Framework and Approaches for Integrated & Systematic Review of Evidence

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Disclaimer: The views presented here are those of the author and do not represent the views or policies of the U.S. EPA.

EPA at 50 Progress for a Stronger Future

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  - Andrew Kraft

Outline

- Set up
- EPA's applications
- Summary
- Discussion

CASHUE Charge

The committee will consider relevant scientific, technical, and policy issues including but not limited to:

- Review of the current situation, to include discussions of epidemiologic investigations, case definitions, study methods, controls, and alternative hypotheses;
- Review the active research agenda, including defining what types of information ought to be collected and archived against possible future needs, and any potential additional studies needed;
- Assist in the optimization and deployment of screening protocols and assessment of treatment options, to include a review of currently available screening devices and technologies, appropriate level of baseline testing for a large number of personnel and policy needs;
- Review data, findings and conclusions generated by and for the US government;
- Review scientific evidence of possible causes and approaches to addressing potential future incidents of unexplained clusters of medical symptoms;
- Determine the need for collection of relevant environmental data (e.g., biologic, acoustic, radiologic, chemical, toxicological) that might be useful in current and future situations.
- Provide guidance on determining a clinical case definition.

Problem Formulation

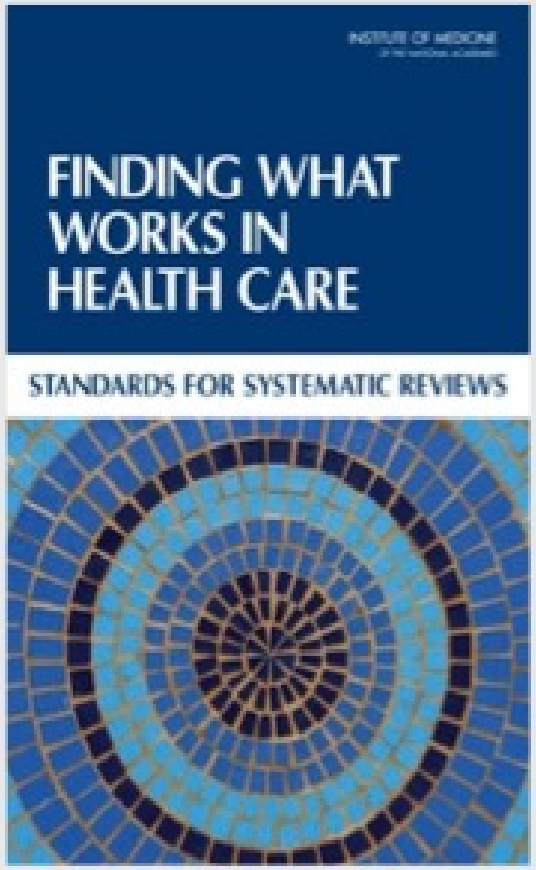
- CASHUE charge theme: review of scientific and technical evidence and findings;
- Existing exposure and health effects evidence is inconsistent and fragmented;
- There is a large body of existing literature with potential to inform hypothesized exposure - effect relationships;
- What process can CASHUE suggest/use to systematically assess the evidence above that is scientifically defensible and transparent to support its findings and recommendations?

What is a Systematic Review?

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

- "As defined by IOM [Institute of Medicine], 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.'" [p. 4] (NRC, 2014)

