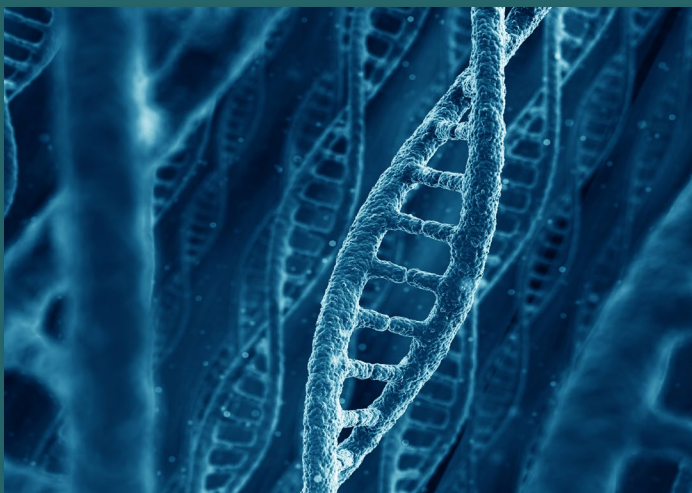


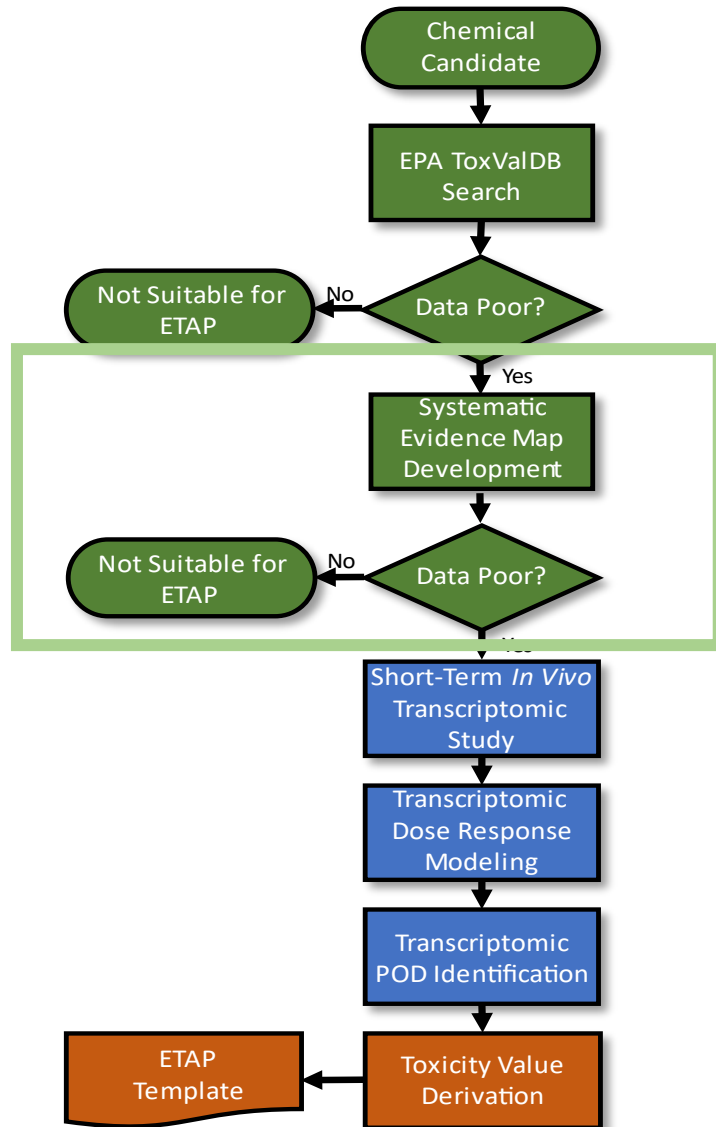
# Database Search and Systematic Evidence Map (SEM)

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*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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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

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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



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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.2022.107363>

<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 from ToxValDB or the SEM
  - Other options also considered (viability of read-across analogue approach)

