Fluoropolymers: State-of-the-science on Toxicity

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TSCA PFAS Toxicity Testing Meeting

Where Fluoropolymers Fit within the PFAS Family Tree

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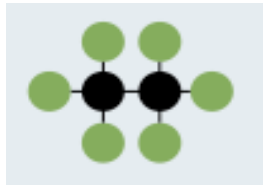
Fluorine
Carbon
Hydrogen

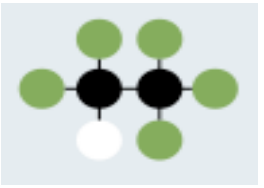
>100,000 Daltons, formed by repeating units of smaller fluorinated molecules

PFAS

< 1,000 Dalton

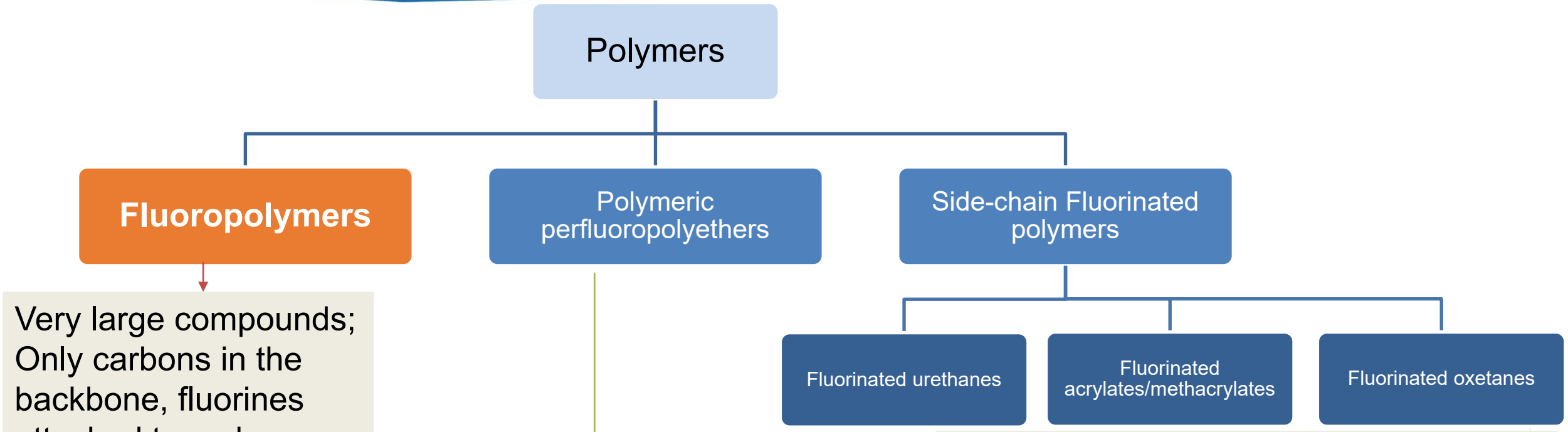
- Polymers
  - **Fluoropolymers**
  - Polymeric perfluoropolyethers
  - Side-chain Fluorinated polymers
- Nonpolymers
  - Perfluoroalkyl substances
  - Polyfluoroalkyl substances





