channel in atrial cells i...	2001	Terrenoire, C.; Lauritzen, I.; Lesage, ...	Circulation Research
0.882	☐	☐	h1067607	Sequencing and cardiac expression of natriuretic...	2007	Del Ry, S.; Cabiati, M.; Lionetti, V.; ...	Peptides
0.882	☐	☐	h465103	Sequencing and cardiac expression of Apelin in ...	2009	Del Ry, S.; Cabiati, M.; Raucci, S.; Si...	Pharmacological Research
0.882	☐	☐	h1025349	Studies on cytochrome oxidase. Partial resolutio...	1976	Phan, S. H.; Mahler, H. R.	Journal of Biological Chemistry
0.714	☐	☐	h3698117	Comparative Pharmacognostic evaluation of so...	2014	Munir, U.; Perveen, A.; Qamarunnisa...	Pakistan Journal of Pharmaceutical S...
0.714	☐	☐	h3698111	Images in emergency medicine. Young woman ...	2014	Greene, S. C.; White, N. R.	Annals of Emergency Medicine
0.714	☐	☐	h1068173	[Polymorphism of the angiotensin-converting en...	2002	Tseluĭko, V. I.; Kravchenko, N. A.; L'...	Tsitologiia i Genetika / Cytology and ...
0.714	☐	☐	h1068108	[Cardiopathy caused by physical or chemical age...	2004	Crippa, M.; Balbiani, L.	La Medicina del Lavoro
0.714	☐	☐	h1066213	[Association between the +491C/T polymorphis...	2007	Li, N. F.; Zhou, L.; Li, T.; Wang, H. ...	Zhonghua Xin-Xueguanbing Zazhi
0.714	☐	☐	h664491	Annual ambient black carbon associated with sh...	2010	Mccracken, J.; Baccarelli, A.; Hoxha, ...	Environmental Health Perspectives
0.714	☐	☐	h3671764	Disinfection by-product exposures and the risk o...	2017	Wright, J. M.; Evans, A.; Kaufman, J....	Environmental Health Perspectives
0.714	☐	☐	h1025408	Endoscopic papillotomy and removal of gall stones	1975	Classen, M.; Safrany, L.	British Medical Journal

Interactive Displays Reveal Data-Rich Topics

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File Tools Reports Help

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

Choose Row/Columns...	Cancer	Cardiovascular	Developmental	Endocrine	Gastrointestinal	Hematological and Immune	Hepatic	Mortality	Musculoskeletal	Neurological	Nutritional and Metabolic	Ocular and Sensory
Animal	594	179	545	454	[illegible]	781	658	617	211	234	609	168
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Folded state of the integral membrane colicin E1 immunity protein in solvents of mixed polarity

Taylor, R. M.; Zakharov, S. D.; Bernard Heymann, J.; Girvin, M. E.; Cramer, W. A..
Biochemistry (2000)

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The colicin E1 immunity protein (ImmE1), a 13.2-kDa hydrophobic integral membrane protein localized in the Escherichia coli cytoplasmic membrane, protects the cell from the lethal, channel-forming activity of the bacteriocin, colicin E1.

Showing 869 of 7701 loaded documents (1 selected; 17 total included; 33 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Authors	Journal
1	☐	☐	h1025065	Optimization of detection of bacterial endotoxin ...	1990	Roth, R. I.; Levin, F. C.; Levin, J.	Journal of Laboratory and Clinical Me...
1	☐	☐	h3698931	Inhibitory Activity of Avicennia marina, a Medici...	2013	Namazi, R.; Zabihollahi, R.; Behbaha...	Iranian Journal of Pharmaceutical Re...
1	☐	☐	h1066699	Evaluation of an egg yolk enzyme-linked immun...	2004	Hagan, J. C.; Ashton, N. J.; Bradbur...	Avian Pathology
1	☐	☐	h1067146	A microtiter plate assay for superoxide dismutas...	2000	Peskin, A. V.; Winterbourn, C. C.	Clinica Chimica Acta
1	☐	☐	h3697437	Comparative Analysis of Denaturing Gradient Ge...	2015	Mohammadi, P.; Hamidkhani, A.; As...	
1	☐	☐	h2836159	Preparation and optimization of ophiopogon pol...	2014	Fan, Y.; Song, X.; Gao, Y.; Chen, Y.;...	International Journal of Pharmaceutics
1	☐	☐	h1444846	Antimicrobial activity of Ficus deltoidea Jack (Ma...	2012	Abd Samah, O.; Zaidi, N.,urTA; Sule...	Pakistan Journal of Pharmaceutical S...
1	☐	☐	h3719028	[Isolation and characterization of a lytic bacterio...	2012	Li, M.; Ji, X.; Wang, B.; Zhang, Q.; L...	Weishengwu Xuebao
1	☐	☐	h645166	Simple salting-out method for DNA extraction fr...	2006	Rivero, E. R.; Neves, A. C.; Silva-Val...	Pathology - Research and Practice
1	☐	☐	h3698137	Evaluation of pre-analytical variables in the quan...	2009	Anwar, A.; Wan, G.; Chua, K. B.; Au...	
1	☐	☐	h3698136	Studies of Antiviral Activity and Cytotoxicity of ...	2009	Selvam, P.; Murugesh, N.; Witvrouw,...	Indian Journal of Pharmaceutical Sci...
1	☐	☐	h3698126	Polyisoprene matrix for progesterone release: in...	2009	Heredia, V.; Bianco, I. D.; Tríbulo, H...	International Journal of Pharmaceutics

Configure Heatmap Displays

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File Tools Reports Help

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

Choose Row/Columns...	Cancer	Cardiovascular	Developmental	Endocrine	Gastrointestinal	Hematological and Immune	Hepatic	Mortality	Musculoskeletal	Neurological	Nutritional and Metabolic	Ocular and Sensory
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Showing 869 of 7701 loaded documents (1 selected; 17 total included;

Configure Heatmap

Category 1 (Rows) Evidence Stream | Pre-filter...

Category 2 (Columns) Health Outcomes

- Health Outcomes
- Topic Models
- Exposure
- Evidence Stream
- Article Type
- Endocrine Disrupting Chemicals
- Characteristics of Cancer

Score	Training Item?	Included?	RefID				Journal
1	☐	☐	h1025065			, F. C.; Levin, J.	Journal of Laboratory and Clinical Me...
1	☐	☐	h3698931			hollahi, R.; Behbaha...	Iranian Journal of Pharmaceutical Re...
1	☐	☐	h1066699			nton, N. J.; Bradbur...	Avian Pathology
1	☐	☐	h1067146			nterbourn, C. C.	Clinica Chimica Acta
1	☐	☐	h3697437			Hamidkhani, A.; As...	
1	☐	☐	h2836159	Preparation and optim		Fan, Y.; Song, X.; Gao, Y.; Chen, Y.;...	International Journal of Pharmaceutics
1	☐	☐	h1444846	Antimicrobial activity		Abd Samah, O.; Zaidi, N.,urTA; Sule...	Pakistan Journal of Pharmaceutical S...
1	☐	☐	h3719028	[Isolation and charac		Li, M.; Ji, X.; Wang, B.; Zhang, Q.; L...	Weishengwu Xuebao
1	☐	☐	h645166	Simple salting-out me		Rivero, E. R.; Neves, A. C.; Silva-Val...	Pathology - Research and Practice
1	☐	☐	h3698137	Evaluation of pre-analytical variables in the quan...	2009	Anwar, A.; Wan, G.; Chua, K. B.; Au...	
1	☐	☐	h3698136	Studies of Antiviral Activity and Cytotoxicity of ...	2009	Selvam, P.; Murugesh, N.; Witvrouw,...	Indian Journal of Pharmaceutical Sci...
1	☐	☐	h3698126	Polyisoprene matrix for progesterone release: in...	2009	Heredia, V.; Bianco, I. D.; Tríbulo, H...	International Journal of Pharmaceutics
1	☐	☐	h1067162	Modification of the Stewart biphasic colorimetric ...	2007	Al-Hanbali, O.; Onwuzo, N. M.; Rutt,...	Analytical Biochemistry
1	☐	☐	h1067168	Modified salting-out method for DNA isolation fr...	2000	Noguera, N. I.; Tallano, C. E.; Bragó...	Journal of Clinical Laboratory Analysis

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

Choose Row/Columns...	Cancer	Cardiovascular	Developmental	Endocrine	Gastrointestinal	Hematological and Immune	Hepatic	Mortality	Musculoskeletal	Neurological	Nutritional and Metabolic	Ocular and Sensory
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Export Tag Heatmap

Category 1 (Rows): Health Outcomes

Category 2 (Columns): Evidence Stream

Document Scope: All documents

Sheet Name: Tag Heatmap

Filepath for the results: Browse...

Ok | Cancel

Showing 869 of 7701 loaded documents (1 selected; 17 tota

Score	Training Item?	Included?					Journal
1	☐	☐	h			C.; Levin, J.	Journal of Laboratory and Clinical Me...
1	☐	☐	h			ahi, R.; Behbaha...	Iranian Journal of Pharmaceutical Re...
1	☐	☐	h			, N. J.; Bradbur...	Avian Pathology
1	☐	☐	h			rbourn, C. C.	Clinica Chimica Acta
1	☐	☐	h			midkhani, A.; As...	
1	☐	☐	h			ao, Y.; Chen, Y.;...	International Journal of Pharmaceutics
1	☐	☐	h			di, N.,urTA; Sule...	Pakistan Journal of Pharmaceutical S...
1	☐	☐	h			B.; Zhang, Q.; L...	Weishengwu Xuebao
1	☐	☐	h			, A. C.; Silva-Val...	Pathology - Research and Practice
1	☐	☐	h			Chua, K. B.; Au...	
1	☐	☐	h			h, N.; Witvrouw,...	Indian Journal of Pharmaceutical Sci...
1	☐	☐	h			I. D.; Tríbulo, H...	International Journal of Pharmaceutics
1	☐	☐	h			uzo, N. M.; Rutt,...	Analytical Biochemistry
1	☐	☐	h			no, C. E.; Bragó...	Journal of Clinical Laboratory Analysis
1	☐	☐	h3718460	Antifungal properties of organic extracts of eight...	2016	Karim, H.; Boubaker, H.; Askarne, L....	Letters in Applied Microbiology

Publication Year by Health Outcome

Choroform 5 Year.xlsx - Excel

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

Send Results Directly to SWIFT Active

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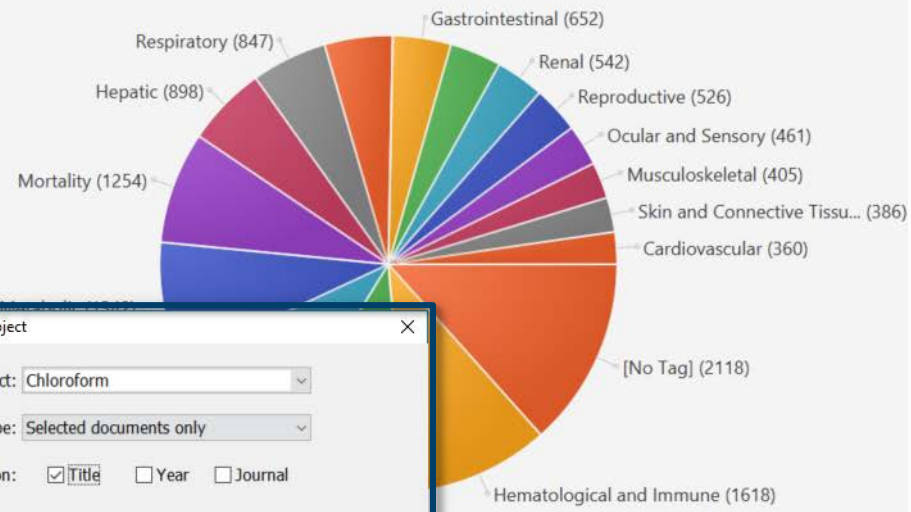
File Tools Reports Help

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

Health Outcomes

Tag	Code(s)	Count
[No Tag]		2118
Hematological and Immune		1618
Developmental		1610
Cancer		1470
Nutritional and Metabolic		1342
Mortality		1254
Hepatic		898
Respiratory		847
Endocrine		761
Gastrointestinal		652
Neurological		577
Renal		542
Reproductive		
Ocular and Sensory		
Musculoskeletal		
Skin and Connective Tissue		
Cardiovascular		

Document Preview | Pie Chart | Bar Chart



Select the Active Screener Project

Project: Chloroform

Document Scope: Selected documents only

De-duplication: ☑ Title ☐ Year ☐ Journal

OK Cancel

Showing 1470 of 7701 loaded documents (17 selected; 20 total included; 40 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Authors	Journal
1			h3697745	Cell proliferation and apoptosis during chlorofor...	2010	Carter, J. H.; Carter, H. W.; Richmon...	Cancer Research
1			h666825	Disinfectants and disinfectant by-products	2000	IPCS,	Environmental Health Criteria 216
0.972			h1026196	Final report on the safety assessment of capsicu...	2007	Johnson, W.	International Journal of Toxicology
0.965			h628926	Mechanisms of chemically induced renal carcino...	1998	Hard, G. C.	Toxicologic Pathology
0.965			h12631	Patterns of chloroform-induced regenerative cell...	1998	Templin, M. V.; Constan, A. A.; Wolf...	Carcinogenesis
0.96			h3719998	Modulatory effects of Cassia fistula fruits against...	2016	Kaur, S.; Kumar, M.; Kaur, P.; Kaur, ...	Food and Chemical Toxicology
0.96			h3718521	Assessment of the in vivo genotoxicity of cadmi...	2015	Wada, K.; Fukuyama, T.; Nakashima,...	Mutation Research: Genetic Toxicolo...
0.96			h2000284	Genotoxic effects in swimmers exposed to disinf...	2010	Kogevinas, M.; Villanueva, C. M.; Fo...	Environmental Health Perspectives
0.959			h1060648	Environmental health criteria for transgenic and ...	2006	Chen, T.; Dean, S.; Douglas, G. R.;	

Automated Priority Ranking

Sciome

ABOUT BLOG CAREERS SOFTWARE CONTACT

SWIFT-Active Screener

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.

IMPROVED RANKING MODEL

The computer suggests the next articles to screen based on previously included articles.

USER FEEDBACK

User screening decisions are used to continuously refine the machine learning model.

GET ACTIVE SCREENER

To use Active Screener, please contact us at swift-activescreener@sciome.com

NEWS

Sciome is pleased to participate in the **4th International Symposium on Systematic Review and Meta-Analysis of Laboratory Animal Studies on August 24-25, 2017** in **RTP, NC**. Our team's work to create new tools and methods to automate and accelerate systematic review will be featured in a number of presentations, including several posters that highlight SWIFT-Review and SWIFT-Active Screener.

SWIFT Active Screener Capabilities - Improved Ranking Model

- Web-based, real-time, collaborative systematic review software application
- State-of-the-art statistical models prioritize articles *as they are being reviewed*
- Machine continually learns from screener-input without training "seeds"
- Option to "seed" studies if relevant on/off topic literature has been identified
- Incorporates a simple, but powerful graphical user interface to provide project status updates
- User-defined screening levels
  - Level 1: Title and Abstract
  - Level 2: Full text screening
  - Level 3: Conflict Resolution

Customize Inclusion/Exclusion Criteria According to the PECO Statement

SWIFT ACTIVESCREENER | Chloroform | MMT_USEPA

Edit Review | Add New Review

Level 1 - Title & Abstract +

Review Name * Chloroform

Level Name * Level 1 - Title & Abstract

Inclusion/Exclusion Question * Include this reference?

Question Type: Radio Buttons — Required?

Answers

Yes, include the reference * — Included

No, exclude the reference * — Excluded

Add Answer

Add Question

How many times would you like the reference to be screened? 1

Screening Users

User	Level Screener	Project Admin
Taylor, Michele	✓	✓

Add/Invite Screeners

Display Additional Options

Save

Automatically Priority Ranks While Screening

SWIFT ACTIVESCREENER | Chloroform | MMT_USEPA

Screening References | Add New Review

0.3% | Level 1 - Title & Abstract

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

SWIFT ACTIVESCREENER Chloroform MMT_USEPA

Screen Reference

Track Progress

Add New Review

Currently Screening: Level 1 - Title & Abstract 0.2%

Inclusion Color
Exclusion Color

1619915: Evolution of chronic toxic encephalopathy induced by organic solvents after the cessation of exposure - Report of a case with a 5-year follow-up

Garnier, R., Reygagne, A., Maladry-Muller, P.; ; Pg349-354; 1991

Case study of a 45-year-old man who was heavily exposed to organic solvents for 20 years and especially to 1,1,1-trichloroethane and dichloromethane for the last 15 years. The cluster of symptoms and occupational injury demonstrated heavy exposure to organic solvents. Five years after the cessation of exposure, disabling sequelae - and especially memory disorders - are still present. Besides, intellectual impairment was responsible for professional disqualification of this patient. These data are discussed together with those from the literature.

