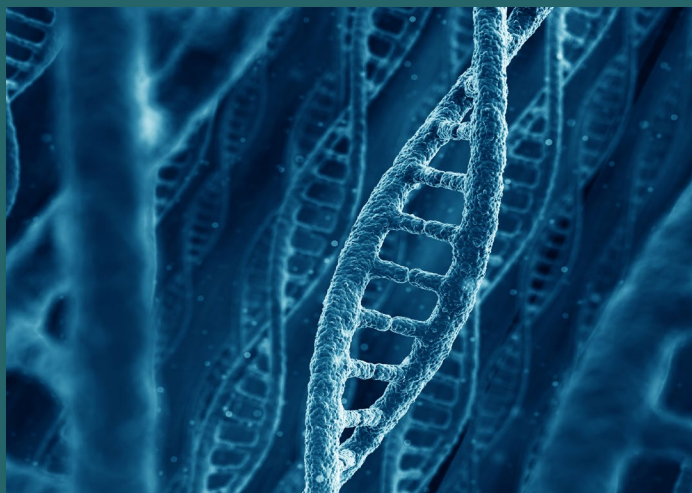


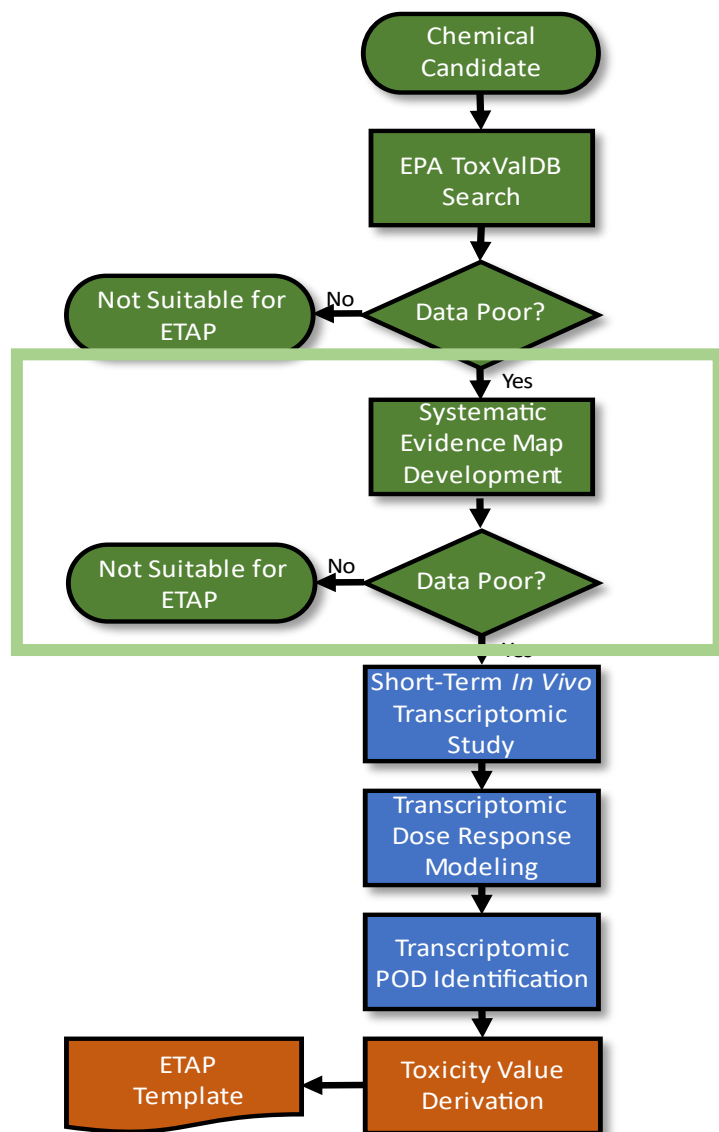
# Database Search and Systematic Evidence Map (SEM)

Avanti Shirke, MPH – Biologist



*The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA*

# Outline



- Systematic evidence map (SEM) overview
- Use of SEMs in context of ETAP
- Specific methods
  - Search strategy
  - Information sources
  - Screening processes
  - Dissemination