Buck et al. 2011; Ameduri 2023

What are Fluoropolymers

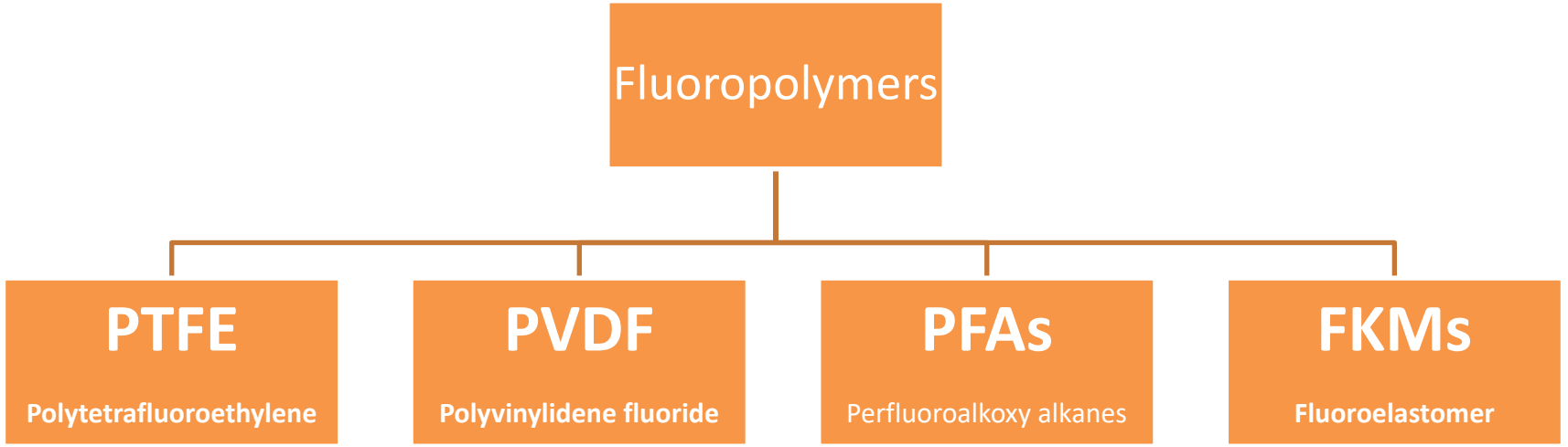


Very large compounds; Only carbons in the backbone, fluorines attached to carbon backbone; think of plastics

Carbon and oxygen backbone, fluorines attached to carbons in backbone; think of lubricants

Backbone does not have fluorines attached directly, instead, has side chains with carbons that have fluorines attached, may be precursors to PFAAs; think of surface protection products

Fluoropolymer (FP) Sub-Categories



- Fluoro-plastic
- Fully fluorinated
- Non-melt processible
- Homopolymers
- Modified polymers

- Fluoro-plastic
- Partially fluorinated
- Melt processible
- Homopolymers
- Copolymers

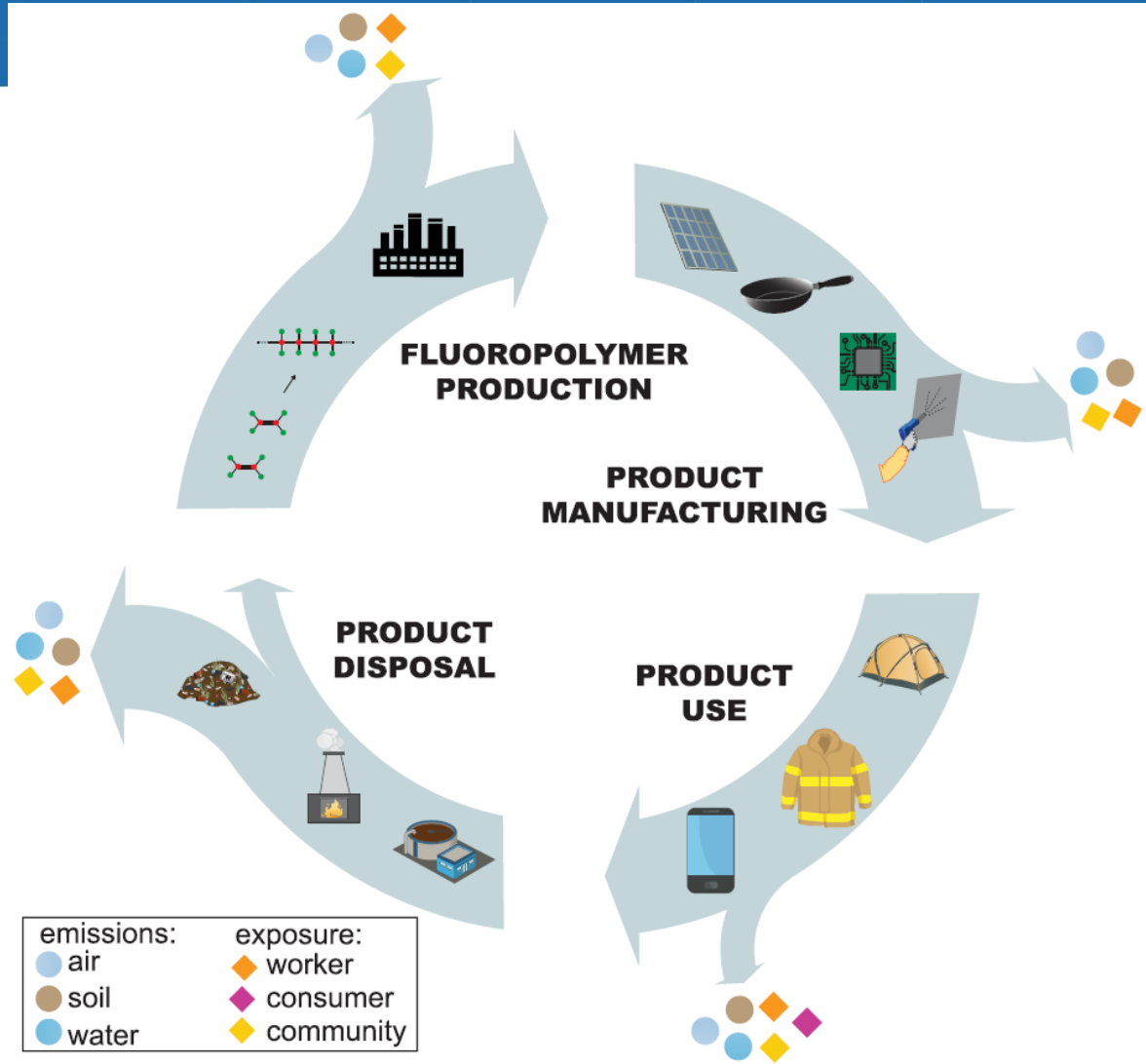
- Fluoro-plastic
- Fully fluorinated
- Melt processible
- Copolymers