Include/Exclude Question

Include this reference? *

- Yes, include the reference
- No, exclude the reference

Save and Next The reference will be excluded Display Instructions

SWIFT ACTIVESCREENER Chloroform MMT_USEPA

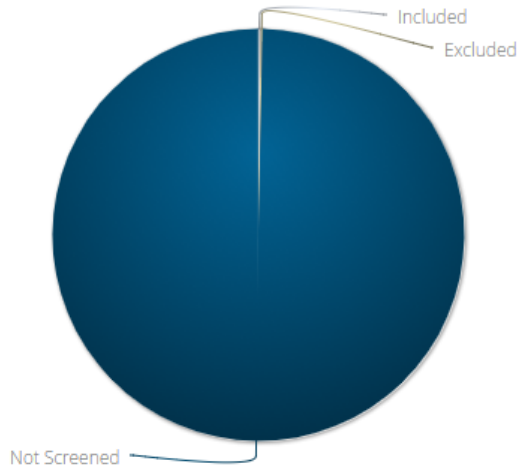
Review Summary

Add New Review

Viewing Project As Taylor, Michele

Chloroform | Level 1 - Title & Abstract

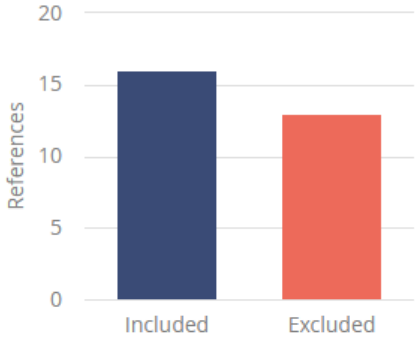
User's Screening Status for Level 1 - Title & Abstract



References: **8620**

Screened: **29** Not Screened: **8591**

User's Screening Progress for Level 1 - Title & Abstract



ActiveScreener model built at: 09/25/2017 15:54

Reviewers

Taylor, Michele

"Seed" studies when Relevant On/Off Topic Literature is Identified

SWIFT ActiveScreener | Chloroform | MMT_USEPA

Manage References

Add New Review

Status | Level

8620 References

Seed	Full Text	History	ID	Title	Current Level	Status
✓			1619917	Predicting rodent carcinogenicity of halogenated hydrocarbons by in vivo biochemical parameters	Level 1 - Title & Abstract	Not Screened
–			1619916	Systemic inflammatory response due to chloroform intoxication--an uncommon complication	Level 1 - Title & Abstract	Included
–			1619915	Evolution of chronic toxic encephalopathy induced by organic solvents after the cessation of exposure - Report of a case with a 5-year follow-up	Level 1 - Title & Abstract	Excluded
–			1619914	Metabolic activation of halogenated hydrocarbons in the conjunctival epithelium and excretory ducts of the intraorbital lacrimal gland in mice	Level 1 - Title & Abstract	Not Screened
–			1619913	Volatile organohalogen compounds in human urine: the effect of environmental exposure	Level 1 - Title & Abstract	Not Screened
–			1619912	Higher urinary elimination of trichloroethylene in the presence of chloroform results in lower liver injury	Level 1 - Title & Abstract	Included
–			1619911	Relative hepatotoxicity of seven halogenated hydrocarbons	Level 1 - Title & Abstract	Not Screened
–			1619910	The occurrence of organohalides in chlorinated drinking waters	Level 1 - Title & Abstract	Not Screened
–			1619909	A retrospective cohort study of trihalomethane exposure through drinking water and cancer mortality in northern Italy	Level 1 - Title & Abstract	Included
–			1619908	Teratology studies on orally administered chloroform in the rat and rabbit	Level 1 - Title & Abstract	Included
–			1619907	Protective effect of diethyldithiocarbamate and carbon disulfide against liver injury induced by various hepatotoxic agents	Level 1 - Title & Abstract	Excluded
–			1619906	Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: a review	Level 1 - Title & Abstract	Not Screened

"Seed" studies when Relevant On/Off Topic Literature is Identified

SWIFT ActiveScreener | Chloroform | MMT_USEPA

Manage References

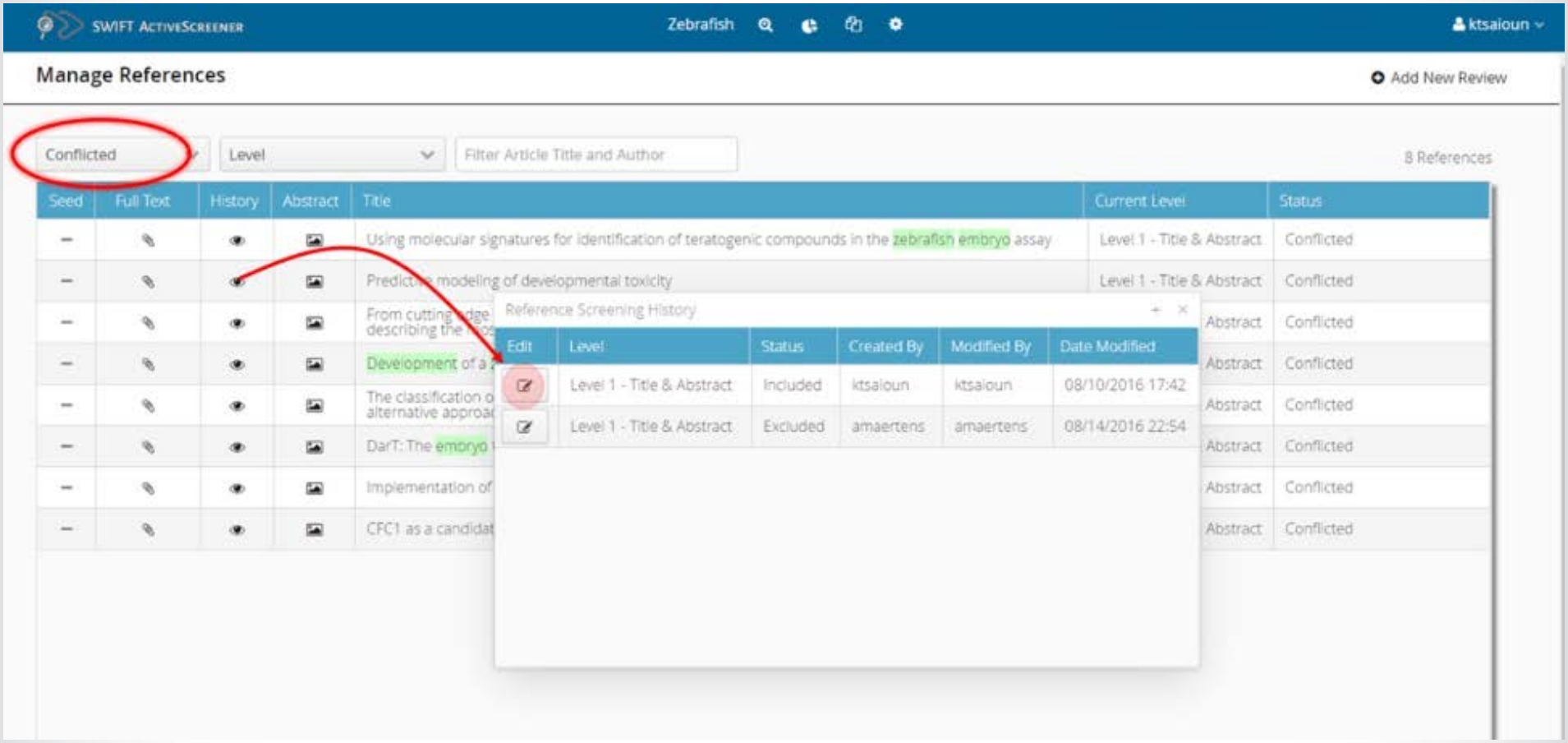
Add New Review

Status | Level | 8620 References

Seed	Full Text	History	ID	Title	Current Level	Status
✓			1619917	Predicting rodent carcinogenicity of halogenated hydrocarbons by parameters	Level 1 - Title & Abstract	Not Screened
–			1619916	Systemic inflammatory response due to chloroform intoxication--an uncommon complication	Level 1 - Title & Abstract	Included
				Evolution of chronic toxic		

The reference will be screened sooner than normal so it can provide its information to the model. This is useful for identifying included references early in the screening process.

Manage References with Conflict Resolution – Track and Archive Changes



SWIFT ACTIVESCREENER Chloroform MMT_USEPA

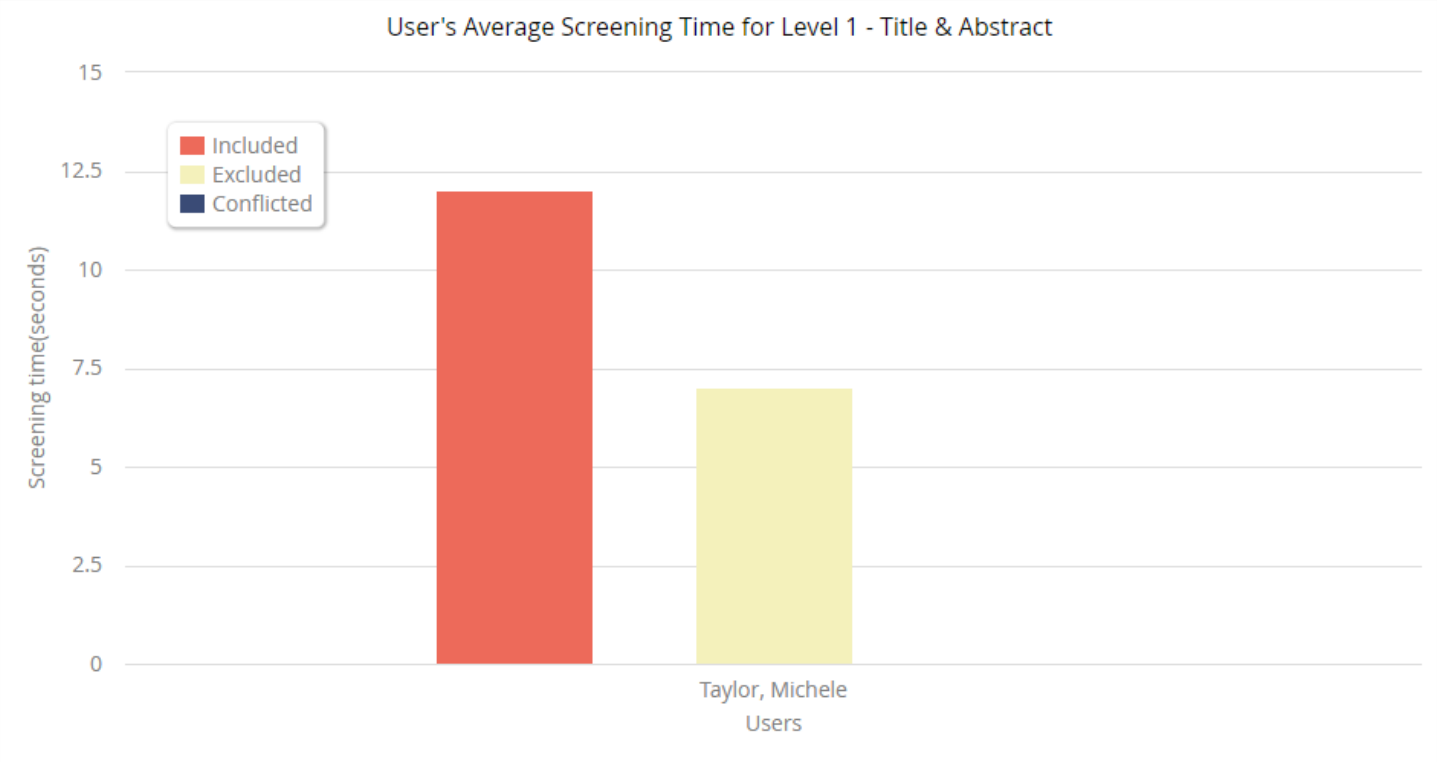
Reports

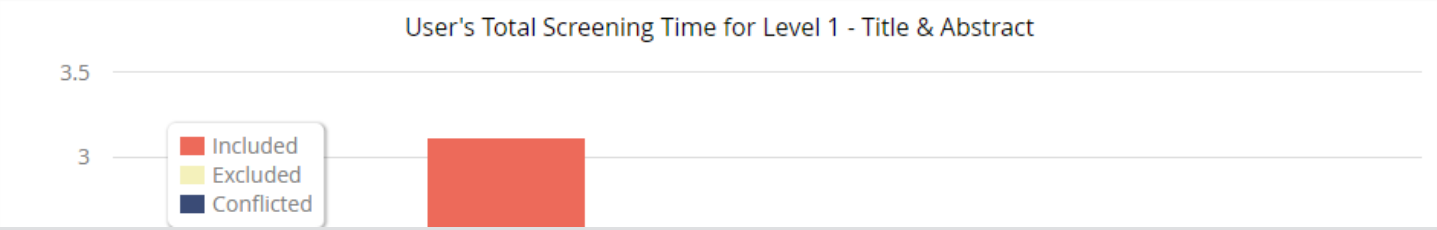
Screening Time ...

Level

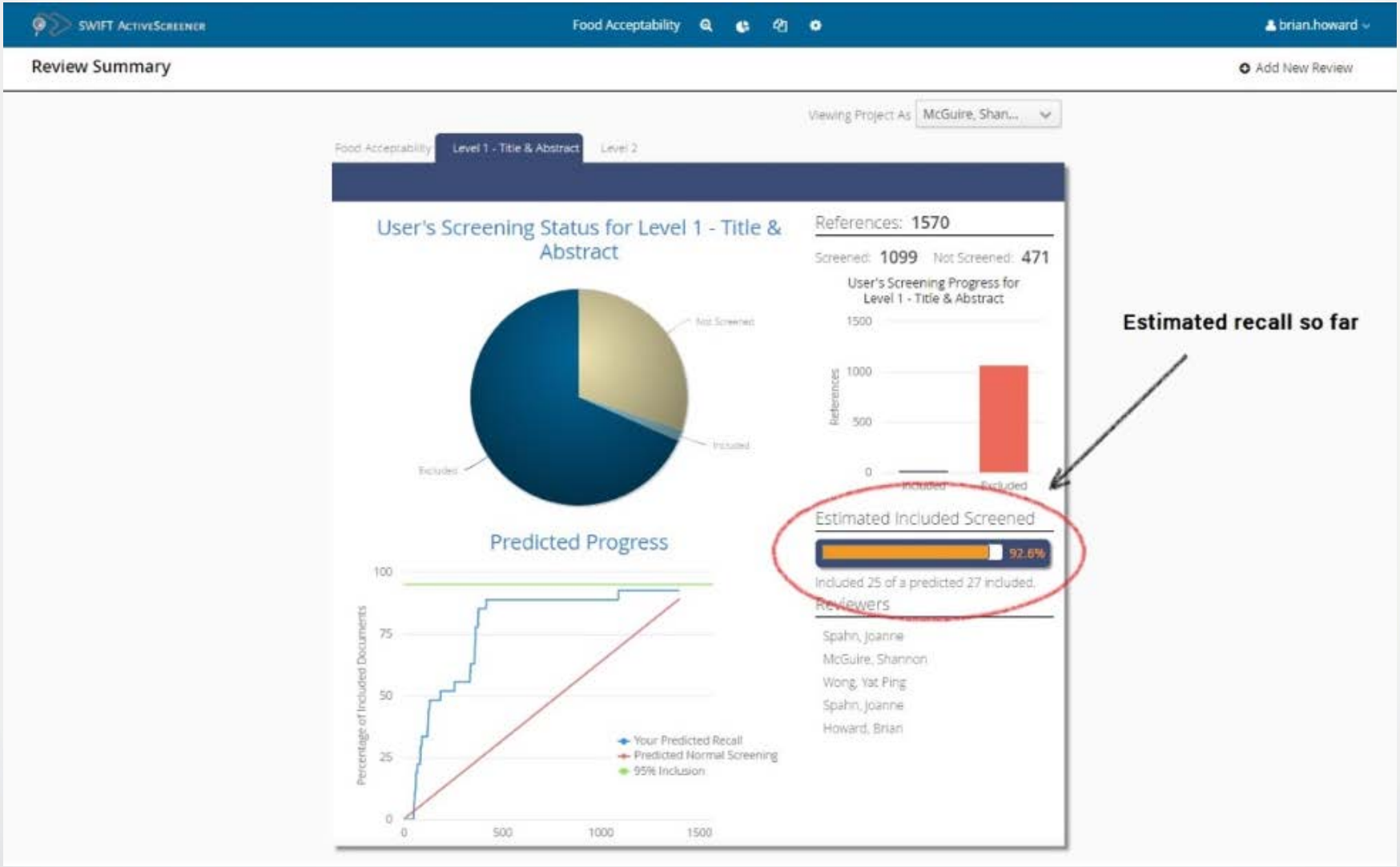
Level 1 - Title & ...

