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Review

Bird's-Eye View: Current Understanding and Future Perspectives on the Biodefluorination of Per- and Polyfluoroalkyl Substances (PFAS)

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ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) have been extensively used in various industrial and manufacturing processes. These compounds pose potential risks to public health and ecosystems because of their persistence, bioaccumulation potential, and toxicity. To date, great efforts have been made to investigate the biotransformation of PFAS, while little is known about their biodefluorination behavior. A comprehensive understanding of biodefluorination mechanisms can not only aid in revealing the environmental fate and effects of these fluorinated chemicals but also advance the design of alternative structures with reduced persistence and environmental impact. In this review, we (1) systematically reviewed the biodefluorination pathways and transformation products of PFAS, with particular emphasis on emerging PFAS, under both aerobic and anaerobic conditions, (2) summarized the responsible microorganisms and enzymes involved, (3) provided critical perspectives on the need to standardize the testing protocol and to generalize the biotransformation prediction approaches, and (4) highlighted the potential of benign-by-design strategies in developing degradable fluorinated alternatives.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) have attracted growing concerns due to their persistence to degradation, bioaccumulation, and toxicities to human and ecosystems (Evich et al., 2022).According to the 2021 OECD guideline, PFAS are fluorinated chemicals with at least one -CF_3 group or one -CF_2- group (without any H/Cl/Br/I attached to it), encompassing a family of over 10,000 synthetic chemicals (Wang et al., 2021). PFAS are highly resistant to various types of degradation, resulting in their long-lasting presence in the environment. Each year, millions of pounds of PFAS waste are generated in the United States, much of which is released into the environment due to the ineffectiveness of traditional treatment methods (EPA, 2020). Their potential for bioaccumulation and suspected toxicity in ecosystems have raised significant public concern (ATSDR, 2021).

Government agencies are taking legislative and regulatory actions to control the historically used PFAS. For instance, perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), the two most heavily used PFAS, have been phased out in commercial manufacturing in North America and Europe (EU, 2006; USEPA, 2022). Additionally, other PFAS including long-chain perfluoroalkyl acids and fluorotelomer alcohols, are also being considered for regulation (ATSDR, 2021). Such regulatory pressure drives manufacturers to develop alternative PFAS structures. These alternatives, with modified structures such as short chains, chlorine substitution, and branched chains, are designed to circumvent regulations targeting specific structures and now playing critical roles in industries and manufacturing. However, the remaining fluorinated carbons may still pose similar or even higher environmental risks (Wang et al., 2017). The definition of PFAS can vary across different studies. To avoid confusion, in this review, we define "legacy PFAS" as long-chain perfluoroalkyl acids (PFAAs) that have been phased out of production in many countries, while "emerging PFAS" refers to fluorinated compounds that are either used as replacements for legacy PFAS or have received comparatively less attention in previous review articles (Boettger et al., 2025; Lei et al., 2024; Munoz et al., 2019; Wang et al., 2013, 2017; Xiao, 2017).

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Innovative treatment technologies for PFAS are urgently needed to address their persistence and environmental risks. While physicochemical treatment of PFAS has been extensively investigated over the past decades (Bentel et al., 2019; Bruton and Sedlak, 2017; Glover et al., 2018; Hao et al., 2021; Wang et al., 2020; Yang et al., 2020), biological treatment technologies remain underdeveloped. The microbial cleavage of C-F bonds, which is a critical step in PFAS degradation, is inherently challenging due to the high bond dissociation energy (Yu et al., 2020; Yue et al., 2021). Additionally, the potential toxicity of PFAS and their transformation products (e.g., fluoride ions) complicates the development of effective biological solutions (Jeong et al., 2023; Stockbridge and Wackett, 2024; Wackett, 2022).

Significant efforts have been made to investigate the biotransformation of PFAS using either pure isolates or microbial communities. Remarkable reviews on PFAS biotransformation have been published over the past decade. Liu et al. summarized the biotransformation of various PFAS structures, including fluorotelomer-based PFAS and perfluoroalkane sulfonamido derivatives, and outlined methodologies forconducting PFAS biotransformation experiments (Liu and Avendaño, 2013). Zhang et al. examined the bacterial and fungal degradation of PFAS such as PFOS, PFOA, fluorotelomer alcohols (FTOHs), and fluorotelomer alkylamines (FTAAs), categorizing these reactions based on the presence or absence of C-F bond cleavage (Zhang et al., 2022). Berhanu and colleagues provided a review of microbial species, routes, and enzymes involved in PFAS biotransformation (Berhanu et al., 2022). Choi et al. focused on the biotransformation of AFFF-derived polyfluoroalkyl substances (Choi et al., 2022).