- Fluoro-elastomer
- Fully fluorinated
- Melt processible
- Co- & terpolymers

Representative of almost all Fluoropolymers commercially produced

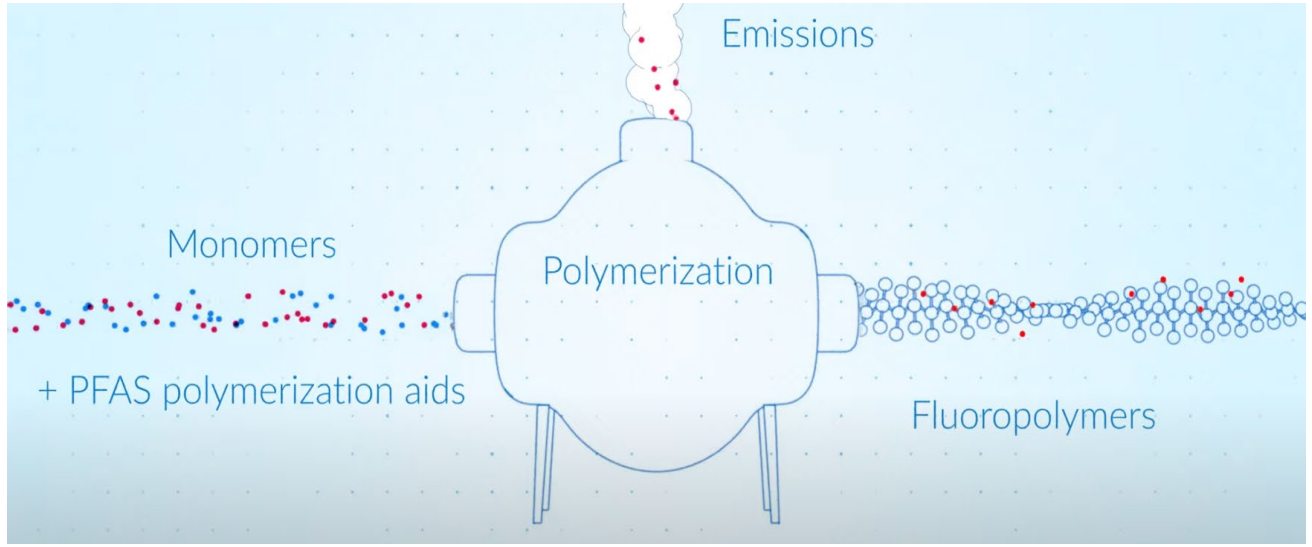
Common Concerns

- FP production using fluorosurfactant processing/ polymerization aids
- Release of processing/ polymerization aids or other monomers during product manufacturing
- Degradation or release of smaller molecules during product use
- End-of-life degradation or release of smaller molecules



Source: Figure 1 from Lohmann, R. et al., 2020. Are fluoropolymers really of low concern for human and environmental health and separate from other PFAS? Environmental Science & Technology, 54(20), pp.12820-12828.