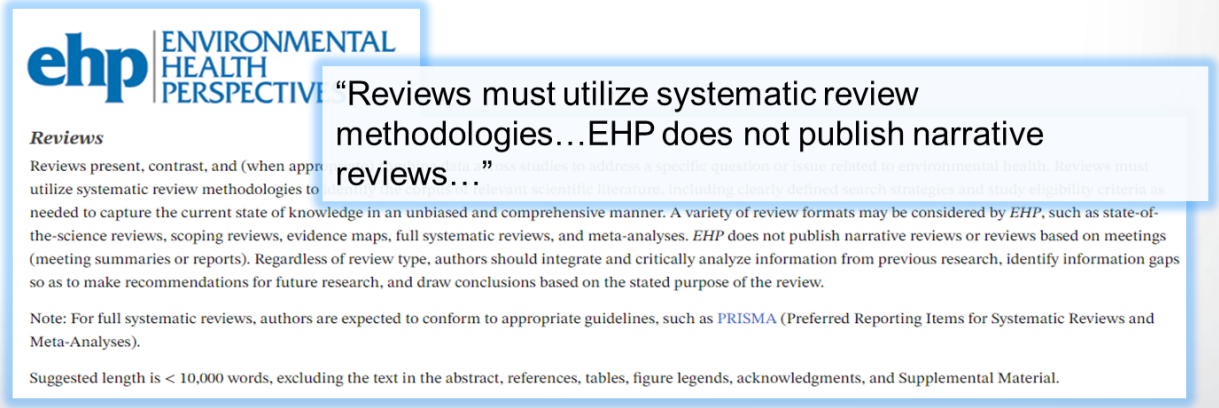
- "The output of a systematic review can be "narrative" (structured review and summary of the available data), "qualitative" (non-numerical conclusions, including conceptual frameworks), or "quantitative" (meta-analysis or meta-regression)." (Deeks et al., 2011 [Cochrane Collaboration])



[1] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011 . https://www.nap.edu/catalog/13059/finding-what-works-in-health-care-standards-for-systematic-reviews

Why Systematic Review?

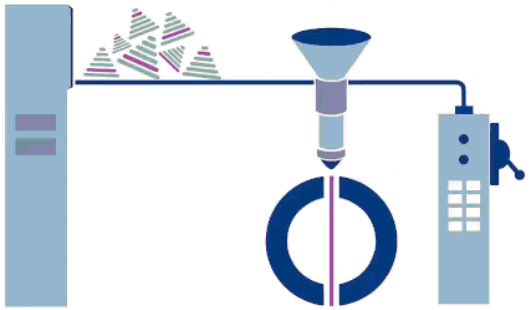
- Enhances **transparency** and **minimizes bias**
- Issues with narrative reviews:
  - Unclear approach to choice of studies
  - No consistent evaluation of studies
  - No clear framework for synthesizing and integrating evidence
  - Difficult to reproduce
- State of the science: becoming difficult to publish narrative reviews



Systematic Review Origins

- Initially developed for evidence-based medicine (clinical trials)
  - **Cochrane:** a non-profit founded 1993 to conduct & share health intervention systematic reviews
- Growing importance for
  - Public health
  - Social interventions
  - Economic evaluations
  - **Environmental science and toxicology**
    - Ecological impacts
    - Human health hazards
    - Exposure

Cochrane



http://www.cochranelibrary.com/

Campbell Collaboration

Better evidence for a better world

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

Collaboration for Environmental Evidence

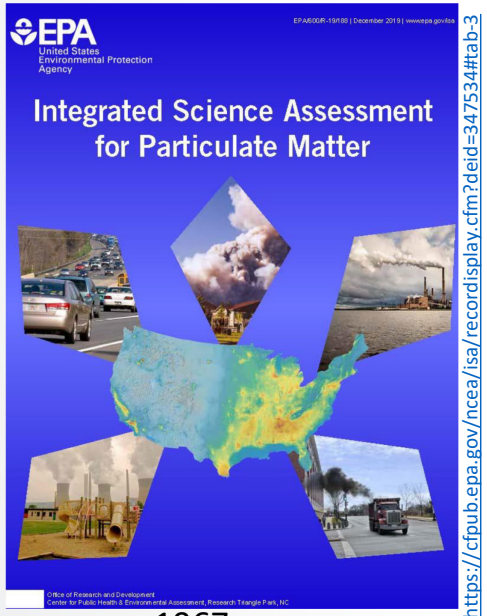
http://www.environmentalevidence.org/

Systematic Review

- **Goal**: analyze and interpret (i.e., draw conclusions) the available evidence on a specific research question
- **Methods**: rigorous, transparent, accessible, and reproducible while minimizing the potential for bias
- **Scope**: identify, select, and conduct critical appraisal of studies; extract and synthesize results across studies; interpret the evidence and present summary findings
- **Presentation**: systematic review document