# Systematic Evidence Map

- Pre-decisional analysis that uses systematic review methods to compile and summarize evidence but does not reach assessment hazard or toxicity value conclusions
  - Front end compilation of evidence
- Used for:
  - Prioritization
  - Problem formulation and scoping
  - Identifying data gaps
  - Determining the need for assessment update

# Systematic Evidence Map Methods



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Environment International

journal homepage: [www.elsevier.com/locate/envint](https://www.elsevier.com/locate/envint)



Short communication

Use of systematic evidence maps within the US environmental protection agency (EPA) integrated risk information system (IRIS) program: Advancements to date and looking ahead

Kristina A. Thayer<sup>a,\*</sup>, Rachel M. Shaffer<sup>a</sup>, Michelle Angrish<sup>a</sup>, Xabier Arzuaga<sup>a</sup>, Laura M. Carlson<sup>b</sup>, Allen Davis<sup>a</sup>, Laura Dishaw<sup>a</sup>, Ingrid Druwe<sup>a</sup>, Catherine Gibbons<sup>a</sup>, Barbara Glenn<sup>a</sup>, Ryan Jones<sup>b</sup>, J. Phillip Kaiser<sup>a</sup>, Channa Keshava<sup>a</sup>, Nagalakshmi Keshava<sup>b</sup>, Andrew Kraft<sup>a</sup>, Lucina Lizarraga<sup>a</sup>, Kristan Markey<sup>a</sup>, Amanda Persad<sup>a</sup>, Elizabeth G Radke<sup>a</sup>, Glenn Rice<sup>a</sup>, Brittany Schulz<sup>c</sup>, Teresa Shannon<sup>a</sup>, Andrew Shapiro<sup>b</sup>, Shane Thacker<sup>b</sup>, Suryanarayana Vulimiri<sup>a</sup>, George Woodall<sup>b</sup>, Erin Yost<sup>a</sup>

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## ARTICLE INFO

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## ABSTRACT

Systematic evidence maps (SEMs) are increasingly used to inform decision-making and risk management priority-setting and to serve as problem formulation tools to refine the focus of questions that get addressed in

<https://doi.org/10.1016/j.envint.2022.107363>



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Environment International

journal homepage: [www.elsevier.com/locate/envint](https://www.elsevier.com/locate/envint)



Full length article

Systematic evidence map (SEM) template: Report format and methods used for the US EPA integrated risk information system (IRIS) program, provisional peer reviewed toxicity value (PPRTV) program, and other “fit for purpose” literature-based human health analyses

Kristina A. Thayer<sup>a,\*</sup>, Michelle Angrish<sup>a</sup>, Xabier Arzuaga<sup>a</sup>, Laura M. Carlson<sup>b</sup>, Allen Davis<sup>a</sup>, Laura Dishaw<sup>a</sup>, Ingrid Druwe<sup>a</sup>, Catherine Gibbons<sup>a</sup>, Barbara Glenn<sup>a</sup>, Ryan Jones<sup>b</sup>, J. Phillip Kaiser<sup>a</sup>, Channa Keshava<sup>a</sup>, Nagalakshmi Keshava<sup>a</sup>, Andrew Kraft<sup>a</sup>, Lucina Lizarraga<sup>a</sup>, Amanda Persad<sup>a</sup>, Elizabeth G. Radke<sup>a</sup>, Glenn Rice<sup>a</sup>, Brittany Schulz<sup>c</sup>, Rachel M. Shaffer<sup>a</sup>, Teresa Shannon<sup>a</sup>, Andrew Shapiro<sup>b</sup>, Shane Thacker<sup>b</sup>, Suryanarayana V. Vulimiri<sup>a</sup>, Antony J. Williams<sup>d</sup>, George Woodall<sup>b</sup>, Erin Yost<sup>a</sup>, Robyn Blain<sup>e</sup>, Katherine Duke<sup>e</sup>, Alexandra E. Goldstone<sup>e</sup>, Pam Hartman<sup>e</sup>, Kevin Hobbie<sup>e</sup>, Brandall Ingle<sup>e</sup>, Courtney Lemeris<sup>e</sup>, Cynthia Lin<sup>e</sup>, Alex Lindahl<sup>e</sup>, Kristen McKinley<sup>e</sup>, Parnian Soleymani<sup>e</sup>, Nicole Vetter<sup>e</sup>

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<https://doi.org/10.1016/j.envint.2022.107468>