Changes in Fluoropolymer Manufacturing Processes and Standards

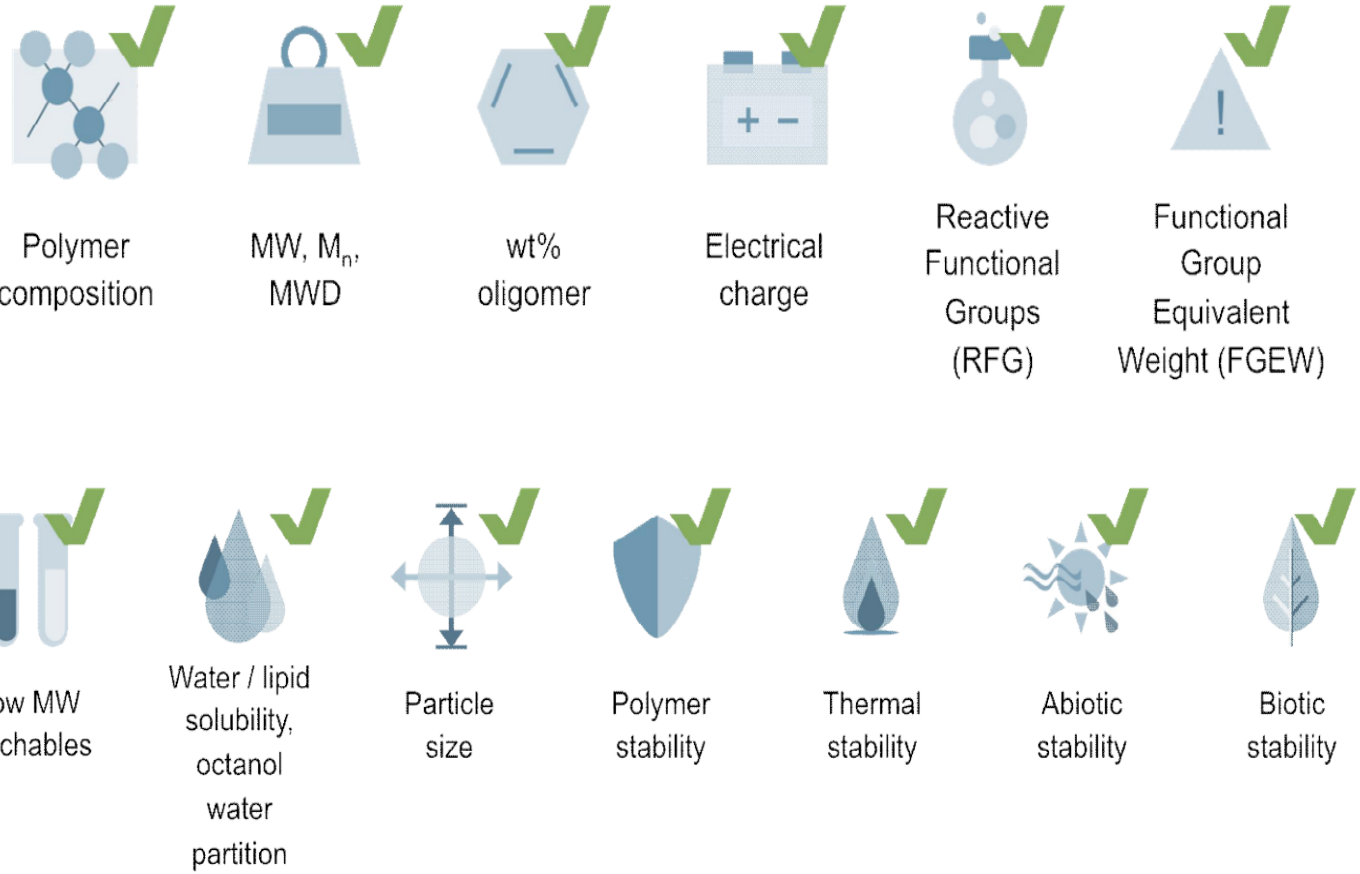


Source: Gujarat Fluorochemicals https://www.youtube.com/watch?v=UjHrMnf7olE

PFAS Polymerization Aids include:
PFOA
PFNA
GenX
Etc.