EPA/ORD's Applications

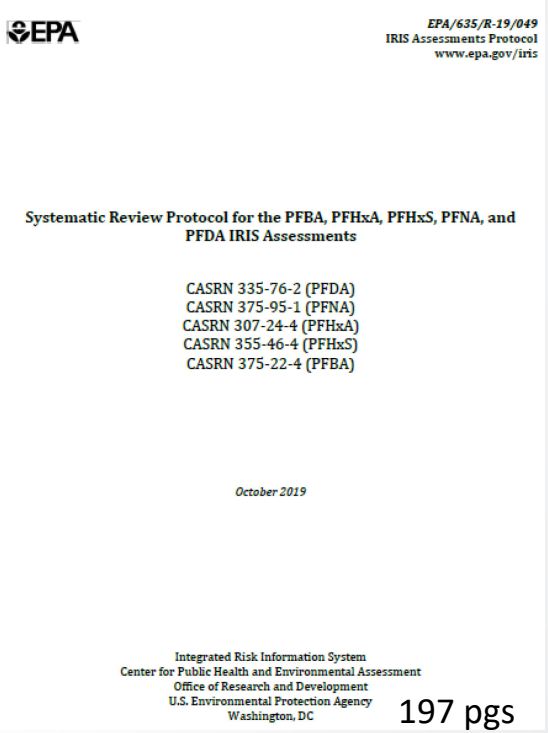
- Integrated science assessment (ISA) in support of the National Ambient Air Quality Standards, e.g. PM2.5



https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=347534#tab-3

1967 pgs

- Chemical assessments in support of the Integrated Risk Information System (IRIS)


EPA

EPA/635/R-19/049
IRIS Assessments Protocol
www.epa.gov/iris

Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA IRIS Assessments

CASRN 335-76-2 (PFDA)
CASRN 375-95-1 (PFNA)
CASRN 307-24-4 (PFHxA)
CASRN 355-46-4 (PFHxS)
CASRN 375-22-4 (PFBA)

October 2019

Integrated Risk Information System
Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345089

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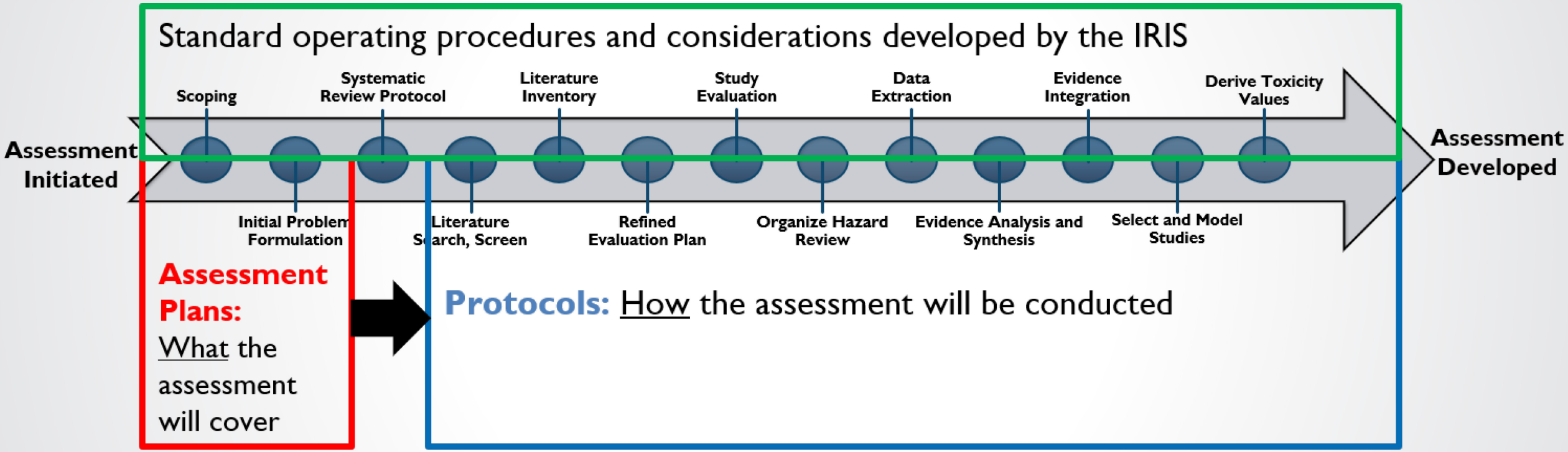
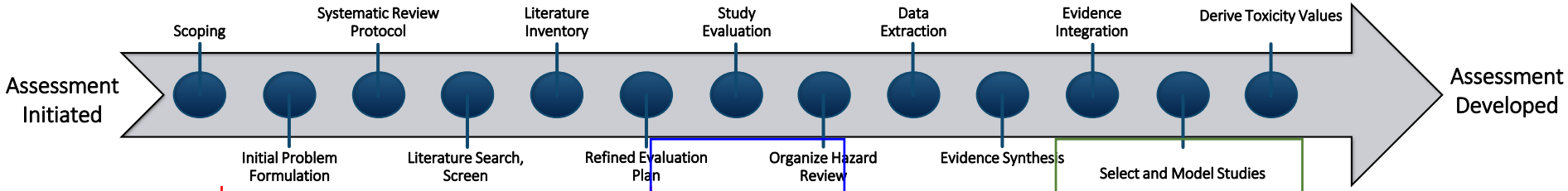
How might these assessment tools and approaches be retrofitted for the needs of CASHUE?