Generate Report





SWIFT Active Screener: Export Reports



SWIFT Active: Data Integration

- **Active Screener integrates with systematic review tools already in use:**
  - Accepts imports from bibliographic databases and reference curation platforms including *SWIFT Review*, EndNote, Mendeley, Zotaro, and PubMed
  - Results from screening in Active Screener can be exported in standard data formats compatible with applications including *HAWC* and Excel, EndNote, Mendeley, and Zotaro

Current Users

National Institute of Environmental Health Sciences (NIEHS)

United States Environmental Protection Agency (EPA)

The Endocrine Disruption Exchange (TEDX)

Johns Hopkins Evidence-Based Toxicology Collaboration (EBTC)

United States Department of Agriculture (USDA)

United States Environmental Protection Agency

Data Management

Kris Thayer, NCEA IRIS Division Director

HAWC: Study Evaluation, Extraction, Visualization and Data Sharing

HAWC
HEALTH ASSESSMENT
WORKSPACE COLLABORATIVE

https://hawcproject.org/

HAWC Capabilities

- **Free and open source**
- **Developed at UNC by Andy Shapiro* with Ivan Rusyn**
- **Literature search and initial screening**
- **Animal bioassay, epidemiological, and in vitro structured data extraction and visualization**
- **Interactive "click to see more" graphics**
- **Risk of bias evaluation**
- **Modular to work with other tools and maximize flexibility for users**

*current affiliation is National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP)

HAWC: Data Extraction Animal Bioassay

HAWC

Contact | About | Public Assessments | Your HAWC

Home / Uranium UHA (2017) / Dublineau I et al. 2014 / Create experiment /

SELECTED ASSESSMENT

Uranium UHA (2017)

AVAILABLE MODULES

- Literature review
- Management dashboard
- Study list
- Risk of bias
- Endpoint list
- Visualizations
- Executive summary

DOWNLOADS

- Download datasets

Create new experiment

Create a new experiment. Each experiment is a associated with a study, and may have one or more collections of animals. For example, one experiment may be a 2-year cancer bioassay, while another multi-generational study. It is possible to create multiple separate experiments within a single study, with different study-designs, durations, or test-species.

Name*

Short-text used to describe the experiment (i.e. 2-year cancer bioassay, 28-day inhalation, etc.).

Type*

Type of study being performed; be as specific as-possible

Chemical name

Chemical identifier (CAS)

CAS number for chemical-tested, if available.

Source of chemical

Chemical purity available?

Purity qualifier

Chemical purity (%)

Percentage (ex: 95%)

Chemical vehicle

If a vehicle was used, vehicle common-name

Diet

Description of animal-feed, if relevant

Guideline compliance

Description of any compliance methods used (i.e. use of EPA OECD, NTP, or other guidelines; conducted under GLP guideline conditions, non-GLP but consistent with guideline study, etc.)

Description and animal husbandry

Contact | About | Public Assessments | Your HAWC

Sprague–Dawley male rats / Create endpoint /

sure-of-effect which was measured in the study. It may or may not contain

n-time, if multiple endpoints have the same observation time.

Effect

Effect, using common-vocabulary

Effect subtype

Effect subtype, using common-vocabulary

Diagnostic

Diagnostic or method used to measure endpoint (if relevant)

e units*

Observation time text

Text for reported observation time (ex: "60-90 PND")

Values estimated

Response values were estimated using a digital ruler or other methods

ata for endpoint are

erature into HAWC

Dataset type*

Continuous

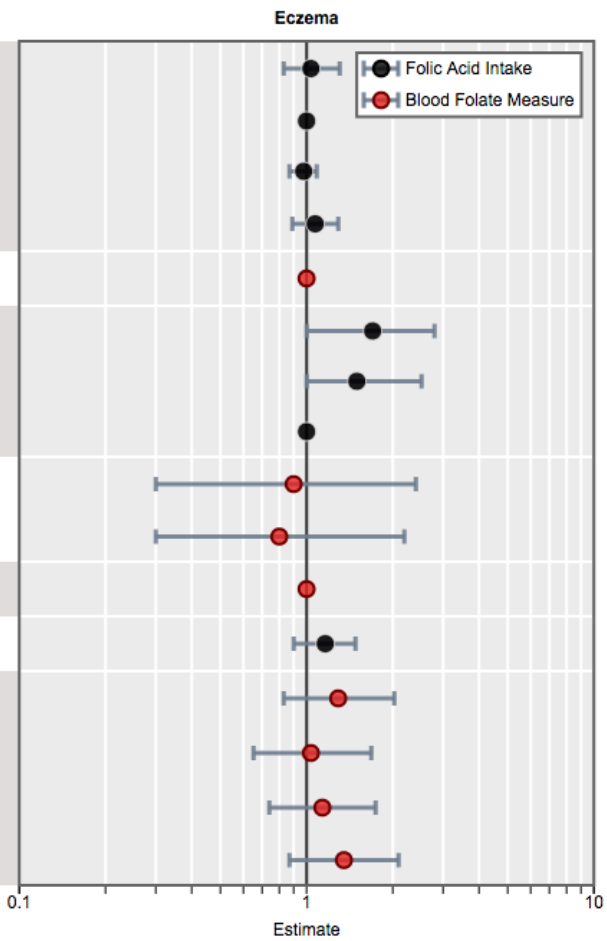
Variance type*

SD

Epidemiology: Click to See More Display

Draft: Eczema, Prospective Studies

Study	Population Name	Assessed Outcome Name	Exposure Measure	Exposure Comparison	Statistical Metric Abbreviation
Bekkers, 2012	PIAMA birth cohort, 1996-1997	Eczema	Folic acid containing supplements during pregnancy	Multivitamin or vitamin B complex supplements	adjPR
				No folic acid use	adjPR
				Folic acid-only supplements	adjPR
				Pre-natal vitamin supplements	adjPR
Dunstan, 2012	Pregnant women in Western Australia	Eczema	Cord blood folate	Tertile 2 (50.3-75.1 nmol/l)	adjOR
Dunstan, 2012	Pregnant women in Western Australia	Eczema	Maternal folic acid intake from supplements in pregnancy	Tertile 3 (500+ µg/day)	adjOR
				Tertile 2 (200-499 µg/day)	adjOR
				Tertile 1 (<200 µg/day)	adjOR
Dunstan, 2012	Pregnant women in Western Australia	Eczema	Cord blood folate	Tertile 1 (<50.3 nmol/l)	adjOR
				Tertile 3 (>75.1 nmol/l)	adjOR
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema until 6-7 yr	Intracellular folic acid (ICF) levels during pregnancy	1st Quintile (≤480 nmol/l)	adjOR
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema until 6-7 yr	Folic acid from supplements in pregnancy	Any folic acid use	adjOR
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema until 6-7 yr	Intracellular folic acid (ICF) levels during pregnancy	2nd Quintile (481-643 nmol/l)	adjOR
				3rd Quintile (644-862 nmol/l)	adjOR
				4th Quintile (863-1139 nmol/l)	adjOR
				5th Quintile (≥1140 nmol/l)	adjOR



NTP Monograph: Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid. 2015 Aug:1-51. http://ntp.niehs.nih.gov/ntp/ohat/folicacid/final_monograph_508.pdf

Epidemiology: Click to See More Display

Draft: Eczema, Prospective Studies

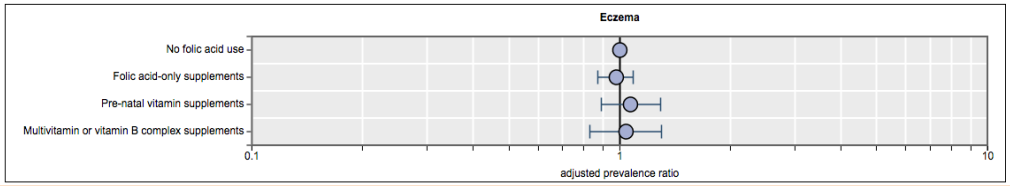
Study	Population Name	Assessed Outcome Name	Exposure Measure	Exposure Comparison Statistical
Bekkers, 2012	PIAMA birth cohort, 1996-1997	Eczema		
Dunstan, 2012	Pregnant women in Western Australia	Eczema		
Dunstan, 2012	Pregnant women in Western Australia	Eczema		
Dunstan, 2012	Pregnant women in Western Australia	Eczema		
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema until 6-7 yr		
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema until 6-7 yr		
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema until 6-7 yr		

Bekkers, 2012 / PIAMA birth cohort, 1996-1997 / Folic acid containing supplements during pregnancy / Eczema

Assessed outcome	Eczema
Population description	PIAMA birth cohort, 1996-1997
Diagnostic	self-reported
Diagnostic description	an itchy rash that came and went on typical eczema sites (the folds of the elbows or behind the knees, around ears or eyes or in front of the ankles)
Main finding supported?	inconclusive
Prevalence Incidence	0.180 - 0.142, reported by age (Table 2)
Statistical metric presented	adjusted prevalence ratio
Statistical metric description	Longitudinally, generalised estimating equations (GEEs) with a log link function were used to obtain prevalence ratios (PRs). GEEs take into account the correlation between repeated measurements in the same individual. An m-dependent correlation structure was used: m=7 for the other outcome measures. An interaction term with age was included in the GEE model to allow the association between maternal use of supplements and the outcomes to vary with age.
Statistical power sufficient?	not reported or calculated
Dose response trend?	not-applicable
Effect tags	dermal, hypersensitivity, immunological
Adjustment factors	• maternal allergy • maternal education • maternal smoking during pregnancy • number older siblings

Exposure-group	N	Adjusted prevalence ratio	*p*-value
No folic acid use	1302	1.0	n.s.
Folic acid-only supplements[a]	1998	0.98 (0.87, 1.09)	n.s.
Pre-natal vitamin supplements	287	1.07 (0.89, 1.29)	n.s.
Multivitamin or vitamin B complex supplements	199	1.04 (0.83, 1.3)	n.s.

[a] Main finding as selected by HAWC assessment authors.



Estimate

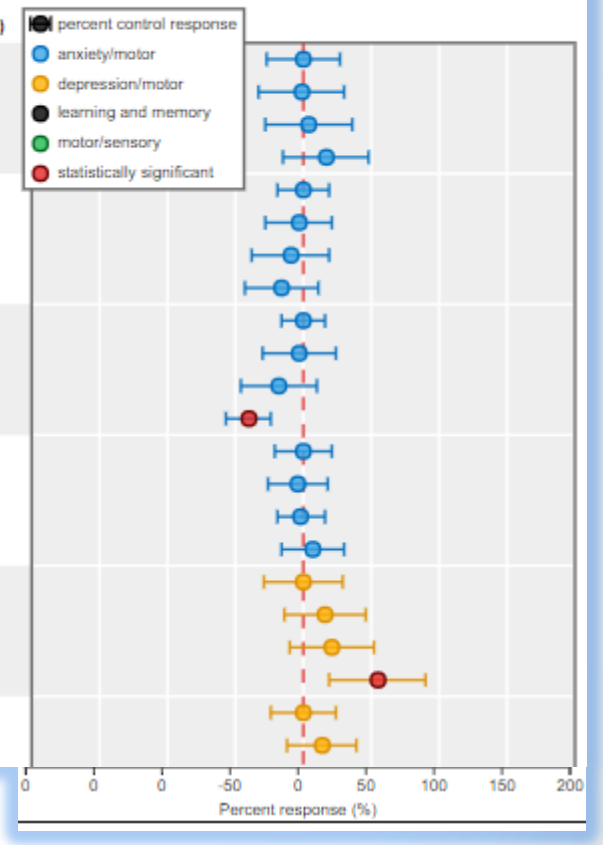
NTP Monograph: Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid. 2015 Aug:1-51. http://ntp.niehs.nih.gov/ntp/ohat/folicacid/final_monograph_508.pdf

Animal Bioassay: Click to See More Display

All behavior at less than 5 ppm

Actions

study	animal description	route	treatment period	endpoint	units	dose (ppm)
Liu et al. 2014	Mouse, BALB/c (♂, N=12)	oral drinking water	subchronic (28 days)	elevated plus maze (closed arm entries)	count	0
						0.9
						2.26
						4.52
Liu et al. 2014	Mouse, BALB/c (♂, N=12)	oral drinking water	subchronic (28 days)	elevated plus maze (open arm entries)	%	0
						0.9
						2.26
						4.52
Liu et al. 2014	Mouse, BALB/c (♂, N=12)	oral drinking water	subchronic (28 days)	elevated plus maze (time in open arms)	%	0
						0.9
						2.26
						4.52
Liu et al. 2014	Mouse, BALB/c (♂, N=12)	oral drinking water	subchronic (28 days)	elevated plus maze (total arm entries)	count	0
						0.9
						2.26
						4.52
Liu et al. 2014	Mouse, BALB/c (♂, N=10)	oral drinking water	subchronic (28 days)	forced swim (immobility time, total 6 min)	sec	0
						0.9
						2.26
						4.52
Liu et al. 2014	Mouse, BALB/c (♂, N=10)	oral drinking water	subchronic (28 days)	tail suspension test (immobility time, total 6 min)	sec	0
						0.9



Animal data can be expressed as effect size, e.g., percent control

NTP (National Toxicology Program). 2016. Systematic Literature Review on the Effects of Fluoride on Learning and Memory in Animal Studies. NTP Research Report 1. Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/01fluoride_508.pdf

Animal Bioassay: Click to See More Display

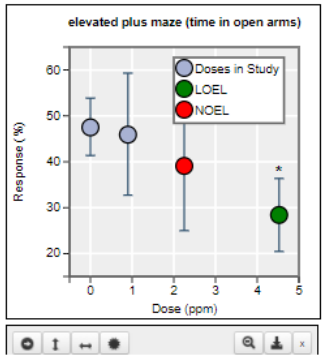
Liu et al. 2014 / 28-day drinking water / male BalB/C mice / elevated plus maze (time in open arms)

Coming soon: Built-in graph digitizer (from graph to numbers)

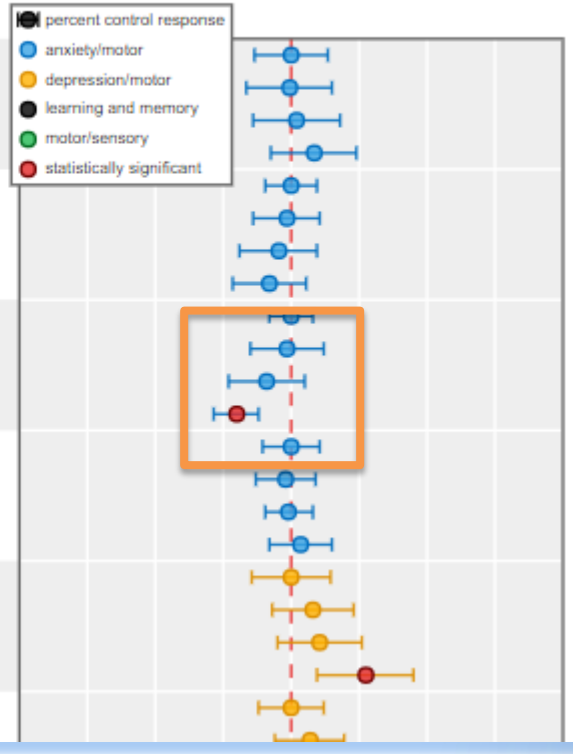
Data reported?	✔
Data extracted?	✔
Values estimated?	✔
Location in literature	Figure 5A
Expected response adversity direction	any change from reference/control group
NOEL	2.26 ppm
LOEL	4.52 ppm
Monotonicity	not-reported
Statistical test description	one-way ANOVA followed by Bonferroni's post hoc test
Trend result	not reported
Power notes	appears appears underpowered (sample size is between 50-100% required), requires approximately 18 animals to detect a 20% change from control
Results notes	percentage of time that the highest dose group spent in the open arms was significantly lower than that in the control group
General notes/methodology	The apparatus was composed of two 25 cm × 5 cm open arms and two 25 cm × 5 cm × 20 cm closed arms. Open and closed arms were cross-shaped; the cross-center was a 5 cm × 5 cm open platform. The maze was 50 cm above the ground. Before the test, the mice were placed in an open field for 5 min and then placed on the central plat-form facing the open wall. The monitor above the maze was used to re-cord the activity of the animals in the maze for 5 min. Test indicators included: (1) the number of closed arms entries, serving as a measure of motor function; (2) the number of open arms entries; (3) the residence time of each mouse in the open arms; and (4) the residence time in the closed arms. When all four paws of a mouse were in one arm, it was recorded as one entry. We used the percentage of open arm entries out of total arm entries and the percentage of time spent in the open arms as measures of anxiety