- Many FPs can now be manufactured without fluorosurfactant (Ameduri 2023) processing/polymerization aids
- Better process controls during manufacturing (Ameduri 2023)

OECD Polymers of Low Concern Criteria



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Critical Review

A Critical Review of the Application of Polymer of Low Concern and Regulatory Criteria to Fluoropolymers

Barbara J Henry,† Joseph P Carlin,† Jon A Hammerschmidt,† Robert C Buck,‡ L William Buxton,‡ Heidelore Fiedler,§ Jennifer Seed,‖ and Oscar Hernandez#*

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Critical Review

A critical review of the application of polymer of low concern regulatory criteria to fluoropolymers II: Fluoroplastics and fluoroelastomers

Stephen H. Korzeniowski,[1] Robert C. Buck,[2] Robin M. Newkold,[2] Ahmed El kassmi,[3] Evan Laganis,[3] Yasuhiko Matsuoka,[4] Bertrand Dinelli,[5] Severine Beauchet,[5] Frank Adamsky,[6] Karl Weilandt,[7] Vijay Kumar Soni,[8] Deepak Kapoor,[9] Priyanga Gunasekar,[9] Marco Malvasi,[10] Giulio Brinati,[10] and Stefana Musio[10]

Henry et al. 2018; Korzeniowski et al. 2022

What Data Exist Regarding FP Risk?

OECD Polymer of Low Concern Criteria

Not a Substance of Very High Concern if:

- High molecular weight
- No hazardous reactive groups or smaller molecules
- Non-mobile
- Insoluble in water
- Negligible oligomeric and leaching content
- Stable – thermally, chemically & biologically
- Durable
- Non-toxic
- Non-bio accumulative
- Non-bio available

What Supporting Data Are Available?

Bioavailable

- Can FP be taken up into the body?
  - Passive absorption
  - Active transport
  - Endocytosis

Toxic

- Exert an adverse effect on the function of an organ, organ system, or causes overall mortality or morbidity
- Dose and duration dependent

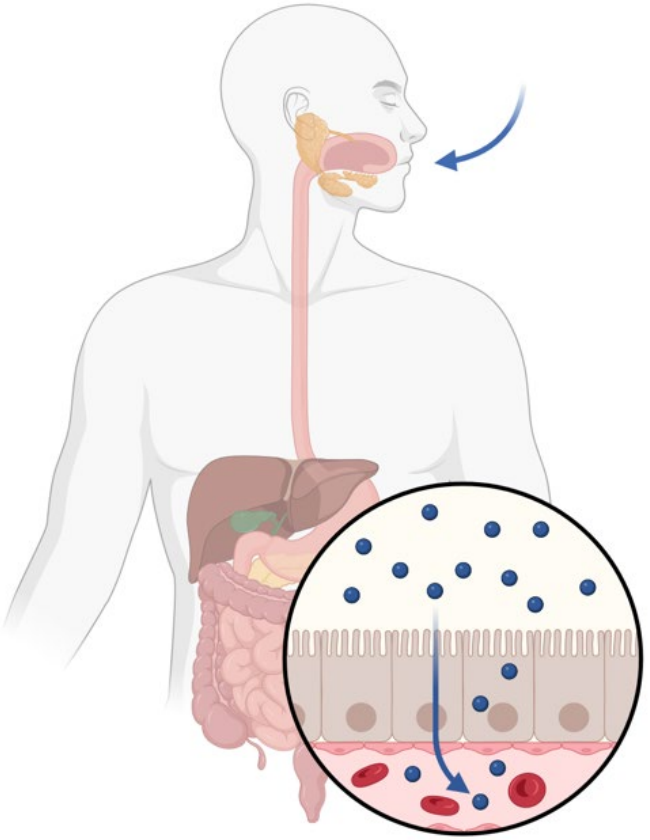
Bioaccumulative

- Rate of intake exceeds the rate of excretion
- Gradual accumulation of a chemical in an organism, such that internal levels are higher than external exposure

Existing Bioavailability Data

- PTFE – 4 week feeding study in mice, no detectable PTFE ~5 µm, and 10-50 µm in blood (Lee et al. 2022)