# Use of SEMs for ETAP

- Assess availability of repeated dose animal toxicity data if no suitable studies are identified in EPA ToxVal database (ToxValDB)
  - ToxValDB collates publicly available toxicity dose–effect related summary values (e.g., REACH data submissions, ToxRefDB, IRIS, PPRTV)
  - ToxValDB may miss recent studies, assessments and pertinent reviews in open literature
- ETAP considered if no repeated dose toxicity studies are available
  - Other options also considered (viability of read-across analogue approach)

# Flow Chart

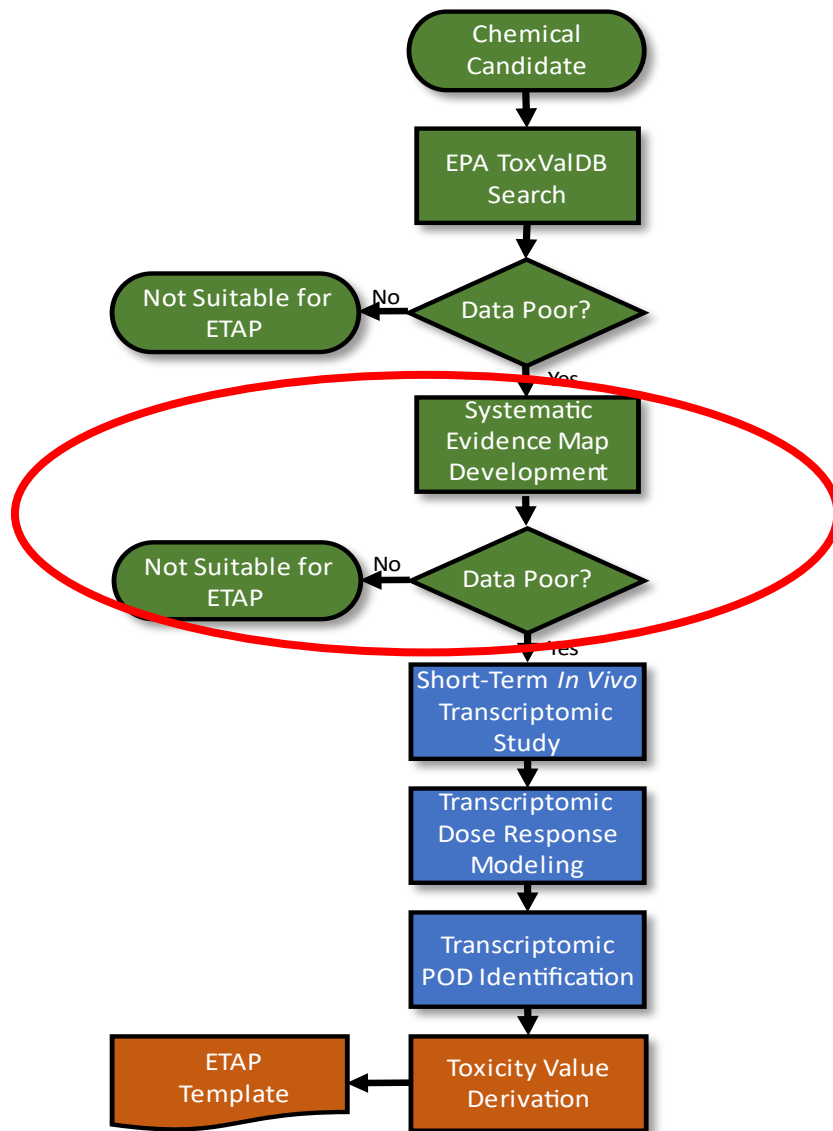


Figure 2-1 From Standard Methods for Development of EPA Transcriptomic Assessment Products (ETAPs)

# Search Strategy

- Literature search has no date or language restriction
- Preferred chemical name, CASRN, DTXSID, and synonyms used as foundation of search
  - Synonyms identified from CompTox Chemicals Dashboard indicated as “valid” or “good”
  - If number of records retrieved are few (i.e., <200), no further filtering undertaken
  - Otherwise, pre-set literature search strategies (“filters”) in SWIFT Review software used to identify human health content (i.e, human, animal models for human health, and *in vitro* studies).

