Systematic Evidence Maps for Scoping and Decision Prioritization of Chemical Assessments

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Systematic Review and Evidence Mapping

Systematic review methods are increasingly being used to support regulatory and non-regulatory decision-making, including the development of chemical health assessments. Such methods facilitate comprehensive summaries of the literature that are transparent and designed to reduce bias, which increases the replicability of the conclusions. In these ways, systematic review represents an improvement on traditional, narrative-based approaches. Systematic methods are more recently being applied to develop pre-decisional analyses that are not systematic reviews, but which provide a survey or summary of assessment-relevant information in ways that suit a specific decision purpose (see Figure 1). For example, rapid reviews are well-suited to address an emergent issue of human exposure requiring immediate, oftentimes interim, decisions. Systematic evidence maps (SEMs; aka evidence maps, scoping reviews) can also be produced rapidly and are designed to present a comprehensive summary of the availability and characteristics of the evidence base to develop a targeted research question used in a systematic review, as discussed below.

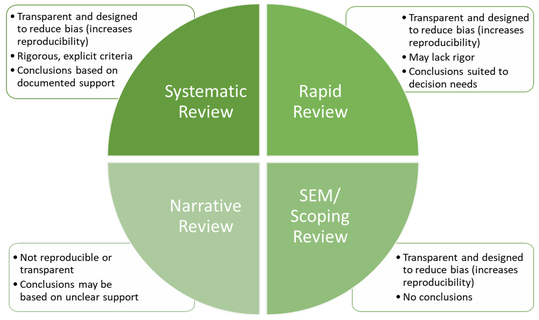

Fig. 1: Systematic methods improve on aspects of traditional narrative reviews

SEMs are gaining visibility in environmental health for their utility to serve as scoping and problem formulation tools. SEMs do not seek to synthesize evidence (or draw assessment conclusions). Rather, these decision tools catalogue evidence, utilizing systematic search and selection strategies to produce searchable databases of studies along with detailed descriptive information (see Figure 2). The workflows, tools, and visualizations being used to develop SEMs are flexible to allow the decision-maker to optimize the streamlined development of SEMs for different decision contexts and audiences. Thus, SEMs are optimized for assessment-relevant purposes such as prioritization, scoping of resource needs, and identification of key areas of scientific complexity and current research gaps. SEMs provide a transparent and highly visual snapshot of the current decision-relevant information; they can be rapidly developed using web-based resources; and they serve as a detailed source of information for deciding if a chemical health assessment can and should be initiated. To highlight the increasing utility of SEMs in chemical health assessment scoping and prioritization decisions, preliminary materials related to the ongoing application of SEMs to scoping and problem formulation decisions being developed for a group of approximately 150 per- and poly-fluoroalkyl substances (PFAS) are discussed.

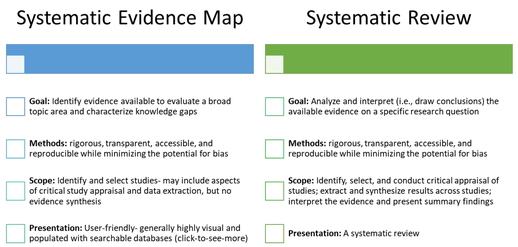

Fig. 2: Systematic evidence maps (SEMs) apply systematic methods to the front end of the process for developing systematic reviews to characterize the available evidence.

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Tiered Toxicity Testing: the PFAS "150"

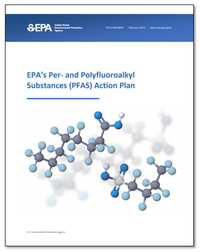

Fig. 3: EPA PFAS Action Plan

The 2019 EPA PFAS Action Plan (Figure 3) outlines a multimedia, multi-program, national research plan to address the challenge of PFAS (https://www.epa.gov/pfas/epas-pfas-action-plan). One component of this strategy involves the use of new approach methods to help fill information gaps. This ongoing work involves tiered toxicity testing of a structurally diverse landscape of procurable PFAS using a suite of in vitro toxicity and toxicokinetic assays (https://www.epa.gov/chemical-research/pfas-chemical-lists-and-tiered-testing-methods-descriptions). The workflow for selecting a representative set of PFAS for testing is outlined by Patlewicz et al. (Figures 4 and 5); https://ehp.niehs.nih.gov/doi/pdf/10.1289/EHP4555).

Fig. 4: Strategy for Prioritizing PFAS

A total of 75 PFAS were initially selected for in vitro toxicity and toxicokinetic testing based on interest to the EPA, compounds within targeted structural categories, structural diversity, exposure considerations, procurability and testability, and availability of existing in vivo toxicity data. An additional 75 PFAS were added to the screening effort at a later date using similar selection considerations.

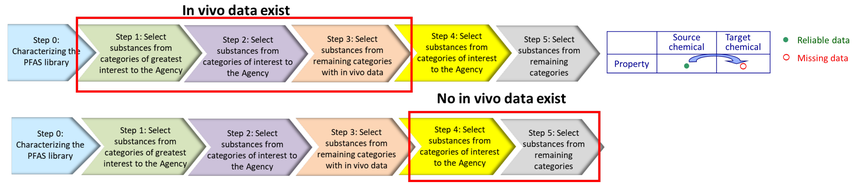

Fig. 5: The top panel illustrates one goal is to use of information for "PFAS source substances" with existing toxicity data to infer (read-across) missing information for a similar PFAS target (similarity starting point is "structural similarity"). A second goal (bottom panel) is to characterize the biological activity of the PFAS landscape that comprises substances of current interest to the Agency, as well as the landscape beyond PFAS of current interest.