# Flow Chart

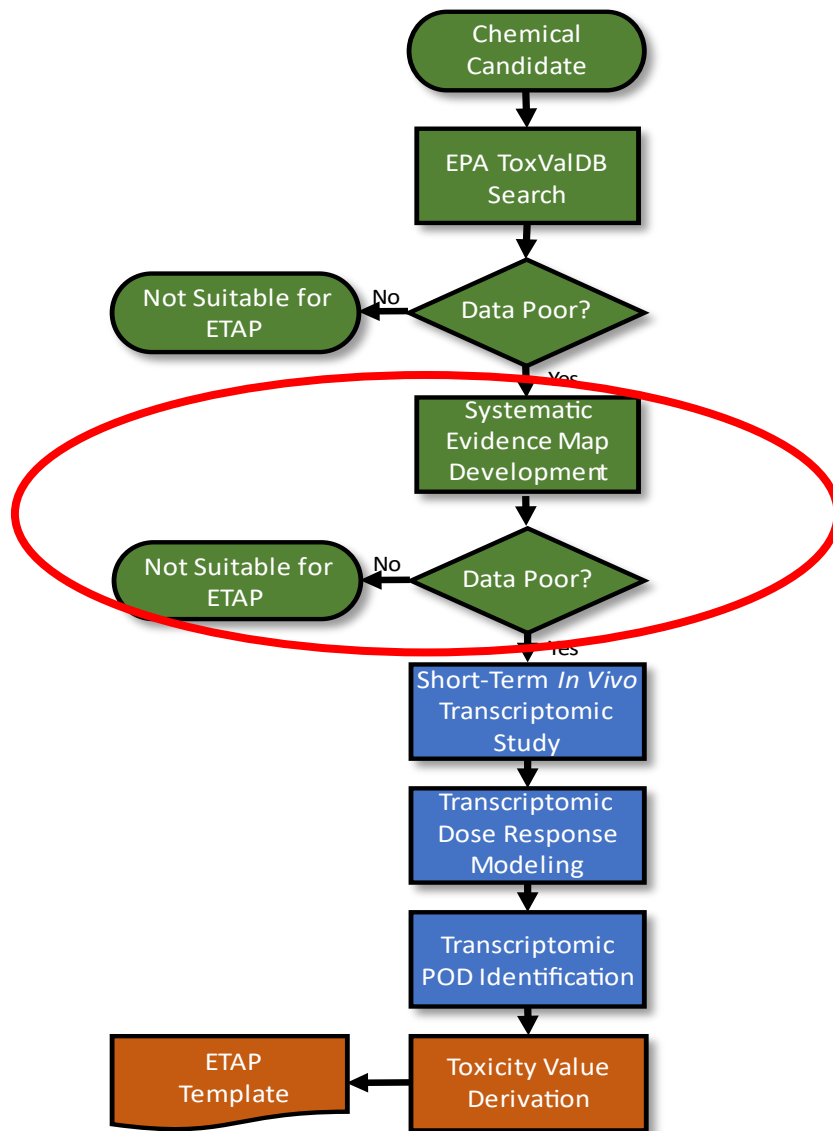


Figure 2-1 From Standard Methods for Development of EPA Transcriptomic Assessment Products (ETAPs)

# 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
  - 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>

# Screening Process

- Each record reviewed independently by 2 screeners at title and abstract (TIAB) and full-text levels
  - PECO criteria guide screening decisions
- 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

**Example:**  
**Perfluoro-3-Methoxypropanoic  
Acid (MOPA)**

# 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)

Export to File    Bibliography Format

### 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... [\[More\]](#)

#### Change View & Sort

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

Results: 5

Sort By: year desc

Publication Date - newest to oldest

Show 10 per page

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Show full text only    [Go](#)

#### Refine Search

[Reset](#)    [Update](#)

Search:

Publication Years:

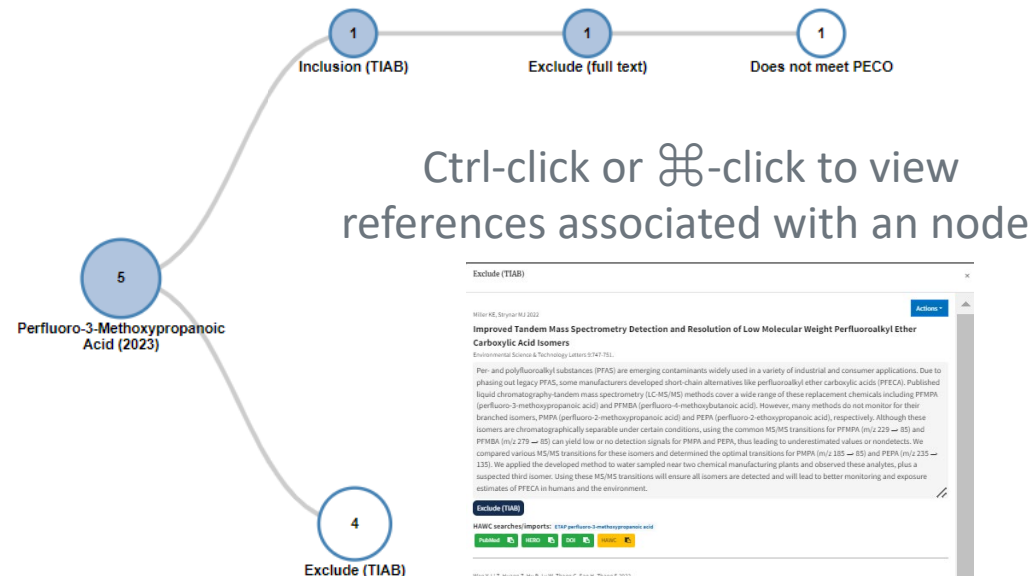
Return articles published in year

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 (PFEECA). Published liquid chromatography-random 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 PEPA (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 PEPA, thus leading to underestimated values or nondetects. We compared various MS/MS transitions for these isomers and determined the optimal transitions for PMPA (m/z 185 → 85) and PEPA (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 PFEECA in humans and the environment.

[Exclude \(TIAB\)](#)

HAWC search(es) import(s): [EPA perfluoro-3-methoxypropanoic acid](#)

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 45 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.

[Exclude \(TIAB\)](#)

HAWC search(es) import(s): [EPA perfluoro-3-methoxypropanoic acid](#)

Zhang W, Cao H, Liang Y 2022  
Plant uptake and soil fractionation of five ether-PFAS in plant-soil systems

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., PFMOPEA, PFMOBA, Geix, ADONA, F3SB) by Carex cornosa (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. cornosa 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, F3SB with the longest carbon chain length and a sulfonic functional group was largely accumulated in C. cornosa 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 logKow values and 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.