CASRN = Chemical Abstracts Service Registry Number; DTXSID = Distributed Structure-Searchable Toxicity (DSSTox) database substance identifier

# Information Sources

- Database searches
  - PubMed
  - Web of Science
  - ProQuest
- Other resources (“grey literature”)
  - Manual review of reference lists in publicly available draft assessments or published journal articles
  - Manual review of reference list from studies meeting inclusion criteria
  - ECHA registration dossiers, EPA ChemView, NTP, OECD Chemicals Database and eChemPortal, EPA ECOTOX database
  - Searches of databases for Confidential Business Information (CBI)

ECHA= European Chemicals Agency; NTP = National Toxicology Program, OECD = Organisation for Economic Cooperation and Development



# Inclusion Criteria

PECO element	Evidence
<b>Populations</b>	<p><b>Human:</b> Any population and lifestage (occupational or general population, including children and other sensitive populations).</p> <p><b>Animal:</b> Non-human mammalian animal species (whole organism) of any lifestage (including fetal, early postnatal, adolescents and adults).</p>
<b>Exposures</b>	<p><b>Relevant forms:</b>            [substance X] (CAS number)            Other forms of [chemical X] that readily dissociate (<i>e.g.</i>, list any salts, etc.).            Known metabolites of interest, including metabolites used to estimate exposures to [chemical X].</p> <p><b>Human:</b> Any exposure to [chemical X] via [oral or inhalation] route[s]. Studies will also be included if biomarkers of exposure are evaluated (<i>e.g.</i>, measured chemical or metabolite levels in tissues or bodily fluids), but the exposure route is unclear or likely from multiple routes. Other exposure routes, such as those that are clearly dermal, are tracked during title and abstract screening and tagged as “potentially relevant supplemental material.”</p> <p><b>Animal:</b> Any exposure to [chemical X] via [oral or inhalation] route[s] of &gt;1 day duration, or any duration assessing exposure during reproduction or development. Studies involving exposures to mixtures will be included only if they include an experimental arm with exposure to [chemical X] alone. Other exposure routes, including [dermal or injection], are tracked during title and abstract as “potentially relevant supplemental material.”</p>
<b>Comparators</b>	<p><b>Human:</b> A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits), or exposure for shorter periods of time, or cases versus controls, or a repeated measures design. However, worker surveillance studies are considered to meet PECO criteria even if no statistical analyses using a referent group is presented. Case reports or case series of &gt; 3 people will be considered to meet PECO criteria, while case reports describing findings in 1–3 people will be tracked as “potentially relevant supplemental material.”</p> <p><b>Animal:</b> A concurrent control group exposed to vehicle-only and/or untreated control (control could be a baseline measurement, <i>e.g.</i>, acute toxicity studies of mortality, or a repeated measure design).</p>
<b>Outcomes</b>	<p>All health outcomes (cancer and non-cancer). In general, endpoints related to clinical diagnostic criteria, disease outcomes, biochemical, histopathological examination, or other apical/phenotypic outcomes are considered to meet PECO criteria.</p>