Dose (ppm) ❯	Number of Animals	Response (%)	Standard Error
0	12	47.6	2.8
0.9	12	46	6
2.26[a]	12	39.2	6.4
4.52[b,c]	12	28.4	3.6

[a] NOEL (No Observed Effect Level)
[b] Significantly different from control ($p < 0.05$)
[c] LOEL (Lowest Observed Effect Level)



Actions

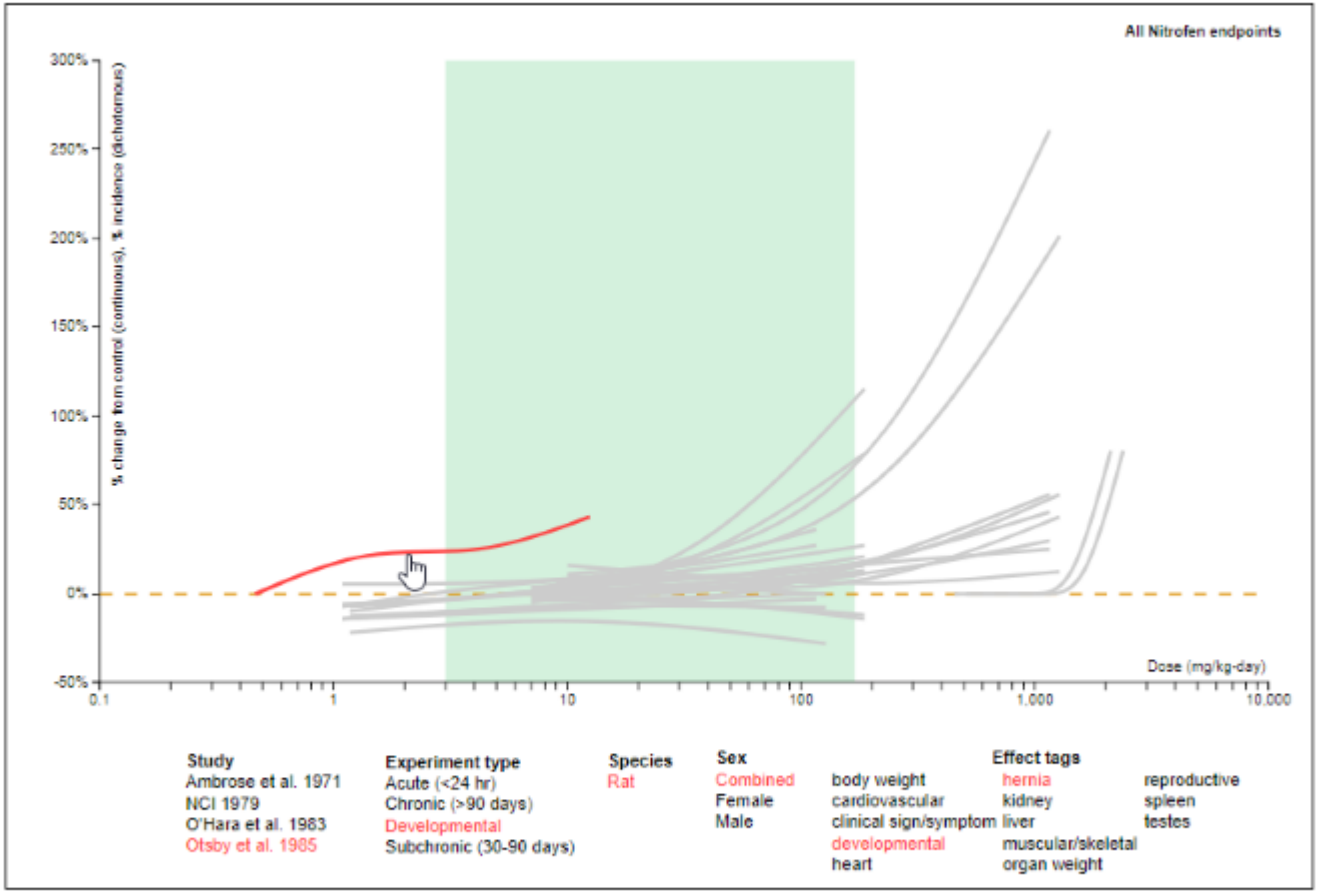


NTP (National Toxicology Program). 2016. Systematic Literature Review on the Effects of Fluoride on Learning and Memory in Animal Studies. NTP Research Report 1. Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/01fluoride_508.pdf

HAWC: Dose-Response Displays

Nitrofen crossview

Actions

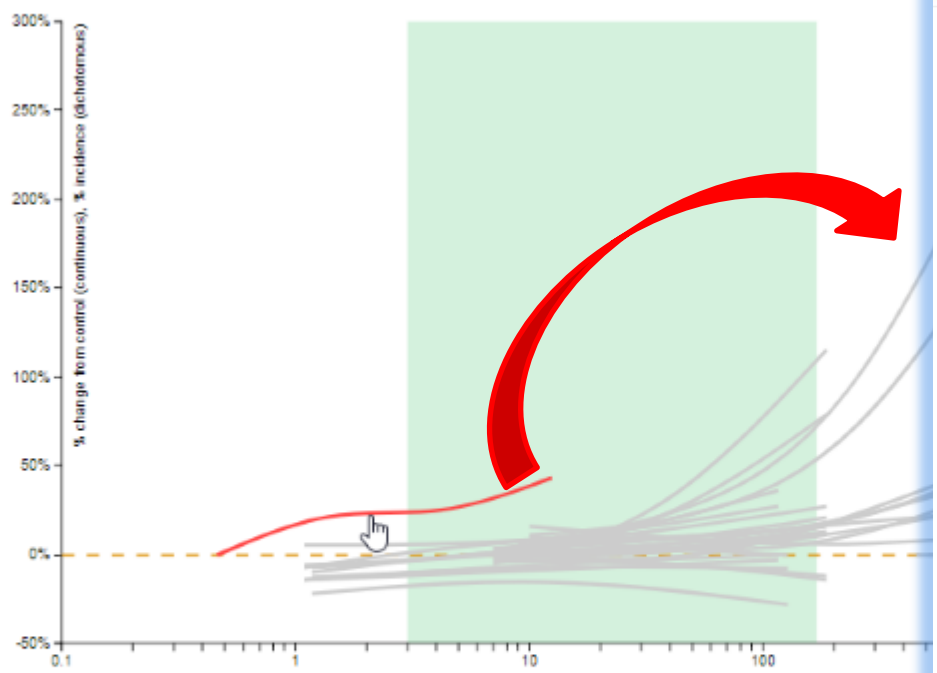


Results in mg/kg-day

HAWC: Dose-Response Displays

Nitrofen crossview

Actions



Study	Experiment type	Species	Sex		Effect tags	
Ambrose et al. 1971	Acute (<24 hr)	Rat	Combined	body weight	hernia	reproductive
NCI 1979	Chronic (>90 days)		Female	cardiovascular	kidney	spleen
O'Hara et al. 1983	Developmental		Male	clinical sign/symptom	liver	testes
Otsby et al. 1985	Subchronic (30-90 days)			developmental	muscular/skeletal	
				heart	organ weight	

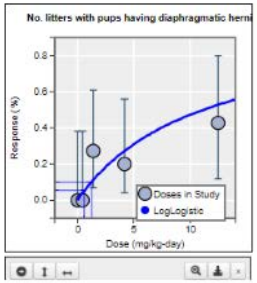
Results in mg/kg-day

Otsby et al. 1985 / Developmental GD8-16 / Pups / No. litters with pups having diaphragmatic hernias

Study | Experiment | Animal Group | Endpoint

Endpoint name	No. litters with pups having diaphragmatic hernias
Effect	developmental abnormalities
Observation time	not-reported
Additional tags	developmental hernia
Data reported?	✔
Data extracted?	✔
Values estimated?	–
BMD	1.238 mg/kg-day
BMDL	0.617 mg/kg-day
Monotonicity	unclear
Trend result	not reported

Dose (mg/kg-day)	Number of Animals	Incidence	Percent Incidence
0	9	0	0%
0.46	9	0	0%
1.39	11	3	27%
4.17	10	2	20%
12.5	7	3	43%



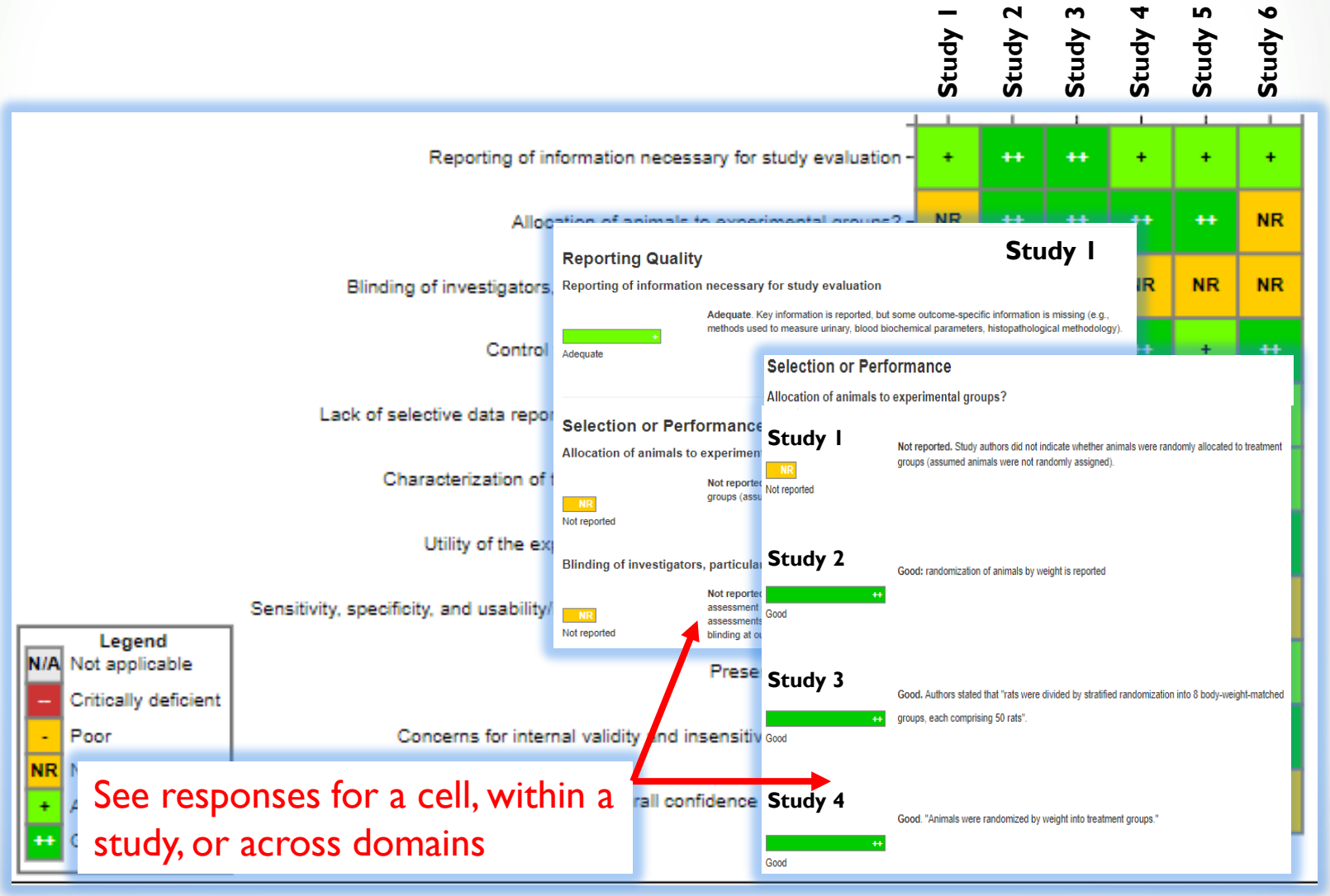
HAWC: Risk of Bias

	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6
Reporting of information necessary for study evaluation	+	++	++	+	+	+
Allocation of animals to experimental groups?	NR	++	++	++	++	NR
Blinding of investigators, particularly during outcome assessment	NR	++	NR	NR	NR	NR
Control for variables across experimental groups	++	+	++	++	+	++
Lack of selective data reporting and unaccounted for loss of animals	++	+	++	+	NR	+
Characterization of the exposure to the compound of interest	++	--	++	+	--	+
Utility of the exposure design for the endpoint of interest	++	++	++	++	++	++
Sensitivity, specificity, and usability/interpretation of the endpoint evaluations	-	-	+	-	-	-
Presentation of results	+	-	+	+	+	+
Concerns for internal validity and insensitivity/Observations	++	+	++	++	+	++
Overall confidence domain (animal)	-	--	+	-	--	-

Legend

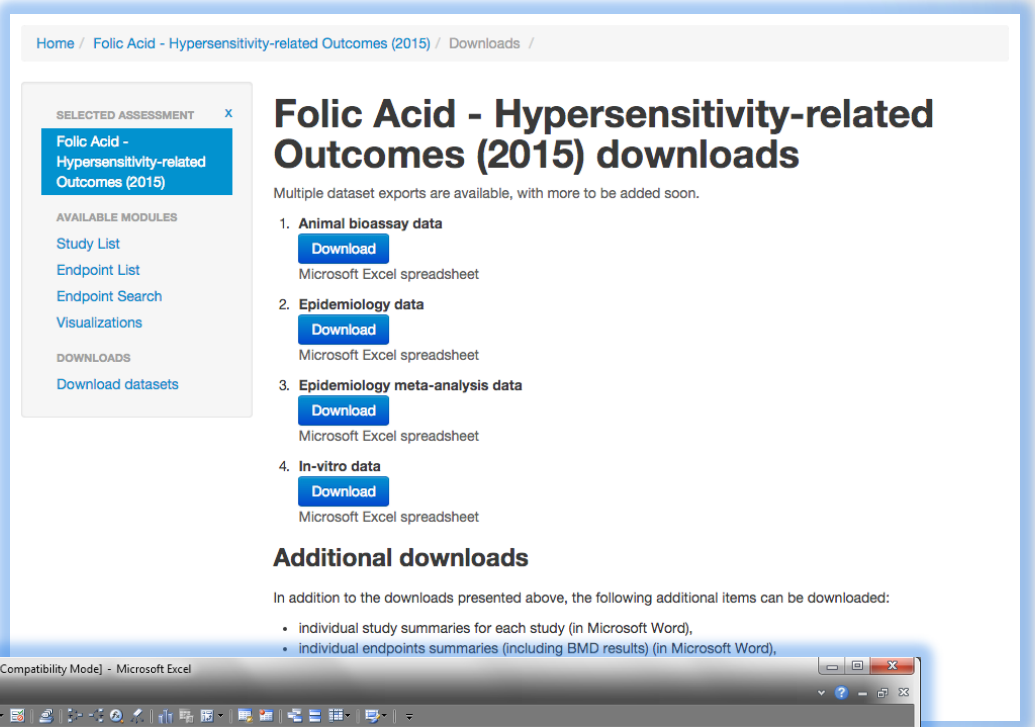
N/A	Not applicable
--	Critically deficient
-	Poor
NR	Not reported
+	Adequate
++	Good