- Lee et al. conclude that physical/chemical characteristics suggest bioavailability unlikely
  - Large MW makes absorption unfeasible
  - Permeability cut-off of the human small intestine is MW of 80,000 Daltons
  - MW of FPs is ~50,000 - >1,000,000 Daltons



Cellular uptake of large MW polymers has been demonstrated (i.e., micro/nano plastics (MP/NP))

- Polystyrene MP found in human blood, stool, cirrhotic livers, placenta
- Some evidence of NP uptake by human gastrointestinal cells (e.g., Ding et al. 2021)
- Uptake hypothesized predominantly via endocytosis
- Highly dependent on:

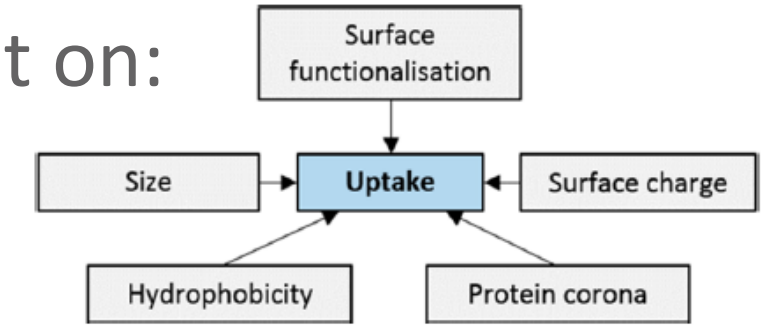


Figure 3. Particle characteristics predicted to influence micro- and nanoplastic uptake.