# Supplemental Material

Category (Tag)	Description
<b>Mechanistic endpoints</b>	Studies that do not meet PECO criteria but report measurements that inform the biological or chemical events associated with phenotypic effects related to a health outcome. Experimental design may include <i>in vitro</i> , <i>in vivo</i> (by various routes of exposure; includes all transgenic models), <i>ex vivo</i> , and <i>in silico</i> studies in mammalian and non-mammalian model systems. Studies using New Approach Methodologies (NAMs; <i>e.g.</i> , high throughput testing strategies, read-across applications) are also categorized here. Studies where the chemical is used as a laboratory reagent ( <i>e.g.</i> , as a chemical probe used to measure antibody response) generally should not be tagged.
<b>Classical pharmacokinetic (PK) or physiologically based pharmacokinetic (PBPK) model studies</b>	<p><b>Classical Pharmacokinetic or Dosimetry Model Studies:</b> Classical PK or dosimetry modeling usually divides the body into just one or two compartments, which are not specified by physiology, where movement of a chemical into, between, and out of the compartments is quantified empirically by fitting model parameters to ADME (absorption, distribution, metabolism, and excretion) data. This category is for papers that provide detailed descriptions of PK models but are not physiologically-based pharmacokinetic (PBPK) models. The data are typically the concentration time-course in blood or plasma after oral and/or intravenous exposure, but other exposure routes can be described.</p> <p><b>Physiologically Based Pharmacokinetic or Mechanistic Dosimetry Model Studies:</b> PBPK models represent the body as various compartments (<i>e.g.</i>, liver, lung, slowly perfused tissue, richly perfused tissue) to quantify the movement of chemicals or particles into and out of the body (compartments) by defined routes of exposure, metabolism, and excretion, and thereby estimate concentrations in blood or target tissues. A defining characteristic is that key parameters are determined from a substance's physicochemical parameters (<i>e.g.</i>, particle size and distribution, octanol-water partition coefficient) and physiological parameters (<i>e.g.</i>, ventilation rate, tissue volumes).</p>
<b>Pharmacokinetic (ADME)</b>	<p>Pharmacokinetic (ADME) studies are primarily controlled experiments, where defined exposures usually occur by intravenous, oral, inhalation, or dermal routes, and the concentration of particles, a chemical, or its metabolites in blood or serum, other body tissues, or excreta are then measured.</p> <p>These data are used to estimate the amount absorbed (A), distributed (D), metabolized (M), and/or excreted (E). ADME data can also be collected from human subjects who have had environmental or workplace exposures that are not quantified or fully defined. ADME data, especially metabolism and tissue partition coefficient information, can be generated using <i>in vitro</i> model systems.</p>
<b>Non-PECO animal model</b>	Studies reporting outcomes in animal models that meet the outcome criteria but do not meet the population criteria in the PECO (non-human mammalian models).

# Supplemental Material, continued

<b>Non-PECO route of exposure</b>	Epidemiological or animal studies that use a non-PECO route of exposure, <i>e.g.</i> , injection studies or dermal studies if the dermal route is not part of the exposure criteria.
<b>Susceptible populations</b>	Studies that help to identify potentially susceptible subgroups, including studies on the influence of intrinsic factors ( <i>e.g.</i> , sex, lifestage, or genotype) to toxicity, as well as some other factors ( <i>e.g.</i> , health status). These studies are often co-tagged with other supplemental material categories, such as mechanistic or ADME. Studies meeting PECO criteria that also address susceptibility should be co-tagged as supplemental.
<b>Human exposure and biomonitoring (no health outcome)</b>	Information regarding exposure monitoring methods and reporting that are unrelated to health outcomes, but which provide information on the following: methods for measuring human exposure, biomonitoring ( <i>e.g.</i> , detection of chemical in blood, urine, hair), defining exposure sources, or modeled estimates of exposure ( <i>e.g.</i> , in occupational settings). Studies that compare exposure levels to a reference value, risk threshold or assessment points of departure are also included in this category.
<b>Mixture study</b>	Mixture studies use methods that do not allow investigation of the health effects of exposure to the chemical of interest by itself [ <i>e.g.</i> , animal studies that lack exposure to chemical of interest alone or epidemiology studies that do not evaluate associations of the chemical of interest with relevant health outcome(s)].
<b>Case reports or case series</b>	Human studies that present an investigation of a single exposed individual or group of $\leq 3$ subjects that describe health outcomes after exposure but lack a comparison group ( <i>i.e.</i> , do not meet the “C” in the PECO) and typically do not include reliable exposure estimates.
<b>Records with no original data</b>	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
<b>Posters or conference abstracts</b>	Records that do not contain sufficient documentation to support study evaluation and data extraction.

# Screening Process

- Each record reviewed independently by 2 screeners at title and abstract (TIAB) and full-text levels
  - PECO criteria guide screening decisions
  - Supplemental tagging can occur at TIAB or full-text levels
- Conflicts tracked for resolution
- TIAB screening
  - Include, exclude, or unclear
- “Include” or “unclear” records advance to full-text
- Specialized systematic review software used to save time and keep track of screening decisions