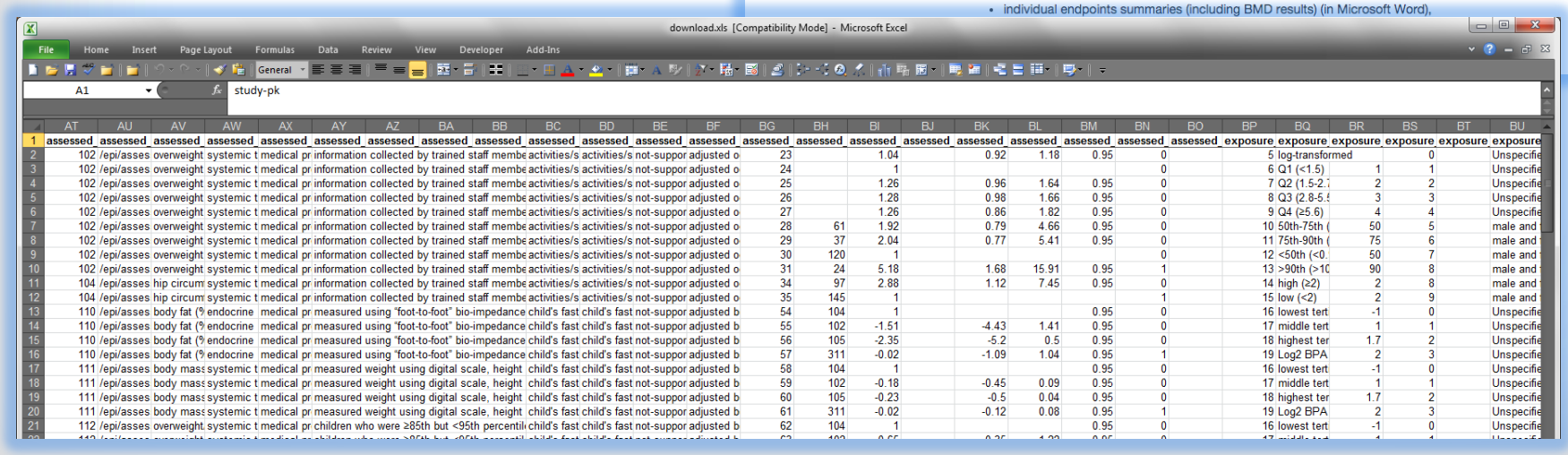
HAWC: Risk of Bias



HAWC: Download Reports

- **Entire database for an assessment can be downloaded in Microsoft Excel exports**





	AT	AU	AV	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH	BI	BJ	BK	BL	BM	BN	BO	BP	BQ	BR	BS	BT	BU
1	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	assessed_	exposure_	exposure_	exposure_	exposure_	exposure_	exposure
2	102	/epi/asses	overweight	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	23		1.04		0.92	1.18	0.95	0		5	log-transformed		0		Unspecifie
3	102	/epi/asses	overweight	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	24		1					0		6	Q1 (<1.5)	1	1		Unspecifie
4	102	/epi/asses	overweight	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	25		1.26		0.96	1.64	0.95	0		7	Q2 (1.5-2.	2	2		Unspecifie
5	102	/epi/asses	overweight	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	26		1.28		0.98	1.66	0.95	0		8	Q3 (2.8-5.	3	3		Unspecifie
6	102	/epi/asses	overweight	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	27		1.26		0.86	1.82	0.95	0		9	Q4 (≥5.6)	4	4		Unspecifie
7	102	/epi/asses	overweight	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	28	61	1.92		0.79	4.66	0.95	0		10	50th-75th (	50	5		male and
8	102	/epi/asses	overweight	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	29	37	2.04		0.77	5.41	0.95	0		11	75th-90th (	75	6		male and
9	102	/epi/asses	overweight	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	30	120	1					0		12	<50th (<0.	50	7		male and
10	102	/epi/asses	overweight	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	31	24	5.18		1.68	15.91	0.95	1		13	>90th (>1(	90	8		male and
11	104	/epi/asses	hip circum	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	34	97	2.88		1.12	7.45	0.95	0		14	high (≥2)	2	8		male and
12	104	/epi/asses	hip circum	systemic t	medical pr	information	collected by	trained staff	membe	activities/s	activities/s	not-suppor	adjusted o	35	145	1					1		15	low (<2)	2	9		male and
13	110	/epi/asses	body fat (%	endocrine	medical pr	measured using	"foot-to-foot"	bio-impedance	child's fast	child's fast	not-suppor	adjusted b		54	104	1				0.95	0		16	lowest tert	-1	0		Unspecifie
14	110	/epi/asses	body fat (%	endocrine	medical pr	measured using	"foot-to-foot"	bio-impedance	child's fast	child's fast	not-suppor	adjusted b		55	102	-1.51		-4.43	1.41	0.95	0		17	middle tert	1	1		Unspecifie
15	110	/epi/asses	body fat (%	endocrine	medical pr	measured using	"foot-to-foot"	bio-impedance	child's fast	child's fast	not-suppor	adjusted b		56	105	-2.35		-5.2	0.5	0.95	0		18	highest ter	1.7	2		Unspecifie
16	110	/epi/asses	body fat (%	endocrine	medical pr	measured using	"foot-to-foot"	bio-impedance	child's fast	child's fast	not-suppor	adjusted b		57	311	-0.02		-1.09	1.04	0.95	1		19	Log2 BPA	2	3		Unspecifie
17	111	/epi/asses	body mass	systemic t	medical pr	measured weight	using digital scale,	height	child's fast	child's fast	not-suppor	adjusted b		58	104	1				0.95	0		16	lowest tert	-1	0		Unspecifie
18	111	/epi/asses	body mass	systemic t	medical pr	measured weight	using digital scale,	height	child's fast	child's fast	not-suppor	adjusted b		59	102	-0.18		-0.45	0.09	0.95	0		17	middle tert	1	1		Unspecifie
19	111	/epi/asses	body mass	systemic t	medical pr	measured weight	using digital scale,	height	child's fast	child's fast	not-suppor	adjusted b		60	105	-0.23		-0.5	0.04	0.95	0		18	highest ter	1.7	2		Unspecifie
20	111	/epi/asses	body mass	systemic t	medical pr	measured weight	using digital scale,	height	child's fast	child's fast	not-suppor	adjusted b		61	311	-0.02		-0.12	0.08	0.95	1		19	Log2 BPA	2	3		Unspecifie
21	112	/epi/asses	overweight	systemic t	medical pr	children who	were ≥85th	but <95th	percentil	child's fast	child's fast	not-suppor	adjusted b	62	104	1				0.95	0		16	lowest tert	-1	0		Unspecifie

HAWC Benchmark Dose Modeling

Benchmark dose modeling

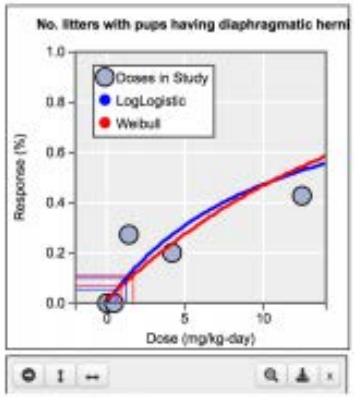
NEW IMPROVED!

BMD setup | Results | Model recommendation and selection

BMDS output summary

Model	Global p-value	AIC	BMD (10%)	BMDL (10%)	Residual of interest	Output
Logistic	0.1974	42.2346	4.60161	2.81096	0.222	View
LogLogistic	0.4283	37.9348	1.23831	0.617243	1.709	View
Probit	0.1974	42.1248	4.26256	2.62289	0.185	View
LogProbit	0.1432	42.643	4.1219	1.71245	0.103	View
Multistage	0.1648	40.7611	1.70173	0.930926	2.039	View
Gamma	0.1648	40.7611	1.70173	0.930926	2.039	View
Weibull	0.1647	40.7611	1.70175	0.930926	2.04	View

Selected model (if any) highlighted in yellow



BMD setup | Results | Model recommendation and selection

Model	Warnings	Recommendation
Logistic AIC: 42.2346 BMD: 4.60161 BMDL: 2.81096	No warnings were found.	Valid
LogLogistic AIC: 37.9348 BMD: 1.23831 BMDL: 0.617243	No warnings were found.	Valid Recommended best-fitting model, based on the lowest BMDL from valid models. Selected as the best-fitting model by the user.
Probit AIC: 42.1248 BMD: 4.26256 BMDL: 2.62289	No warnings were found.	Valid
LogProbit AIC: 43.643 BMD: 4.1219 BMDL: 1.71245	No warnings were found.	Valid
Multistage AIC: 40.7611 BMD: 1.70173 BMDL: 0.930926	Questionable warnings • Residual of interest (=2.039) is greater than than threshold value (2)	Questionable

The USEPA BMDS software is integrated into HAWC for fitting dose-response models to animal bioassay data.

Model recommendations also performed using BMDS technical guidance and automation approaches from Wignall et al. 2014.

Selections must be done manually.

HAWC Web-Based Interactive Reports

1. Introduction
2. Data Review
2.1. Human studies
2.2. Animal studies
3. Provisional Value Derivation
3.1. Oral Reference Values
3.1.1. Chronic p-RfD
3.1.2. Subchronic p-RfD
3.2. Inhalation Reference Values
3.3. Cancer Weight-of-Evidence Descriptor
3.4. Provisional Cancer Potency Values
3.4.1. Oral slope factor (p-OSF)
3.4.2. Inhalation unit risk (p-IUR)

3. Provisional Value Derivation

3.1. Oral Reference Values

3.1.1. Chronic p-RfD

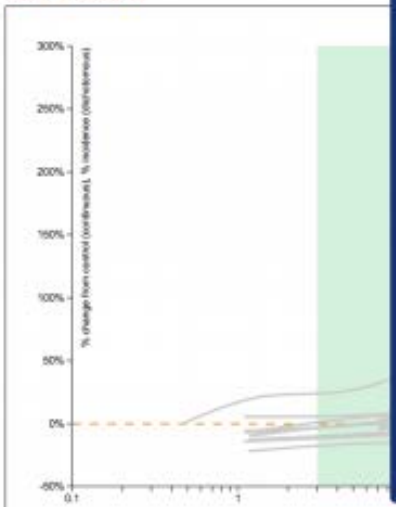
Although chronic toxicity testing of nitrofen has been conducted, effects in the endpoint is diaphragmatic hernias as indicated by Otsby et al. 1985. The

Consistent with the practice of the EPA, the developmental period is recognized as more sensitive to developmental effects than lifetime exposure (U.S. EPA, 1991b). Therefore,

3.1.2. Subchronic p-RfD

Although chronic toxicity testing of nitrofen has been conducted, effects in the endpoint is diaphragmatic hernias as indicated by Otsby et al. 1985. This

Nitrofen crossview



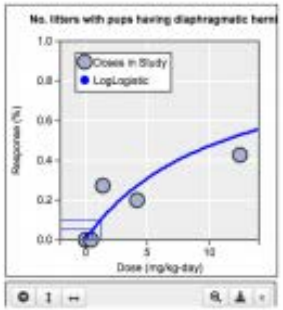
Study	Experiment type	Species	Sex		Effect tags	
Ambrose et al. 1971	Acute (<24 hr)	Rat	Combined	body weight	hernia	reproductive
NCI 1979	Chronic (>90 days)		Female	cardiovascular	kidney	spleen
O'Hara et al. 1983	Developmental		Male	clinical sign/symptom	liver	testes
Otsby et al. 1985	Subchronic (30-90 days)			developmental	musculoskeletal	
				heart	organ weight	

Otsby et al. 1985 / Developmental GD8-16 / Pups / No. litters with pups having diaphragmatic hernias

Study | Experiment | Animal Group | Endpoint

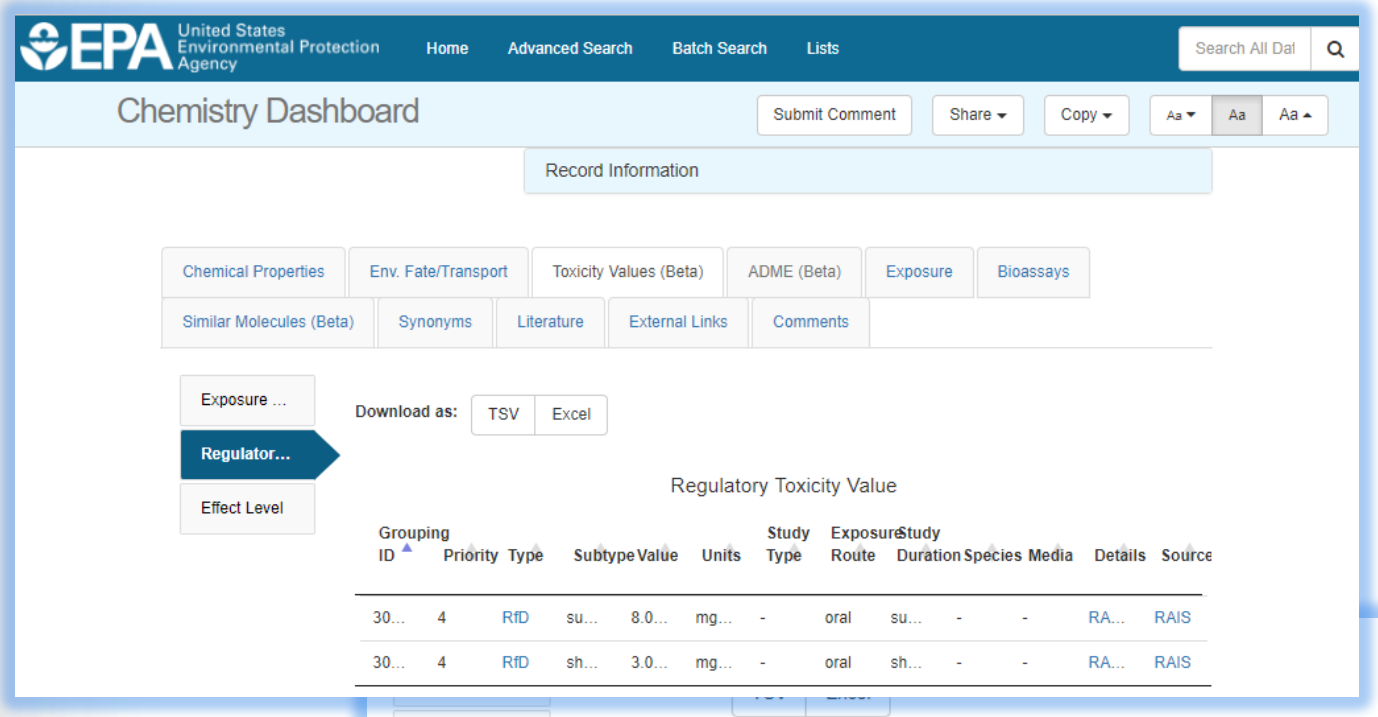
Endpoint name	No. litters with pups having diaphragmatic hernias
Effect	developmental abnormalities
Observation time	not-reported
Additional tags	developmental hernia
Data reported?	✔
Data extracted?	✔
Values estimated?	–
BMD	1.238 mg/kg-day
BMDL	0.617 mg/kg-day
Monotonicity	unclear
Trend result	not reported

Dose (mg/kg-day)	Number of Animals	Incidence	Percent Incidence
0	9	0	0%
0.46	9	0	0%
1.39	11	3	27%
4.17	10	2	20%
12.5	7	3	43%

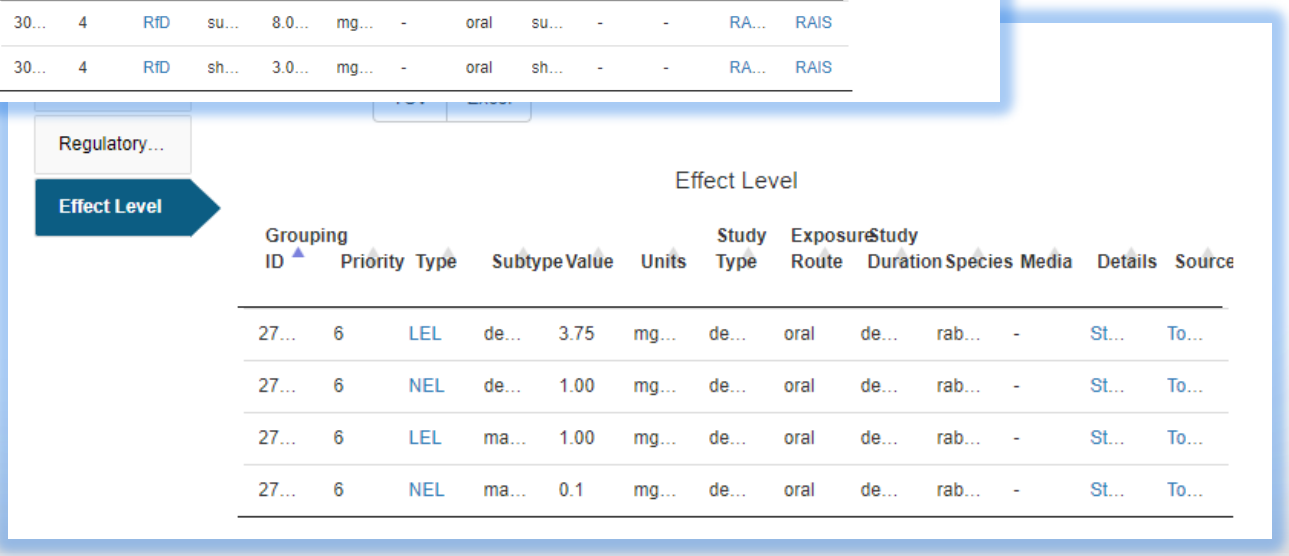


Close

HAWC: Enhance Interoperability of Data Platforms



Grouping ID	Priority	Type	Subtype	Value	Units	Study Type	Exposure Route	Study Duration	Species	Media	Details	Source
30...	4	RfD	su...	8.0...	mg...	-	oral	su...	-	-	RA...	RAIS
30...	4	RfD	sh...	3.0...	mg...	-	oral	sh...	-	-	RA...	RAIS



Grouping ID	Priority	Type	Subtype	Value	Units	Study Type	Exposure Route	Study Duration	Species	Media	Details	Source
27...	6	LEL	de...	3.75	mg...	de...	oral	de...	rab...	-	St...	To...
27...	6	NEL	de...	1.00	mg...	de...	oral	de...	rab...	-	St...	To...
27...	6	LEL	ma...	1.00	mg...	de...	oral	de...	rab...	-	St...	To...
27...	6	NEL	ma...	0.1	mg...	de...	oral	de...	rab...	-	St...	To...