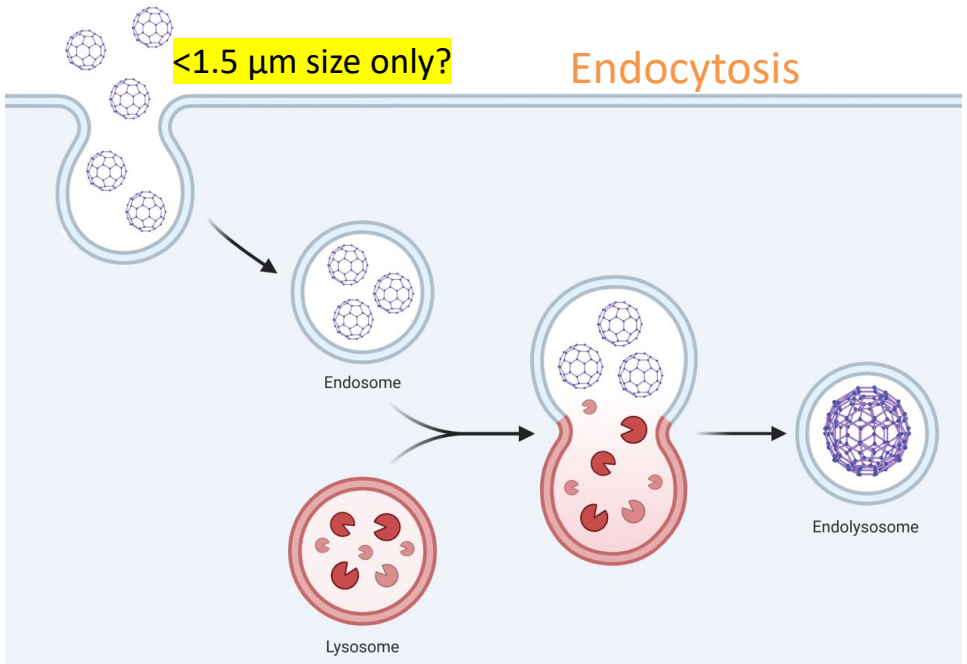


Image from BioRender

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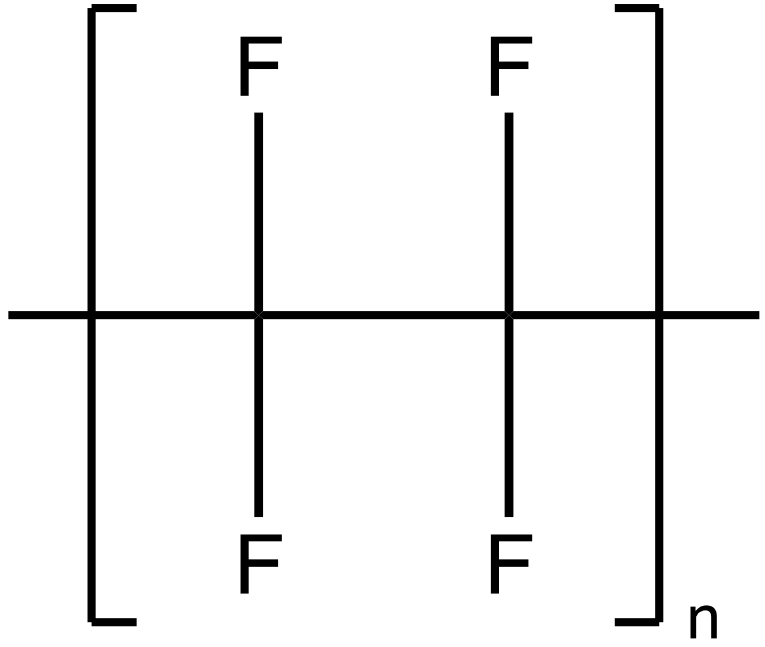
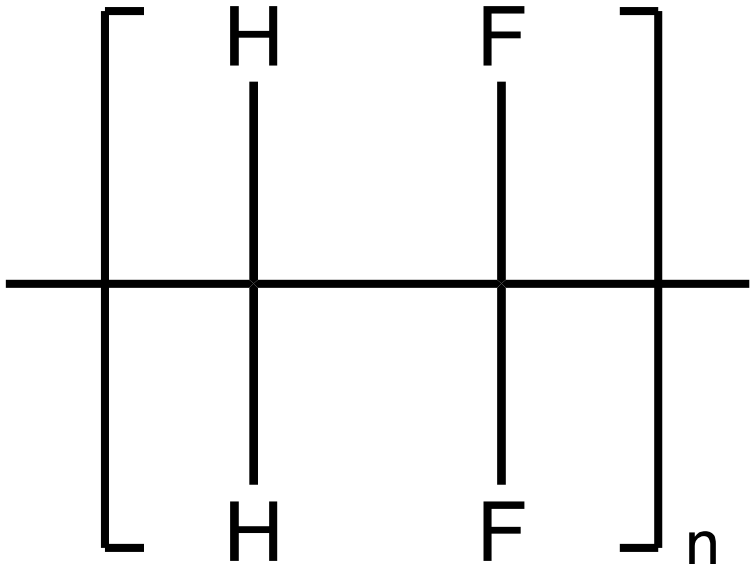
Existing Toxicity Data – PTFE
(CAS RN 9002-84-0)

PTFE

- Occupational guidelines
- Human Medical Literature (solid plastic state)
  - Example: Brand and Brand (1980) implants – chronic epi study, evaluated cancer risk
- Rat 90-day feeding studies (peer-reviewed but not publicly available; Naftalovich et a;/ 2016)
  - No observed adverse effects in rats exposed to up to 25% PTFE in the diet for up to 90 days
- Mouse 4-week feeding study (Lee et al. 2022)
  - Two sizes: ~5 µm, and 10-50 µm mixture
  - NO EFFECT at the highest dose of 2,000 mg/kg
- Industry MSDSs report no reproductive toxicity
- Negative for skin irritation tests



Existing Toxicity Data – PVDF
(CAS RN 24937-79-9)



homopolymer

Polyvinylidene Fluoride - Homopolymer

- Occupational guidelines
- IUCLID summary reports available only:
- Rat reproduction/developmental screen (OECD 422)
  - NO EFFECT at high dose tested of 1,000 mg/kg-day for systemic toxicity and reproductive parameters
- Not mutagenic or genotoxic