# Documentation

Search	Search Strategy	Date and Results
<b>WOS</b>	TS="2,2,3,3-Tetrafluoro-3-(trifluoromethoxy)propanoic acid" OR TS="377-73-1" OR TS="O=C(O)C(F)(F)C(F)(F)OC(F)(F)F" OR TS="Perfluoro-3-methoxypropanoic acid" OR TS="Perfluoro-4-oxapentanoic acid" OR TS="Propanoic acid, 2, 2, 3, 3- tetrafluoro-3- (trifluoromethoxy) -" OR TS="BRN 1795024" OR TS="Perfluoromethoxypropionic acid" OR TS="PERFLUORO PFMPA" OR TS="PF4OPeA" OR TS="PF-4O-PeA" OR TS="PFMOPrA" OR TS="PFMPA" OR TS="PFPE-2" OR TS="Propionic acid, 2,2,3,3-tetrafluoro-3-(trifluoromethoxy)-"	12/19/2022 5 results
<b>PubMed</b>	"2,2,3,3-Tetrafluoro-3-(trifluoromethoxy)propanoic acid"[tw] OR "377-73-1"[tw] OR "377-73-1"[rn] OR "O=C(O)C(F)(F)C(F)(F)OC(F)(F)F"[tw] OR "Perfluoro-3-methoxypropanoic acid"[tw] OR "Perfluoro-4-oxapentanoic acid"[tw] OR "Propanoic acid, 2, 2, 3, 3- tetrafluoro- 3- (trifluoromethoxy) -"[tw] OR "BRN 1795024"[tw] OR "Perfluoromethoxypropionic acid"[tw] OR "PERFLUORO PFMPA"[tw] OR "PF4OPeA"[tw] OR "PF-4O-PeA"[tw] OR "PFMOPrA"[tw] OR "PFMPA"[tw] OR "PFPE-2"[tw] OR "Propionic acid, 2,2,3,3-tetrafluoro-3-(trifluoromethoxy)-"[tw]	12/19/2022 4 results
<b>ProQuest</b>	ABSTRACT,TITLE("2,2,3,3-Tetrafluoro-3-(trifluoromethoxy)propanoic acid") OR ABSTRACT,TITLE("377-73-1") OR ABSTRACT,TITLE("O=C(O)C(F)(F)C(F)(F)OC(F)(F)F") OR ABSTRACT,TITLE("Perfluoro-3-methoxypropanoic acid") OR ABSTRACT,TITLE("Perfluoro-4-oxapentanoic acid") OR ABSTRACT,TITLE("Propanoic acid, 2, 2, 3, 3- tetrafluoro- 3- (trifluoromethoxy) -") OR ABSTRACT,TITLE("BRN 1795024") OR ABSTRACT,TITLE("Perfluoromethoxypropionic acid") OR ABSTRACT,TITLE("PERFLUORO PFMPA") OR ABSTRACT,TITLE("PF4OPeA") OR ABSTRACT,TITLE("PF-4O-PeA") OR ABSTRACT,TITLE("PFMOPrA") OR ABSTRACT,TITLE("PFMPA") OR ABSTRACT,TITLE("PFPE-2") OR ABSTRACT,TITLE("Propionic acid, 2,2,3,3-tetrafluoro-3-(trifluoromethoxy)-")	12/19/2022 3 results
<b>Total unique references found</b>		<b>5</b>

Appendix 1 From EPA Transcriptomic Assessment Product (ETAP) for Perfluoro-3-Methoxypropanoic Acid

# Dissemination

The five unique references identified for perfluoro-3-methoxypropanoic acid are:

1. Miller, KE; Strynar, MJ. (2022). Improved Tandem Mass Spectrometry Detection and Resolution of Low Molecular Weight Perfluoroalkyl Ether Carboxylic Acid Isomers Environmental Science & Technology Letters 9:747-751. <http://dx.doi.org/10.1021/acs.estlett.2c00509> HERO ID: 10584196
2. Wan, Y; Li, Z; Huang, Z; Hu, B; Lv, W; Zhang, C; San, H; Zhang, S. (2022). Wafer-Level Self-Packaging Design and Fabrication of MEMS Capacitive Pressure Sensors <http://dx.doi.org/10.3390/mi13050738> HERO ID: 10603997
3. Woodlief, T; Vance, S; Hu, Q; Dewitt, J. (2021). Immunotoxicity of per- and polyfluoroalkyl substances: Insights into short-chain PFAS exposure Toxics 9:100. <http://dx.doi.org/10.3390/toxics9050100> HERO ID: 9959537
4. Zhang, W; Cao, H; Liang, Y. (2021). Plant uptake and soil fractionation of five ether-PFAS in plant-soil systems Science of the Total Environment 771:144805. <http://dx.doi.org/10.1016/j.scitotenv.2020.144805> HERO ID: 9952516
5. Kometani, N; Kaneko, M; Morita, T; Yonezawa, Y. (2008). The formation of photolytic silver clusters in water/supercritical CO2 microemulsions Colloids and Surfaces A: Physicochemical and Engineering Aspects 321:301-307. <http://dx.doi.org/10.1016/j.colsurfa.2008.02.005> HERO ID: 5387167