Advantages

- Structured data extraction to promote consistency and completeness
- Free, open source and customizable
- Enhance database interpretability
- Integration with automated data-extraction tools
- Web-based to promote team collaboration
- Ability to export data files promotes independent analysis of findings and quantification (in assessments or for methods development)
  - Exploring the creation of meta-analysis using the R metafor library
- Creates possibilities for web-based, interactive reports
- Systematic review tools like HAWC could be "repurposed" for next generation of journal submission practices

United States Environmental Protection Agency

Study Evaluation

Xabier Arzuaga, Ph.D
Beth Radke, Ph.D

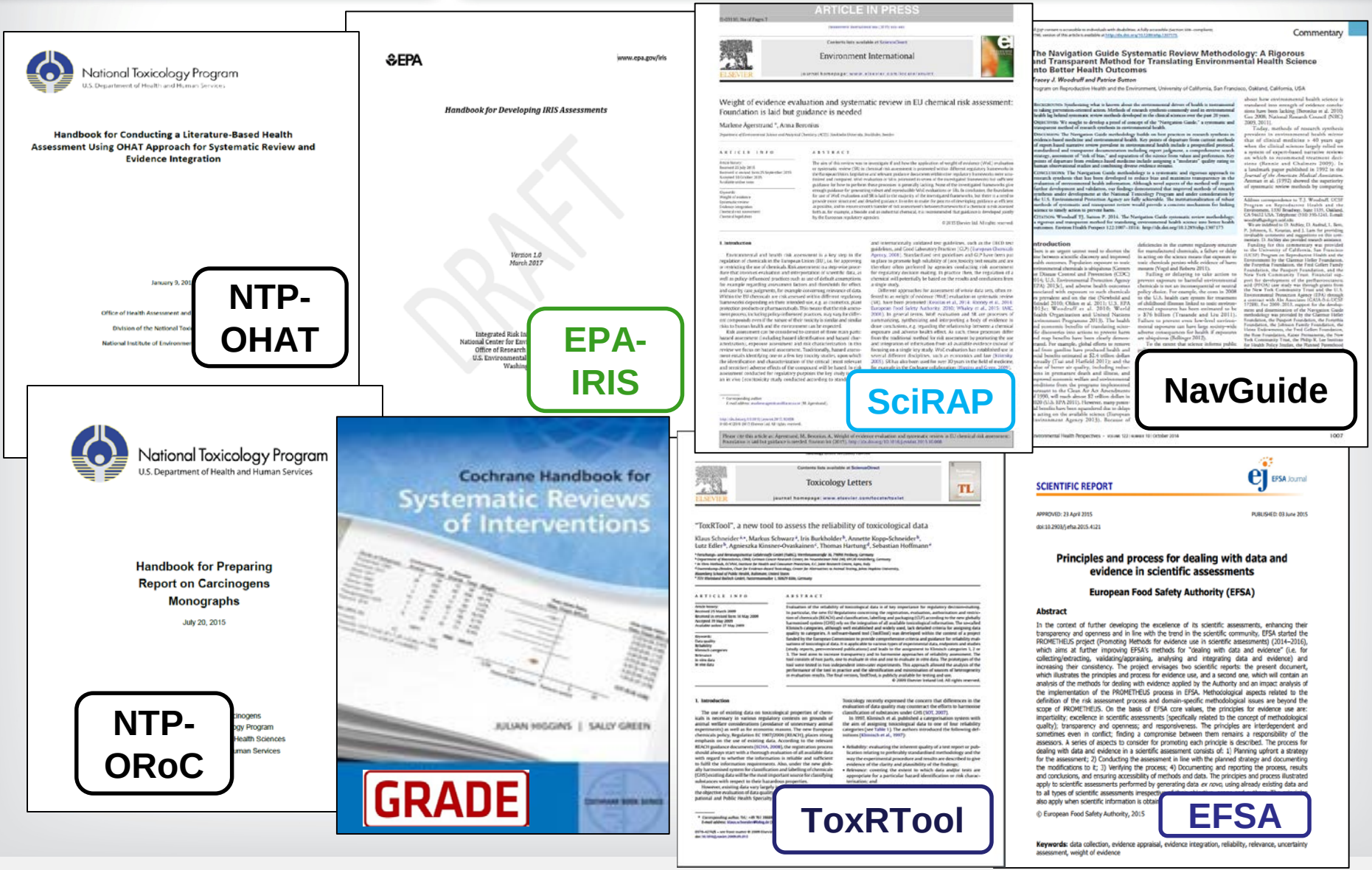
Office of Research and Development
NCEA, IRIS

Evaluating Studies

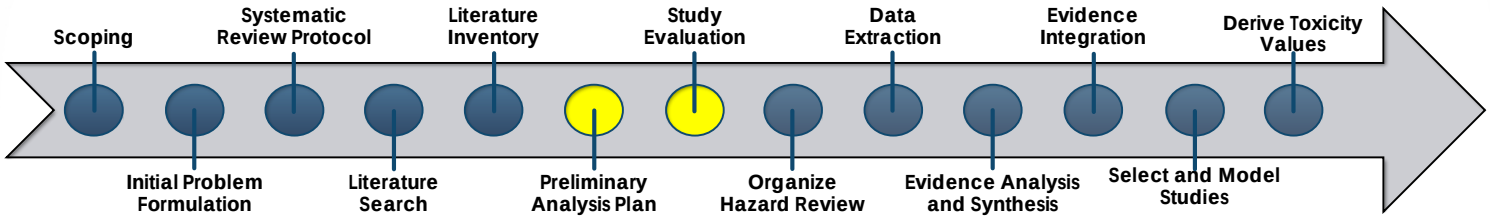
Structured approaches to study evaluation help to:

- **Identify the most informative studies for synthesizing evidence**
- **Provide a standardized, documented process**
- **Increase transparency of assessments**

Evolving Approaches



Evaluation of Individual Studies



- General approach same for human and animal studies
- Evaluation process focused on:
  - Internal validity/bias
  - Sensitivity
  - Applicability; relevance to the question
  - Reporting quality

Development of Evaluation Strategies

- Subject-matter knowledge is used to formulate a list of issues to consider in the evaluation
- Questions in IRIS Protocol Template highlights general study attributes or elements to consider
- Develop a set of considerations based on exposure and outcome-specific knowledge

Overview of Study Evaluation in IRIS

Individual Study (or Analysis) Evaluation Domains:

↓

Domain Specific Evaluation Classifications

- Good
- Adequate
- Poor
- Not Reported
- Critically Deficient

↓

Individual Study Overall Confidence

- High
- Medium
- Low
- Uninformative

Ratings for Individual Domains

	IRIS Judgement	How to interpret
	Good	Appropriate study conduct relating to the domain & minor deficiencies not expected to influence results.
	Adequate	A study that may have some limitations, but not likely to be severe or to have a substantive impact on results.
	Poor	Identified biases or deficiencies interpreted as likely to have had a substantial impact on the results or prevent reliable interpretation of study findings.
	Critically Deficient	A flaw that is so serious that the study could not be used.

Overall Study Confidence

Rating	Description
High	No notable deficiencies or concerns identified; potential for bias unlikely or minimal and sensitive methodology.
Medium	Possible deficiencies or concerns noted, but resulting bias or lack of sensitivity would be unlikely to be of a substantive degree.
Low	Deficiencies or concerns were noted, and the potential for substantive bias or inadequate sensitivity could have a significant impact on the study results or their interpretation.
Uninformative	Serious flaw(s) makes study results unusable for hazard identification

Evaluation of Animal Toxicology Studies

Risk of Bias (Internal Validity)

- This evaluation assesses whether notable methodological concerns or uncontrolled variables have been introduced into the experiment, thereby influencing the results

Sensitivity

- The evaluation of sensitivity addresses whether the experiment would be able to detect and characterize the potential effect(s) in question

General Considerations to Evaluate Outcomes From Animal Toxicology Studies

Domain	Metric
Reporting Quality	Reporting of information necessary for study evaluation
Selection or Performance Bias	Allocation of animals to experimental groups
	Blinding of investigators, particularly during outcome assessment
Confounding/Variable Control	Control for variables across experimental groups
Reporting or Attrition Bias	Lack of selective data reporting and unaccounted for loss of animals
Exposure Methods Sensitivity	Characterization of the exposure to the compound of interest
	Utility of the exposure design for the endpoint of interest
Outcome Measures and Results Display	Sensitivity and specificity of the endpoint evaluations
	Usability and transparency of the presented data
Other	Optional Example 1: Control for other threats to internal validity: animal husbandry concerns, reports of pre-dosing toxicity or infection, etc.

Overview of the Evaluation Process for Animal Toxicology Studies

Individual Study (or Analysis) Evaluation Domains:

- Reporting Quality
- Selection or Performance Bias
- Confounding/Variable Control
- Reporting or Attrition Bias
- Exposure Methods Sensitivity
- Outcome Measurements and Results Display

→

Domain Specific Evaluation Classifications

- Good
- Adequate
- Poor
- Not Reported
- Critically Deficient

→

Individual Study Overall Confidence

- High
- Medium
- Low
- Uninformative

Epidemiology Study Evaluation

- Approach based on the Cochrane Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I)[1], modified for environmental and occupational exposures
- Start by considering an "ideal" study for each domain, identifying "critical deficiencies", then developing criteria to define other levels of confidence
- Emphasis is on discerning bias that would produce a substantive change in the estimated effect estimate.

[1]Sterne, Hernan, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355:i4919.

Epidemiology Evaluation Domains

Domain	Core Question
Exposure measurement	Does the exposure measure reliably distinguish between levels of exposure in an appropriate time window?
Outcome ascertainment	Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?
Population selection	Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and outcome?
Confounding	Is confounding of the effect of the exposure likely?
Analysis	Does the analysis strategy and presentation convey the necessary familiarity with the data and assumptions?
Sensitivity	Are there concerns for study sensitivity?

Example of Considerations by Domains

Domain	Core Question
Exposure measurement	Does the exposure measure reliably distinguish between levels of exposure in an appropriate time window?

Examples of Prompting Questions:

- Does the exposure measure capture the sources of variability in exposure among the participants, considering intensity, frequency, and duration of exposure?
- Does the exposure measure reflect a relevant time window?
- Was exposure measurement likely to be affected by knowledge of outcome or by presence of the outcome (i.e., reverse causality)?

Examples of Follow-up Questions:

- Is the degree of exposure misclassification likely to vary by exposure level?
- If there is a concern about the potential for bias, what is the predicted direction of the bias on the effect estimate?

Study Evaluation: Final Review in HAWC

HAWC

Contact About Public Assessments Your HAWC

Home / Chloroform UHA (2017) / Gold et al. (2010) / Gold et al. (2010) (Risk of bias) /

SELECTED ASSESSMENT

Chloroform UHA (2017)

AVAILABLE MODULES

Literature review
Management dashboard
Study list
Risk of bias
Endpoint list
Visualizations
Executive summary

DOWNLOADS

Download datasets

Final Review edit

Justification for risk of bias assessment of selected study. Each row contains the selected domain, a description of the question to be answered, and an area for the user to detail the bias selection and notes for justification.

Selection or Performance

Participant selection

Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and to outcome?

Elizabeth Radke

Adequate

Good. Case-control study. 181 cases (71% participation), 52% participation in controls

Controls identified from previous study of NHL, general pop identified with RDD and Medicare files.

Case participation not assoc. with site, age, or gender. Control participation associated with age, not site or gender.

Copy Notes

Amanda Persad

Adequate

Good-Fair. Cases from SEER. Inclusion criteria and participation rates included. Controls selected either through random digit dialing or Medicare/ Medicaid Service files. Eligibility criteria for cases and controls mentioned. Study design is not a cohort or nested case-control design.

Copy Notes

Adequate

Normal

Good-Fair. Case-control study. Cases from SEER. 181 cases (71% participation), 52% participation in controls. Inclusion criteria and participation rates included. Controls selected either through random digit dialing or Medicare/ Medicaid Service files. Eligibility criteria for cases and controls mentioned. Study design is not a cohort or nested case-control design. Control participation associated with age.

Exposure Methods Sensitivity

Exposure measures

Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?

Elizabeth Radke

Poor

Limited-CD. Job exposure matrix.

Collected information on all jobs held for at least 1 year. Dates, title, duties. Job-specific questionnaires developed by industrial hygienist had questions on work environment, job-specific tasks, chemicals used. Job coded according to SOC system.

Exposure metrics of probability, frequency, intensity, and confidence were assigned by modifying JEMs (unvalidated)

Potential for recall bias, with cases more likely to be thorough. Depending on reliability of JEMs for chloroform, could be critically deficient.

Amanda Persad

Poor

Limited. In-person interview on 'occupational histories, dates and frequencies of exposure." Participants were asked to report information about job start and end time, job title, and employers for every job since age 18. (high likelihood of recall bias). JEM created to determine probability of exposure. Actual exposure measures were not used.

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ed. In-person interview on 'occupational histories, dates and frequencies of exposure." Participants were asked to report information about job start and end time, job title, and employers very job since age 18. (high likelihood of recall bias). JEM created to determine probability of exposure. Actual exposure measures were not used. Potential for recall bias, with cases likely to be thorough. Depending on reliability of JEMs for chloroform, could be critically deficient.

Questions, instruction text, and drop down rating options are customizable by user

Study Evaluation: Final Review in HAWC

Elizabeth Radke

Adequate

Good. Case-control study. 181 cases (71% participation), 52% participation in controls

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Individual Studies in HAWC

Medium confidence

Uninformative

Individual Studies in HAWC

++

Good

Very Good. AGD measurement at 1-2 days post birth, by study protocol. Averaged 3 measurements for each data point, inter- and intra-examiner variation analyzed.

Medium confidence

Study Evaluation Summary in HAWC

Population selection	++	+	++	-	++	+
Exposure measurement	-	-	-	-	-	-
Outcome ascertainment	++	++	++	+	-	++
Confounding	+	+	+	-	+	+
Analysis	++	++	++	+	-	+
Other Sensitivity Concerns	+	-	+	-	-	+
Overall study confidence	+	-	+	-	-	+

Legend

- N/A Not applicable
- -- Critically deficient
- - Poor
- NR Not reported
- + Adequate
- ++ Good

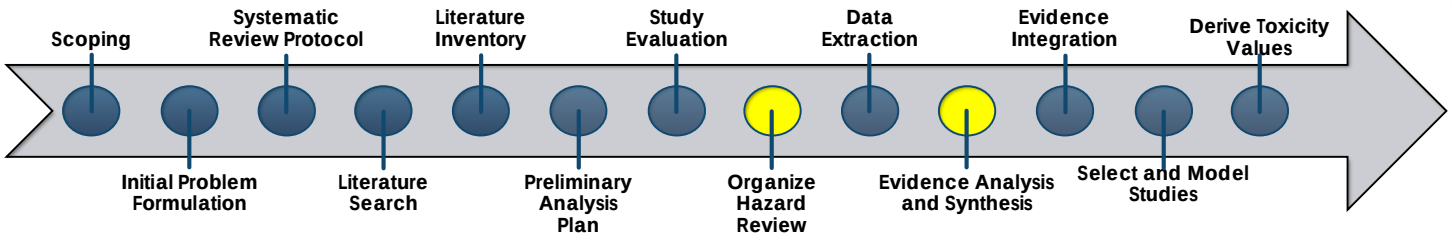
United States Environmental Protection Agency

Evidence Synthesis and Integration

Barbara Glenn, Ph.D
Andrew Kraft, Ph.D

Office of Research and Development
NCEA, IRIS

Synthesis and Integration of Evidence Linking Exposure and Health Effects: Purpose



Organize and analyze evidence

- Synthesis of each line of evidence (human, animal and mechanistic evidence) - to identify important health effects potentially linked to exposure, and to analyze results to inform strength of evidence

Develop judgements regarding strength of evidence

- Integration within evidence streams – to develop judgements about the strength of evidence for health effects in each human and animal evidence stream incorporating mechanistic information
- Integration across evidence streams - to develop a conclusion about whether exposure to a substance may cause a health effect in humans

Synthesizing Evidence on Health Effects – Organization and Structure

- What outcomes are relevant to each health hazard domain and at what level (e.g., health effect or subgroupings) should synthesis occur?
- What populations were studied (e.g., general population, occupations, life stages, species, etc)
- Can study results be described across varying exposure patterns, levels, duration or intensity?
- Are there differences in the confidence in study results for different outcomes, populations, or exposure?
- Does toxicokinetic information influence differences in responses across route of exposure, other aspects of exposure, or life stages?
- How might dose response relationships be presented (specific study results or across study results)?