Experimental Process and Design for Applying Principles of Systematic Review in a Literature Based Chemical Assessment



- Assessment Plans (IAPs) are problem formulation and scoping documents that include elements of systematic review
- Protocols outline methods, including updates to the Assessment Plans

Fit-for-Purpose Software Tools Used Within IRIS



SWIFT Review
Problem formulation and screening prioritization
HAWC (manual only)
Distiller* (manual, but also has machine learning)
SWIFT Active* (machine learning)
Reference screening and tagging
Qlik Sense, Tableau, Power BI
Interactive screening results and literature inventory

HAWC
Modules to track multiple reviewer study evaluations*

Extracted data storage

HAWC
Interactive graphical display, evidence profile tables*

BMDS, Metaphor, Other
Dose-response, meta-regression, categorical regression, model averaging

Many tools available; can reduce screening burden by >50%

**supports (or will support) multiple evaluators and tracking*

Systematic Evidence Map

Is a pre-decisional systematic review analysis that compiles and summarizes evidence but does NOT reach assessment conclusions (aka systematic map or scoping review)

Summarize

- summarize evidence base characteristics to…

Allocate

- Allocate resources depending on step-wise scoping, planning and problem formulation;

Prioritize

- Prioritize reference chemicals with a range of potencies for model and test guideline development;

Identify

- Identify data gaps for new test method development.

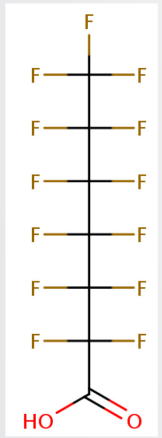
Systematic Evidence Mapping

A systematic review approach that informs but doesn't draw conclusions.