# Dissemination, continued

## Health & Environmental Research Online (HERO)

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### Perfluoro-3-Methoxypropanoic Acid

5 References Were Found:

- Select All 5 References
- Show Only Selected References

1. Peer Reviewed Journal Article  
**Improved Tandem Mass Spectrometry Detection and Resolution of Low Molecular Weight Perfluoroalkyl Ether Carboxylic Acid Isomers**

Authors: Miller, KE; Strynar, MJ (2022) Environmental Science & Technology Letters 9:747-751. HERO ID: 10584196

Per- and polyfluoroalkyl substances (PFAS) are emerging contaminants widely used in a variety of industrial... [\[More\]](#)

[Details](#)

2. Journal Article  
**Wafer-Level Self-Packaging Design and Fabrication of MEMS Capacitive Pressure Sensors**

Authors: Wan, Y; Li, Z; Huang, Z; Hu, B; Lv, W; Zhang, C; San, H; Zhang, S (2022) HERO ID: 10603997

This paper reports a MEMS capacitive pressure sensor (CPS) based on the operating principle of touch... [\[More\]](#)

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Current View: All References For Perfluoro-3-Methoxypropanoic Acid; (sorted by publication year - descending)

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Search:

Publication Years:

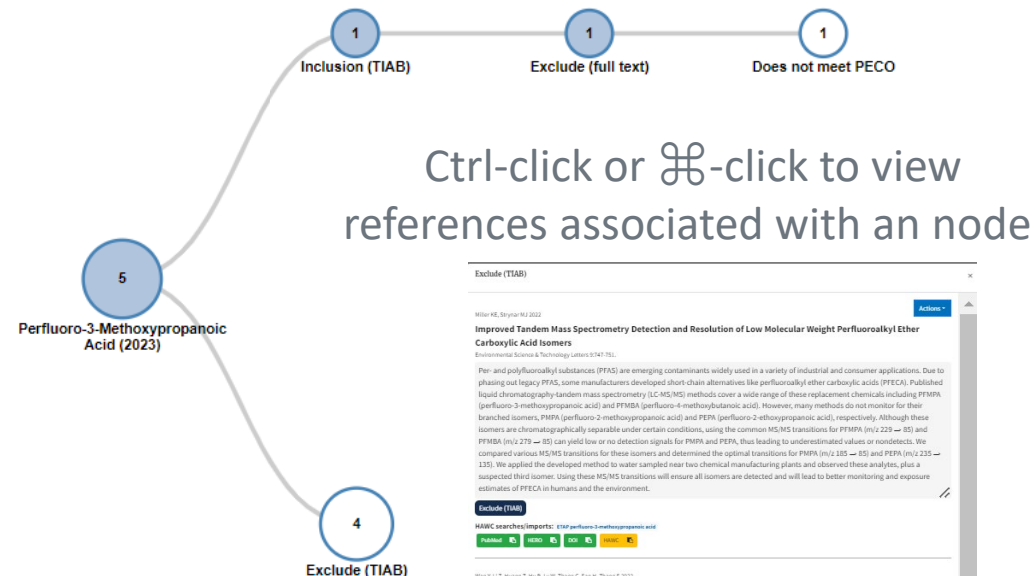
Return articles published in year

Or between years

Options:

Display references tagged with ANY

## Health Assessment Workspace Collaborative (HAWC)



Ctrl-click or ⌘-click to view references associated with an node

**Exclude (TIAB)**

Miller, KE, Strynar, MJ (2022)  
**Improved Tandem Mass Spectrometry Detection and Resolution of Low Molecular Weight Perfluoroalkyl Ether Carboxylic Acid Isomers**  
 Environmental Science & Technology Letters 9:747-751.