- **The ~150 PFAS being tested exist as 2 lists on the EPA CompTox Chemicals dashboard:**
  https://comptox.epa.gov/dashboard/chemical_lists/epapfas75s1
  https://comptox.epa.gov/dashboard/chemical_lists/EPAPFAS75S2
- **The chemical library of 430 unique, DMSO-solubilized PFAS assembled for chemical screening, analytical method development, and other research needs is available at:**
  https://comptox.epa.gov/dashboard/chemical_lists/EPAPFASINV

SEMs for the PFAS "150" are being developed in parallel to support the tiered toxicity testing

SEMs for the PFAS "150"

Fig. 6: PFAS 150 Literature Inventory Screening- Tableau Dashboard of Toxicological Studies
Links to interactive figures are available at: https://public.tableau.com/views/PFAS-150EvidenceMapVisualizations/AnimalStudies?:display_count=y&:origin=viz_share_link
Interactive Features:
- Ability to 'filter' all visuals by clicking any item in any visual on the dashboard
- Additional information can be shown in tooltips when users hover over certain features
- Clickable HERO links for each reference
- Downloadable

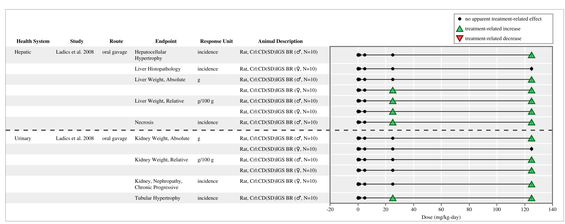

Fig. 7: PFAS 150 Pilot Extraction Exposure-Response Array for 8:2 Fluorotelomer Alcohol Exposure
Links to interactive figures will be made available at: https://hawcprd.epa.gov/
Interactive Features:
- Additional information on methods and results revealed when users click on features in visuals
- Study appraisals in progress
- Downloadable and linked to BMD software
- Results will be made available in the EPA CompTox Chemicals Dashboard

Illustration of SEM Content (PFHpA)

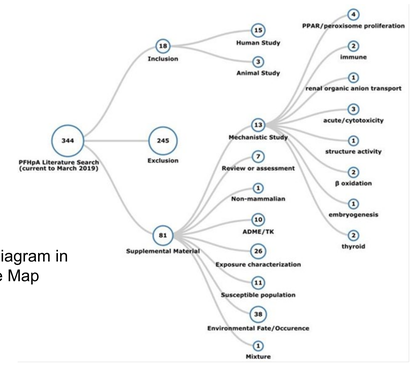

Fig. 8: Study Flow Diagram in PFHpA Evidence Map

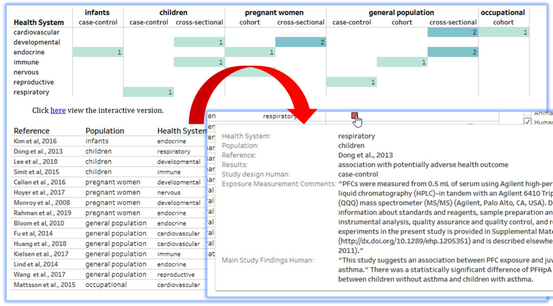

Fig. 9: Literature Inventory in PFHpA Evidence Map

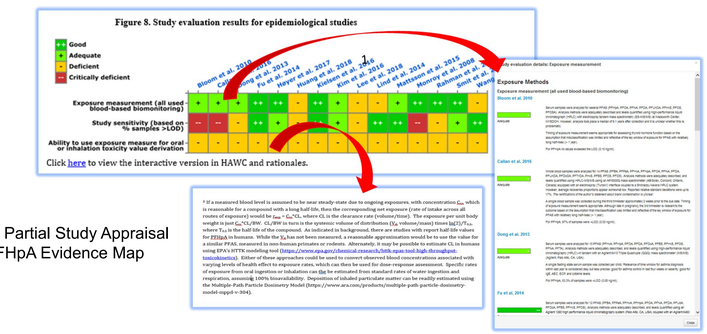

Fig. 10: Partial Study Appraisal in PFHpA Evidence Map

Summary

SEMs represent a useful tool for the rapid development of scoping and prioritization documents in support of chemical health assessments and other environmental health decision needs. Once workflows for their development have been optimized, SEMs do not require significant resources. For example, for the ongoing project illustrated above, using specialized web-based collaborative systematic review software tools, the PFHpA evidence map took approximately 10 work-day person-hours (across a team of EPA staff) to develop, while the literature screening and inventory (including initial data extraction and visualization efforts) for the PFAS "150" required less than 40 work-day person-hours (again, across a team of contributors). Once the data are extracted into the flexible software tools used to develop SEMs, both the developer and the end user have access to numerous presentation formats to visualize the extracted, publicly accessible information at different levels of granularity and organization. As illustrated using the PFAS "150" example, these rapidly produced, modular documents provide users with a highly visual summary of the available evidence relevant to a potential chemical assessment to support a wide range of decision contexts.