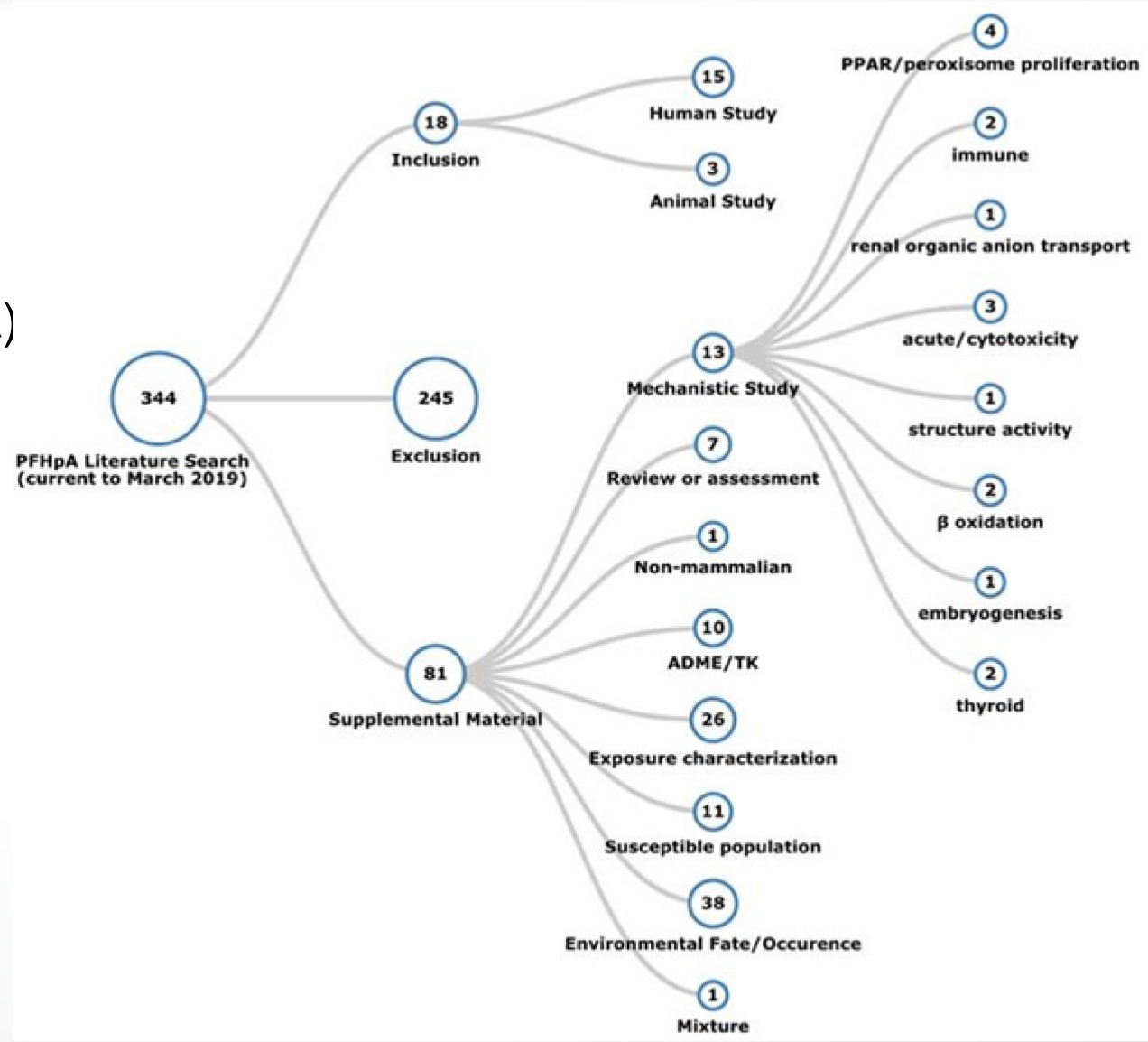
- **Goal**: identify evidence available to evaluate a broad topic area and characterize knowledge gaps
- **Methods**: rigorous, transparent, accessible, and reproducible while minimizing the potential for bias
- **Scope**: identify and select studies – may include aspects of critical study appraisal and data extraction, but no evidence synthesis
- **Presentation**: user-friendly, generally highly visual and populated with searchable databases (click-to-see-more)

Chemical Centric Evidence Flow Diagram

For Perfluoroheptanoic Acid (PFHpA)



But, imagine for any chemical, biological, or physical hazardous agent,



Example Work Flow

1. Bound the literature search by well characterized molecular targets/exposures and outcome of regulatory concern.

Bound literature search by:
- **Inorganic arsenic exposure**
- Cancer Outcomes

2. Title and Abstract screen results for potentially relevant studies and tag for evidence stream and health outcome.

Tag for evidence stream:
- Animal
- Human
- *In vitro*

Tag for health outcome
- Hepatic
- Cardiovascular
- **Cancer**
- Etc.