Per- and polyfluoroalkyl substances (PFAS) are emerging contaminants widely used in a variety of industrial and consumer applications. Due to phasing out legacy PFAS, some manufacturers developed short chain alternatives like perfluoroalkyl ether carboxylic acids (PFECA). Published liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods cover a wide range of these replacement chemicals including PFMPA (perfluoro-3-methoxypropanoic acid) and PFMDA (perfluoro-4-methoxybutanoic acid). However, many methods do not monitor for their branched isomers, PMPA (perfluoro-2-methoxypropanoic acid) and PEPFA (perfluoro-2-ethoxypropanoic acid), respectively. Although these isomers are chromatographically separable under certain conditions, using the common MS/MS transitions for PFMPA (m/z 229 → 85) and PFMDA (m/z 279 → 85) can yield low or no detection signals for PMPA and PEPFA, thus leading to under-estimated values or non-detects. We compared various MS/MS transitions for these isomers and determined the optimal transitions for PMPA (m/z 185 → 85) and PEPFA (m/z 235 → 135). We applied the developed method to water sampled near two chemical manufacturing plants and observed these analytes, plus a suspected third isomer. Using these MS/MS transitions will ensure all isomers are detected and will lead to better monitoring and exposure estimates of PFECA in humans and the environment.

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Wan Y, Li Z, Huang Z, Hu B, Lv W, Zhang C, San H, Zhang S (2022)  
**Wafer-Level Self-Packaging Design and Fabrication of MEMS Capacitive Pressure Sensors**

This paper reports a MEMS capacitive pressure sensor (CPS) based on the operating principle of touch mode. The CPS was designed and fabricated using wafer-level self-packaged MEMS processes. The variable capacitance sensing structure was vacuum-sealed in a cavity using the Si-glass anodic bonding technique, and the embedded Al feedthrough lines at the Si-glass interface were used to realize the electrical connections between the parallel plate electrodes and the electrode pads through Al vias. The optimal design of the CPS structure was performed to trade-off the performance and reliability using finite element simulation. The CPS based on a circular-shaped diaphragm with a radius of 2000 μm and a thickness of 40 μm exhibits good comprehensive performance with a sensitivity of 52.3 pF/MPa and a nonlinearity of 2.74e-5 in the pressure range of 100-500 kPa when the ambient temperature is less than 95 °C.

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Zhang W, Cao H, Liang Y (2022)  
**Plant uptake and soil fractionation of five ether-PFAS in plant-soil systems**  
 Science of the Total Environment 811:4460.

Considering the grave concerns caused by conventional per- and polyfluorinated substances (PFAS), production and use of fluoralkylether compounds (ether-PFAS) have been on the rise. These ether-PFAS are deemed as PFAS replacement chemicals. To understand distribution of ether-PFAS in plant-soil systems, we investigated plant uptake of five selected ether-PFAS (i.e., PFMOFA, PFMOBA, GenX, ADONA, F53B) by Carex comosa (longhair sedge) and the fractionation of these compounds in soil. Our results demonstrated that all five ether-PFAS in this study were taken up by C. comosa and translocated to plant shoots to different extents. Exposure concentration and time both positively affected plant uptake of ether-PFAS. Unlike the other four ether-PFAS, F53B with the longest carbon chain length and a sulfonic functional group was largely accumulated in C. comosa roots with limited translocation to plant shoots. Results from sequential extractions revealed that the five ether-PFAS had different distributions in soil with regard to extractable by water, basic methanol, acidic methanol and non-extractable. Concentration of ether-PFAS in water-soluble fraction increased with decreasing carbon chain length and higher values had a positive linear relationship with the mass of ether-PFAS in plant shoots (R<sup>2</sup> = 0.64) and in whole plants (R<sup>2</sup> = 0.94). Our results also indicated that the aging process could facilitate ether-PFAS to become non-extractable, hence reducing their mobility in soil and bioavailability to plants.

[https://hero.epa.gov/hero/index.cfm/project/page/project\\_id/4746](https://hero.epa.gov/hero/index.cfm/project/page/project_id/4746)

# Summary

- SEMs are a comprehensive approach to identifying data using systematic review methods.
- By using the SEM approach, we have a high degree of confidence that no data exist and ETAP is an appropriate next step.



# Questions?