Example Health Hazard Domain - Nervous System

Studies in Humans

Several low confidence studies reporting symptoms, prevalence variable and one medium confidence study that conducted functional tests of neurological function in highly exposed occupational groups

Synthesis Narrative

- Medium confidence study of neurological function
- Minimal summary low confidence studies of symptom prevalence

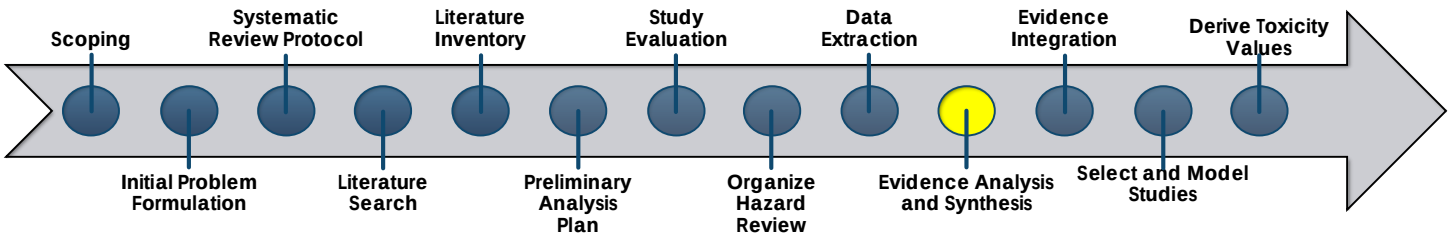
Studies in Animals

Several studies of rats and mice exposed as adults, variety of endpoints with varying level of utility (e.g., cage side observations of activity were considered less informative than automated motor activity tests), effects more prevalent and severe in rats, toxic metabolite found at higher levels in rats, one study of postnatal exposure reported stronger responses, and at lower levels

Synthesis Narrative

- Separately describe the more informative endpoints by species (emphasizing high & medium confidence studies)
- Highlight difference in metabolism, a possible explanation for the lesser effects in mice
- Point out potential early life-stage vulnerability

Scientific Judgment in Analysis and Synthesis of Evidence



- Synthesis of evidence is more than counting the number of "positive" and "negative" studies
- Must systematically consider the influence of bias and sensitivity when describing study results and synthesizing evidence
- Synthesis should primarily be based on studies of medium and high confidence (when available)
- Analysis should also address composite evidence from collections of studies

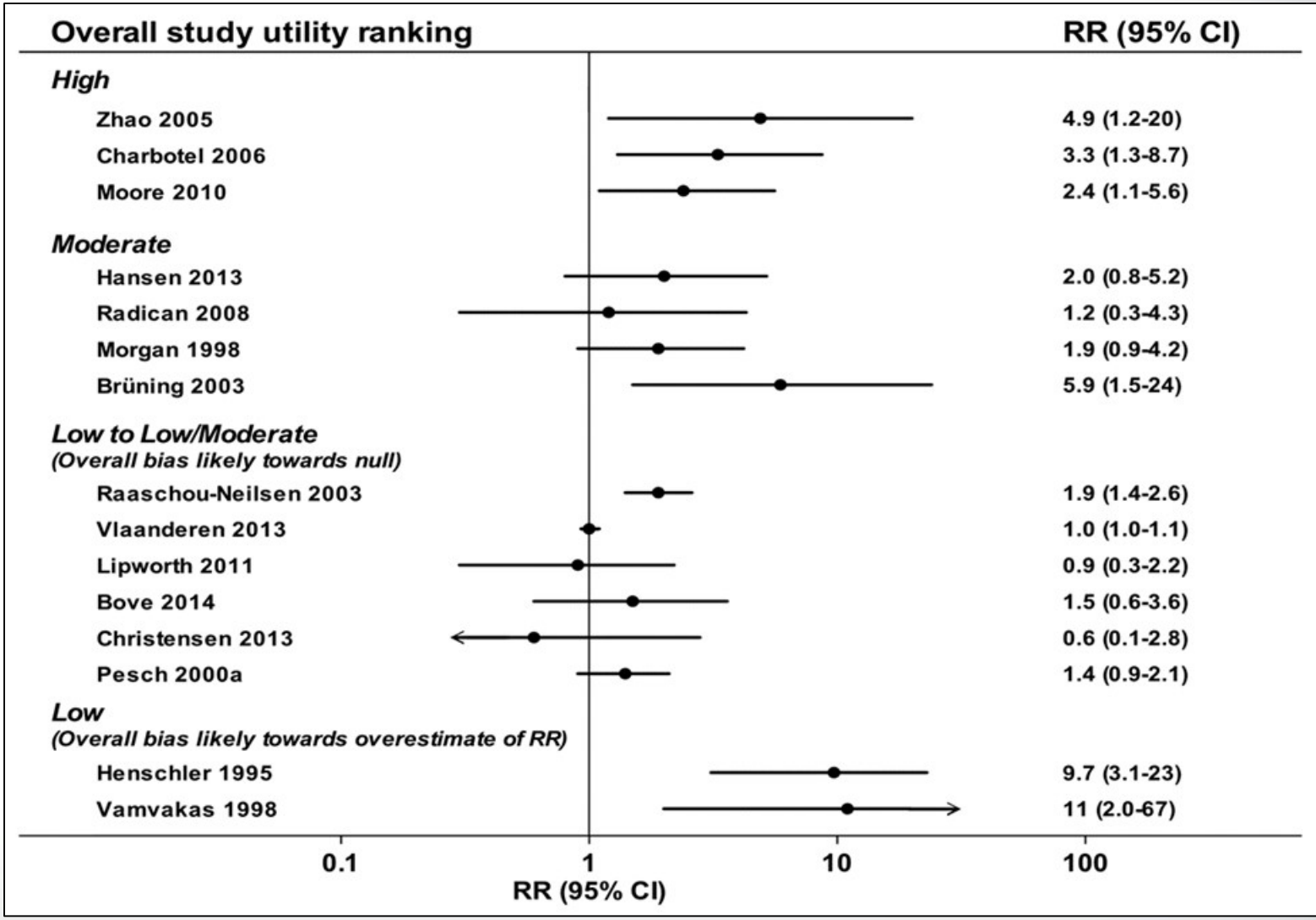
Synthesis Considerations for Determining Strength of Evidence

Epidemiology evidence	Animal toxicology evidence
Study evaluation conclusions (risk of bias, sensitivity, and directness) are incorporated into analyses of each of the following considerations (adapted Hill considerations):	
Consistency	
Effect magnitude/ precision	
Biological gradient/ dose-response	
Coherence	
Natural experiments	
Temporality	

- Informative human and animal health effect evidence is analyzed and synthesized separately.
- Mechanistic evidence is synthesized that informs the conclusions regarding the human and animal health effect evidence.

Synthesis Examples: Epidemiology

TCE and kidney cancer: stratification by utility

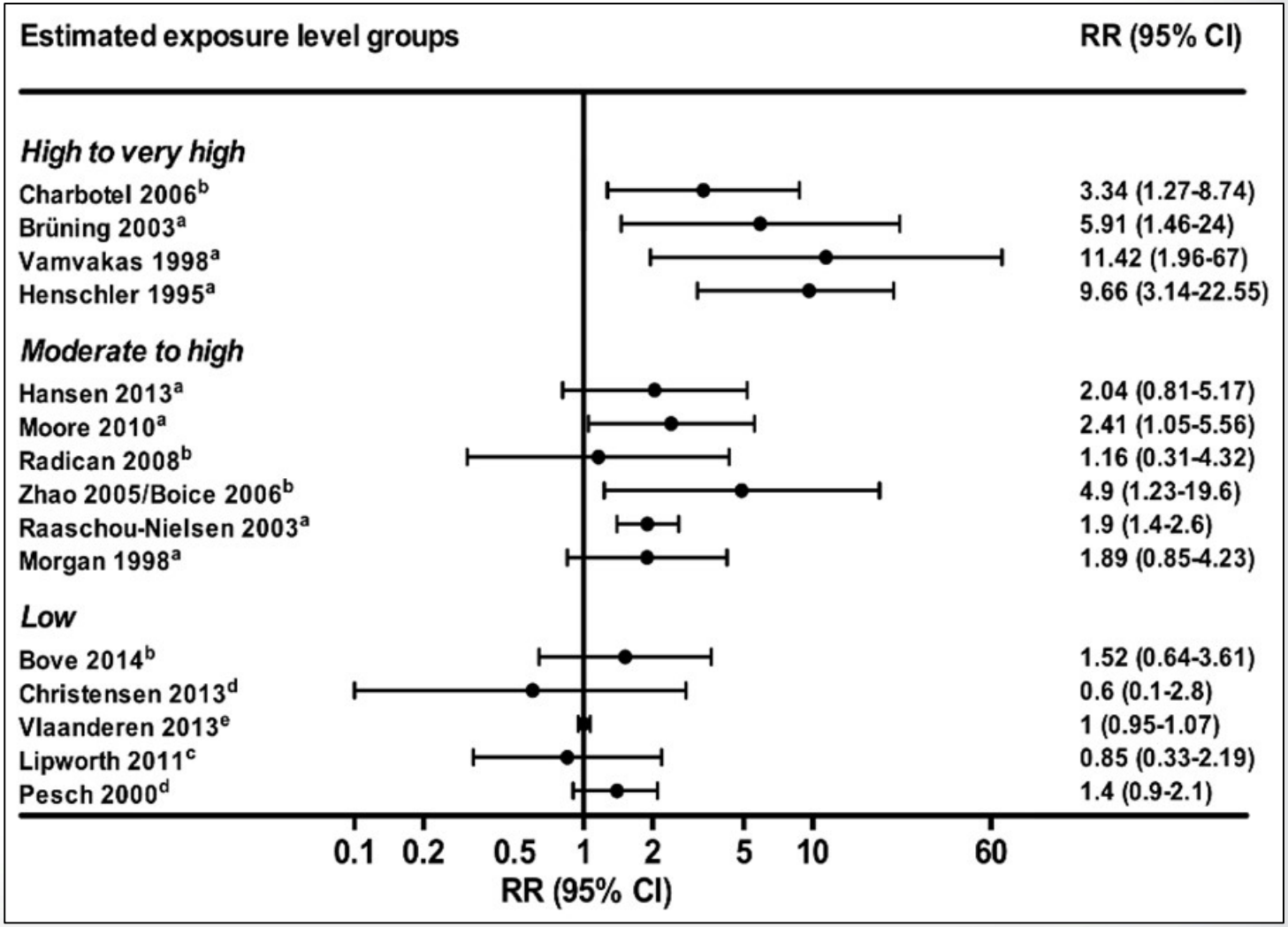


Highest exposure level graphed for each study

RoC Monograph on Trichloroethylene. January 2015. https://ntp.niehs.nih.gov/go/797306

Synthesis Examples: Epidemiology

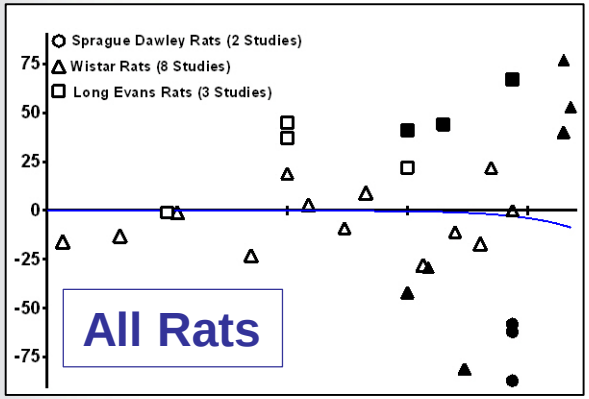
TCE and Kidney Cancer: stratification by exposure level

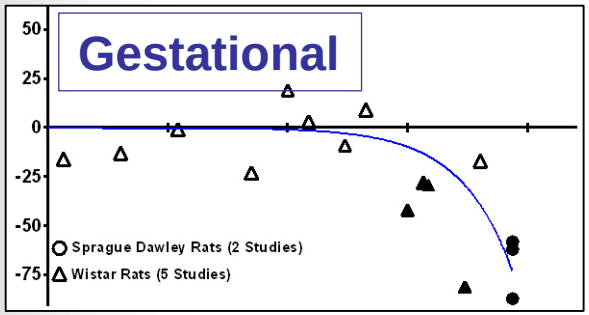


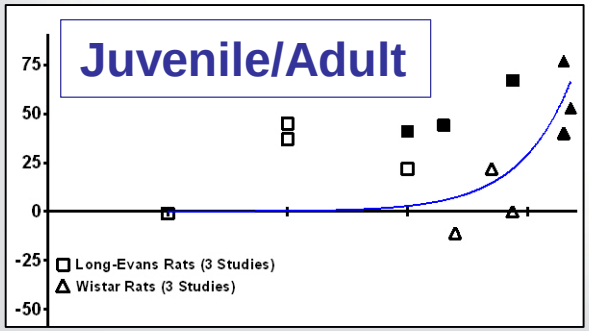
EPA. 2011. Toxicological Review of Trichloroethylene