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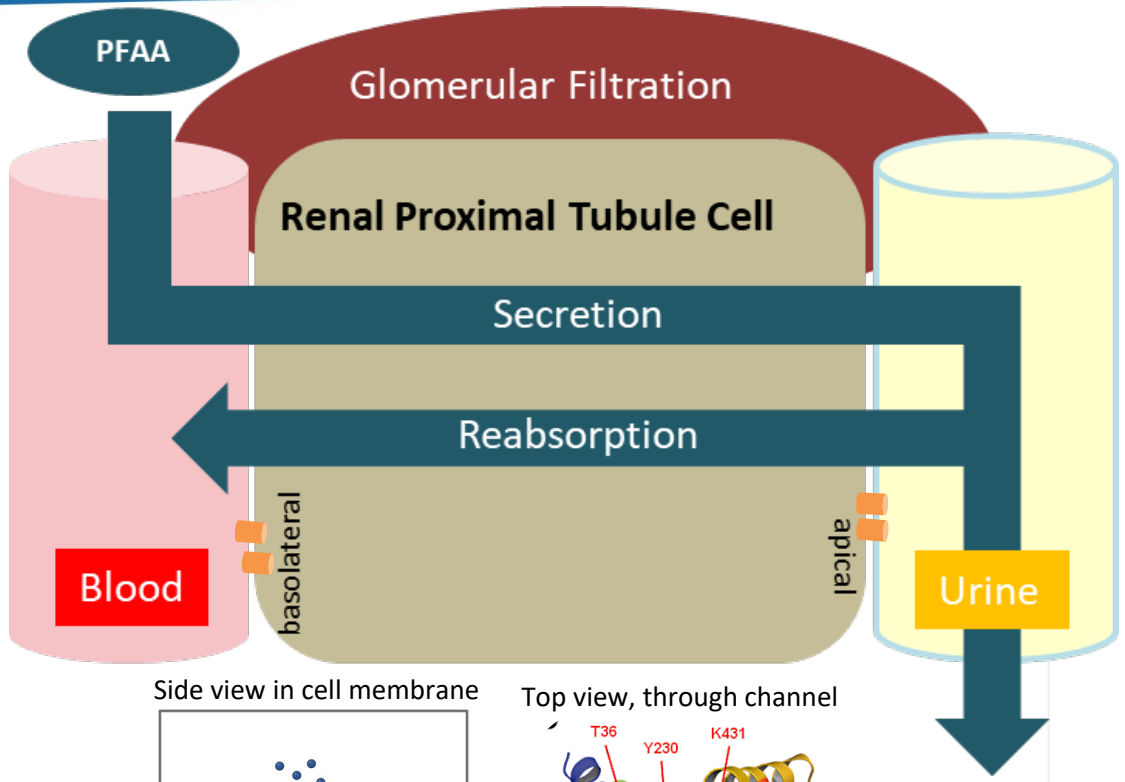
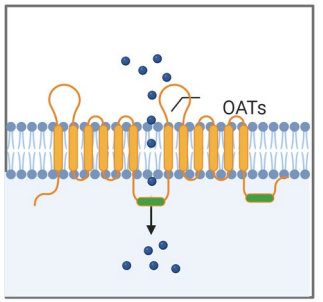
Existing Bioaccumulation Data

- To be bioaccumulative, a compound must be bioavailable
- Often, bioaccumulative compounds bind to internal proteins (e.g., PFOA and organic anion transporters (OATs) proteins in kidney, serum albumin)
- Size of FPs suggests this is unlikely
  - Human proteins =
    - Generally 5,000 – 600,000 Daltons; nm particle size range
  - Fluoropolymers =
    - 50,000 - >1,000,000 Daltons; 50-500 µm particle size

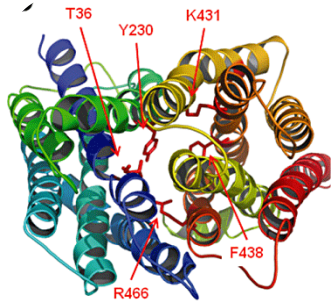


Side view in cell membrane



BioRender.com

Top view, through channel



Roth et al. (2011) British J Pharmacology, Volume: 165, Issue: 5, Pages: 1260-1287

Fluoropolymer Data Summary

Bioavailable

- Limited direct evidence suggests not bioavailable
- More data needed

Toxic

- Available data is limited, suggests non-toxic in subchronic exposure scenarios tested
- Data gaps on chronic exposure, cancer
- Complete data gaps for several FPs

Bioaccumulative

- Given large MW and insolubility in water, unlikely to bioaccumulate
- No studies have been conducted to directly assess bioaccumulation

Key Toxicological Questions Remain

1. Is there even exposure to Fluoropolymers in the environment?
2. Can Fluoropolymers get taken up into mammalian cells?
3. Does chronic exposure to Fluoropolymers result in any toxicity?

THANK YOU

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Science · Strategy · Solutions

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