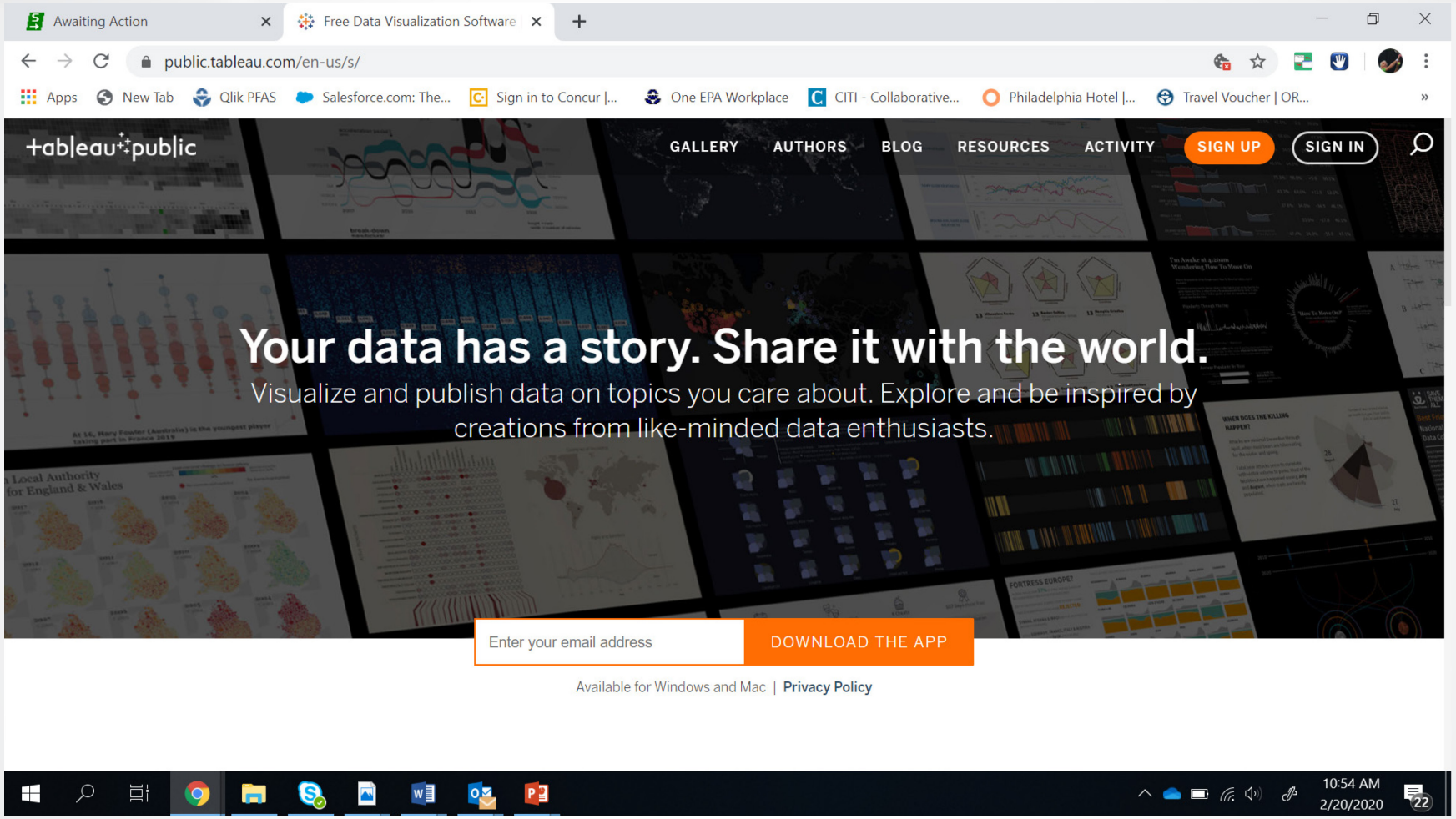
3. Subset studies tagged for cancer health outcomes, screen for relevant studies, and tag for.

Subset studies tagged for **Cancer** health outcomes, full text screen for relevance and tag for **DNA methylation**

4. Create an evidence inventory from well characterized studies that includes information on changes in DNA methylation.

Inventory reported evidence

Dashboard Literature Inventory & Access



https://public.tableau.com/views/PFAS-150EvidenceMapVisualizations/AnimalStudies?:display_count=y&:origin=viz_share_link

Summary

- CASHUE charge theme relates to “review and assessment of evidence;”
- Evidence available to CASHUE is inconsistent and fragmented;
- There is an extensive body of relevant literature relating to suspected exposures and observed effects;
- Systematic review and evidence mapping can provide a fit for purpose structured approach to consideration of available evidence;
- Considering the nature of CASHUE evidence, approach to review and mapping will need retrofitting