Synthesis Examples: Animal Toxicology

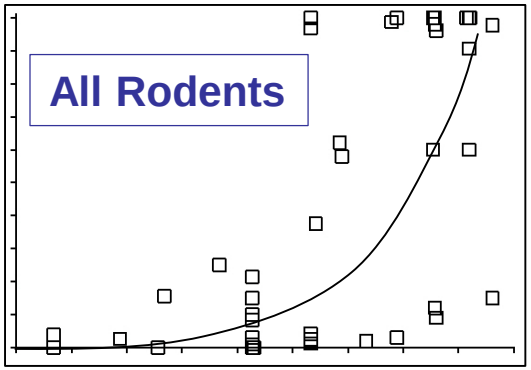
Hormone Level

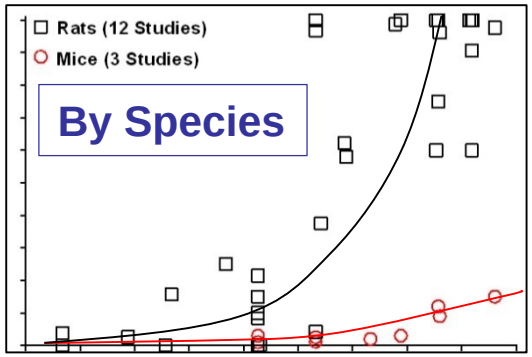


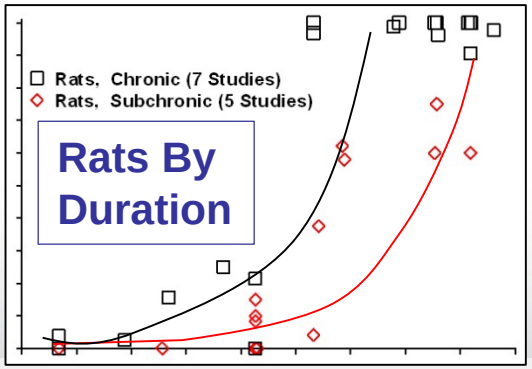




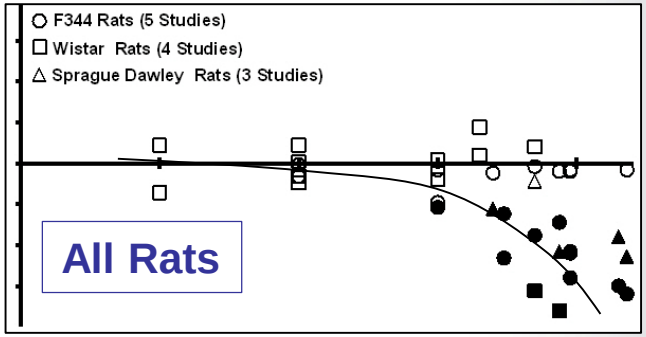
Pathology Incidence

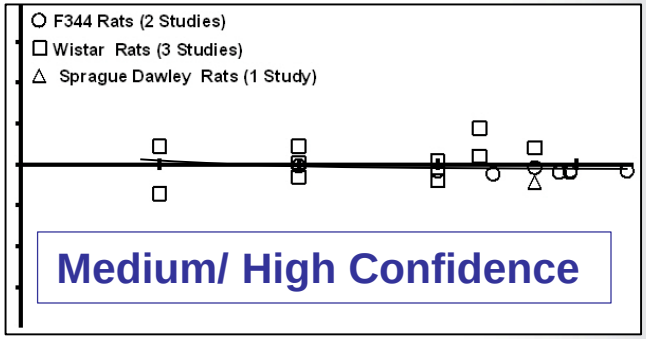


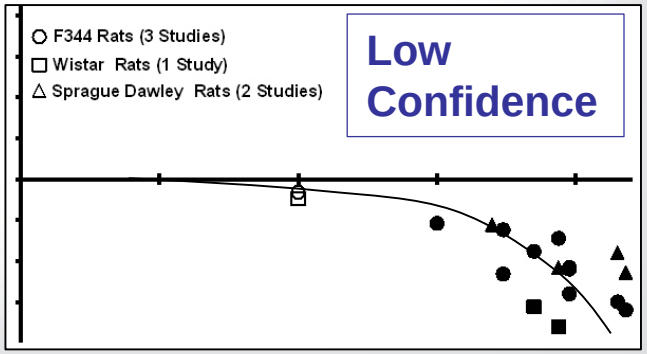




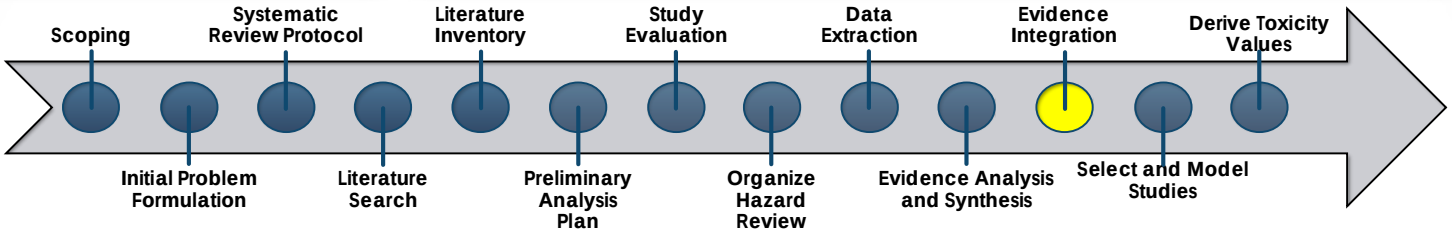
Behavioral Function







Moving from Synthesis to Integration



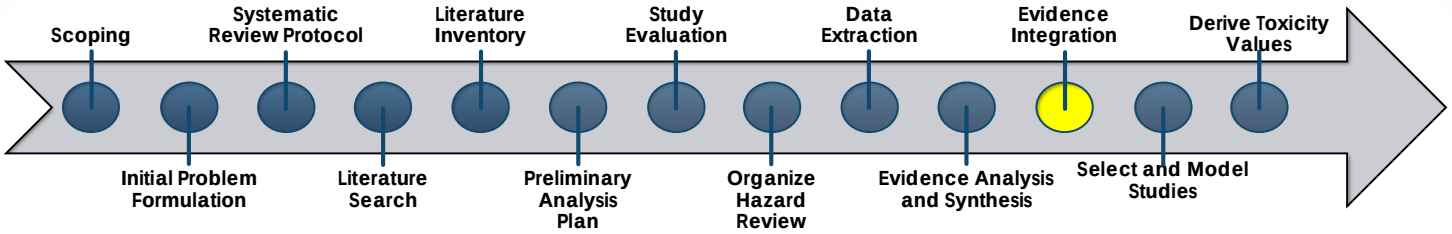
Outputs of Evidence Synthesis

- Results of Human Health Effect Study Synthesis
- Results of Animal Health Effect Study Synthesis
- Results of Synthesis of Mechanistic Evidence Informing the Human and Animal Syntheses

Evidence Integration

Transparent and Structured Processes for Drawing Summary Conclusions Across Lines of Evidence

Evidence Integration Involves a Sequential, Two-Step Process



- **Evidence synthesis interpretations for each consideration relating to causality are combined across lines of evidence using transparent, structured frameworks**

Step 1: "Within-Stream" Integration	Step 2: "Across-Stream" Integration
Judge the Strength of the Evidence from the: • **Human Evidence Stream** • **Animal Evidence Stream**	Draw Overall Evidence Integration Conclusions based on: • Combined **Human** and **Animal Evidence Streams**
consideration are integrated in light of mechanistic evidence in exposed humans or human cells (or other human models)	The judgements regarding the strength of the human and animal evidence streams are integrated in light of evidence on the human relevance of the findings in animals, susceptibility, and the coherence of the findings across evidence streams.
Characterize the Strength of the Evidence for an Effect in Animals (**Animal Evidence Stream Judgement**)	
Animal health effect study synthesis conclusions for each consideration are integrated in light of mechanistic evidence in exposed animals or animal cells (or other relevant models)	

Within-Stream (Human; Animal Stream) Evidence Judgement Considerations

NAS (2011): "the weight of evidence descriptions need to indicate the various determinants of weight... The reader needs to be able to understand what elements (such as consistency) were emphasized in synthesizing the evidence"

	Synthesis of Each Line of Evidence				
Criteria (based on Bradford-Hill)	**Human Health Effect Study Synthesis**		**Animal Health Effect Study Synthesis**		**Mechanistic Evidence Synthesis**
Consistency	In the Context of Study Evaluation	↑↓	In the Context of Study Evaluation	↑↓	
Dose-response		↑		↑	
Magnitude and Precision		↑↓		↑↓	
Natural experiments		↑↓			
Coherence		↑↓		↑↓	↑↓ **Human or Animal**
Temporality		***During Study Evaluation**			
Biological Plausibility					↑↓ **Human or Animal**

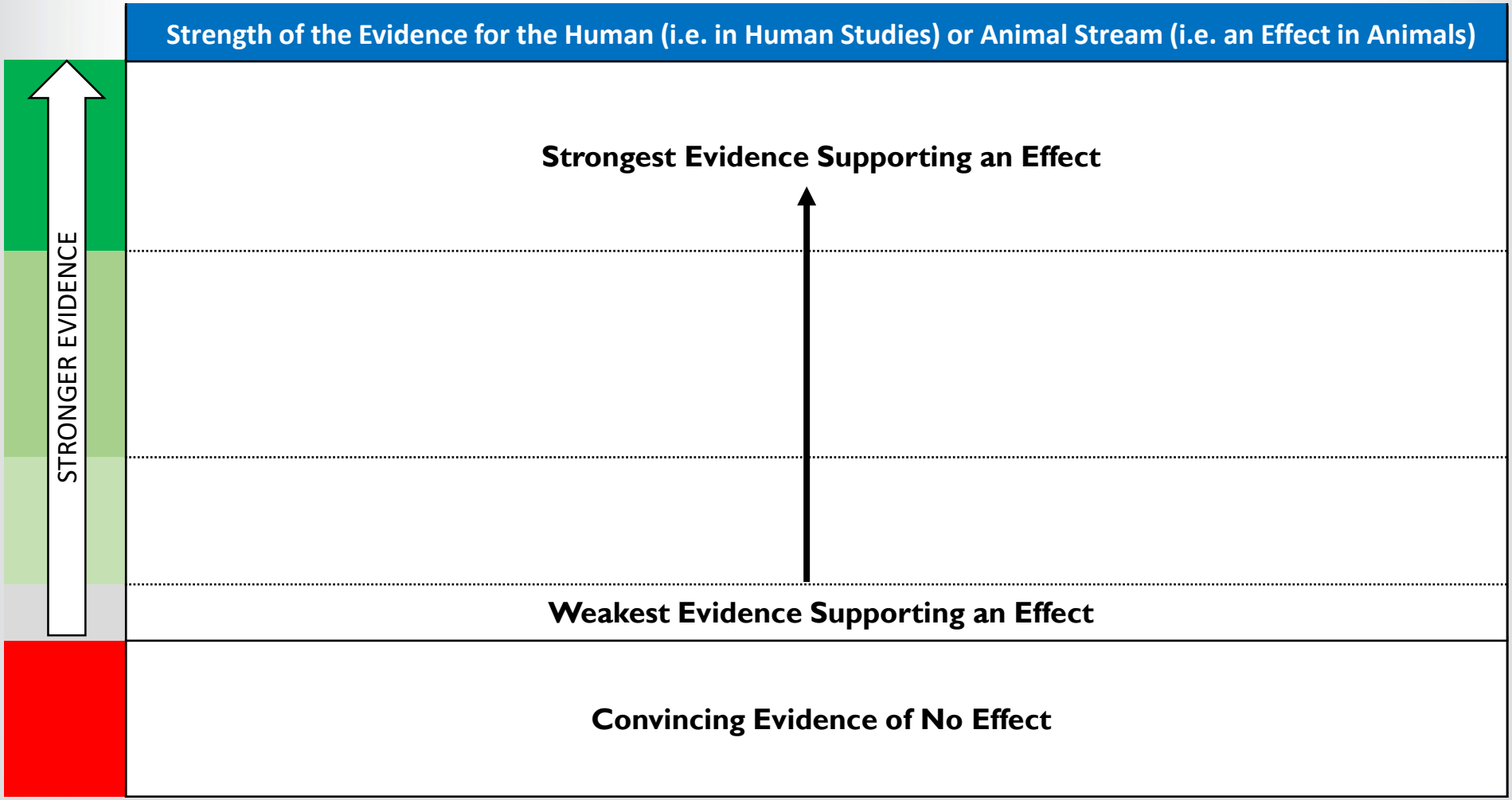
Within-Stream (Human; Animal Stream) Evidence Judgement Considerations

	Human Evidence Stream	Animal Evidence Stream
Confidence	*High* or *medium* confidence studies provide stronger evidence (consider biological significance, and findings across studies, not just statistical significance)	
Consistency	Different studies or populations increase evidence strength	Different studies, species, or labs increase evidence strength
Dose-response	Simple or complex (nonlinear) relationships stronger, but if lacking don't dismiss (consider other studies and known biology as explanatory)	
Magnitude and Precision	Large or severe effects can increase strength, but don't dismiss small changes (consider variability, historical data, and bias as explanatory)	
Natural experiments	Rarely available, but can be persuasive	N/A
Coherence	Biologically related findings within an organ system, within or across studies, or across populations (e.g., sex) increase evidence strength (temporal or dose-dependent linkage evaluated); Conversely, an observed lack of expected changes could weaken	
	Informed by mechanistic evidence on the biological development of the health effect or toxicokinetic/ dynamic knowledge of the chemical or related chemicals	
Temporality	N/A (considered in study evaluation)	N/A
Biological Plausibility	Mechanistic evidence in humans or animals of precursors or biomarkers of health effects, or of changes in established biological pathways or a theoretical mode-of-action can strengthen within-stream evidence; Conversely, lack of mechanistic understanding does not weaken evidence outright, but can if well-conducted experiments exist to demonstrates that effects are unlikely	

Light blue rows highlight inferences for each line of evidence based on mechanistic evidence

Step 1: Framework for Within-Stream Evidence Judgements

The Hill-based considerations are applied to categorize evidence streams according to their strength (aka, confidence in the conclusions for the two evidence streams)



Step 2: Framework for Overall Evidence Integration Conclusions

Judgements regarding the strength of the human and animal evidence streams are combined to conclude confidence in the evidence for a human health effect

STRONGER CONCLUSION

Strongest Conclusion of Confidence in the Evidence for a Human Health Effect

Weakest Conclusion of Confidence in the Evidence for a Human Health Effect

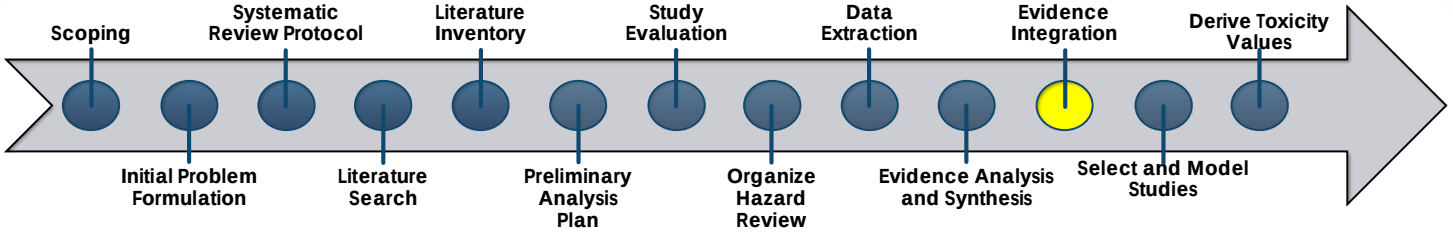
Conclusion of Confidence in the Evidence for No Human Health Effect

Evidence Profile Tables: Complement Narrative Summary of the Integration of All Evidence

"No matter what method is used to integrate the different kinds of evidence available for an IRIS assessment, using a template for the evidence-integration narrative could help to make IRIS assessments more transparent." [NAS, 2014]

Studies and confidence (risk of bias, sensitivity)	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Within stream evidence strength judgements	Inference across evidence streams	Final evidence integration conclusion
[Health Effect or Outcome Grouping]						
Evidence from Human Studies (Route)						
• *References* • *Study confidence and explanation* • *Study design description*	• *Consistency* • *Dose-response gradient* • *Coherence of observed effects (apical studies)* • *Effect size (magnitude, severity)* • *Biological plausibility* • *Low risk of bias/ high quality* • *Insensitivity of null/ negative studies* • *Natural experiments* • *Temporality*	• *Unexplained inconsistency* • *Imprecision* • *Indirectness/ applicability* • *Poor study quality/ high risk of bias* • *Other (e.g., Single/Few Studies; small sample size)* • *Evidence demonstrating implausibility*	• *Results information (general endpoints affected/ unaffected) across studies* • *Human evidence informing biological plausibility: discuss how mechanistic data influenced the within stream judgement (e.g., evidence of precursors in exposed humans).* *Could be multiple rows (e.g., grouped by study confidence or population) if this informs results heterogeneity*	*Describe confidence in evidence from human studies, and primary basis:* ⊕⊕⊕ Strongest evidence ⊕⊕○ ⊕○○ ○○○ Weakest evidence ⊖⊖⊖ Convin. no effect	• *Human relevance of findings in animals* • *Cross-stream coherence (i.e. for both health effect-specific and mechanistic data)* • *Other inferences:* o *Information on susceptibility* o *MOA analysis inferences: precursors, cross-species inferences of toxicokinetics, or quantitative implications* o *Relevant information from other sources (e.g., read across; other, potentially related health hazards)*	*Describe conclusion(s) and primary basis for the integration of all available evidence (e.g., across human, animal, and mechanistic):* ⊕⊕⊕ Strongest Conclusion ⊕⊕○ ⊕○○ ○○○ Weakest Conclusion ⊖⊖⊖No effect Conclusion
Evidence for an Effect in Animals (Route)						
• *References* • *Study confidence and explanation* • *Study design description*	• *Consistency and Replication* • *Dose-response gradient* • *Coherence of observed effects (apical studies)* • *Effect size (magnitude, severity)* • *Biological plausibility* • *Low risk of bias/ high quality* • *Insensitivity of null/ negative studies*	• *Unexplained inconsistency* • *Imprecision* • *Indirectness/ applicability* • *Poor study quality/ high risk of bias* • *Other (e.g., Single/Few Studies; small sample size)* • *Evidence demonstrating implausibility*	• *Results information (general endpoints affected/ unaffected) across studies* • *Evidence informing biological plausibility for effects in animals: discuss how mechanistic data influenced the within stream judgement (e.g., evidence of coherent molecular changes in animal studies)* *Could be multiple rows (e.g., by study confidence, species, or exposure duration) if this informs results heterogeneity*	*Describe confidence in evidence for an effect in animals, and primary basis:* ⊕⊕⊕ Strongest evidence ⊕⊕○ ⊕○○ ○○○ Weakest evidence ⊖⊖⊖ Convin. no effect		

Evidence Integration Conclusions



- For Cancer, conclusions on the integrated evidence for each cancer type (or grouping) are evaluated in the context of MOA information to define a descriptor for carcinogenicity:
  - **carcinogenic** to humans;
  - **likely** to be carcinogenic or [toxic] to humans;
  - **suggestive** evidence of carcinogenic or [toxic] potential;
  - **inadequate** information to assess carcinogenic or [toxic] potential; or
  - **not likely** to be carcinogenic or [toxic] to humans.
- For Noncancer, while a structured framework for evaluating the integrated evidence has been developed, the specific manner in which these conclusions are summarized is currently being tested and discussed with EPA partners

United States
Environmental Protection
Agency

THANK YOU FOR YOUR ATTENTION