While these reviews have laid a strong foundation for understanding PFAS biotransformation, they primarily focus on legacy PFAS and their precursors, and in many cases, defluorination pathways are not well addressed. Recent discoveries involving emerging PFAS structures (i.e., short chain PFAS, ether PFAS, unsaturated per- and polyfluorinated carboxylic acids, polyfluorinated aromatic compounds, and chlorinated PFAS) have not been adequately covered. Although the exact applications of many emerging PFAS are not fully disclosed due to proprietary or confidential business information, they are often used as alternatives to legacy PFAS or as intermediates in manufacturing processes, and in some cases, are formed as byproducts. Therefore, a systematic review is needed to consolidate this information, guide future research efforts, and support a more coherent understanding of PFAS biotransformation. This mini-review aims to zoom in on this specific and underexplored aspect of PFAS research and to: (1) provide a timely discussion of recently discovered biodefluorination mechanisms for emerging PFAS (Table 1); (2) offer the first comprehensive summary of PFAS biodefluorination pathways; (3) provide critical perspectives on the need to standardize testing protocols and develop generalized biotransformation prediction framework; and (4) highlight the potential of benign-by-design strategies for developing future ready-to-be-biotransformed fluorinated alternatives.

2. Aerobic biodefluorination of PFAS

To the best of our knowledge, no aerobic biodefluorination has been reported for any perfluorinated compounds with solid evidence mapping the defluorination products with the released fluoride ion thus far (Liou et al., 2010; Ochoa-Herrera et al., 2016; Sáez et al., 2008). It supports the hypothesis that aerobic defluorination requires a carbon-hydrogen bond at the alpha carbon position for the initial enzymatic reaction (Key et al., 1998). Aerobic PFAS biotransformation was documented on 5:3 polyfluorinated carboxylic acid (PFCA) and n:2 FTOH, and fluorine removal could be inferred from the generation of chain-shortening perfluorinated acids (Dinglasan et al., 2004; Liu et al., 2007; Wang et al., 2012). In the last decade, biodefluorination of polyfluorinated structures has been reported by several microbial communities and pure cultures (Che et al., 2021; Jin et al., 2023b; Kim et al., 2012; Lewis et al., 2016; Mothersole et al., 2024; Yu et al., 2022b). Fluoride quantification in these studies provides critical evidence for defluorination and, together with the identification of biotransformation products, facilitate the understanding of the underlying mechanism. These findings underscore the significance of specific structural requirements for the microbial biotransformation of PFAS under aerobic conditions. With the understanding the biodefluorination pathways and enzymes, we could advance the design of biodegradable fluorinated chemicals and the development of biological PFAS remediation technologies.

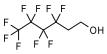
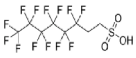
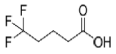
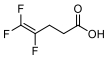
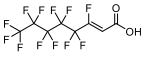
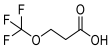
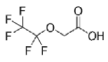
2.1. Fluorotelomer structures

One carbon removal pathway was proposed for 5:3 fluorotelomer carboxylic acid (FTCA), in which defluorination occurred through HF elimination and HF exchange following decarboxylation (Wang et al., 2012). Fluorine removal could be inferred from the formation of 4:3 FTCA, 3:3 FTCA, perfluoropentanoic acid (PFPeA), and perfluorobutanoic acid (PFBA), while fluoride released was not quantified in this study. 4:2 FTOH was documented to have 37 % defluorination by *P. butanovora* (Kim et al., 2012), and 14 % defluorination was achieved by *Dietzia aurantiaca* J3, forming 3:3 FTCA and 3:3 FTUCA as defluorination products possibly via HF elimination and HF exchange (Bhardwaj et al., 2024). 6:2 fluorotelomer alcohol could be transformed to 6:2 fluorotelomer unsaturated carboxylic acid (FTUCA) through oxidation and HF elimination (Fig. S1a). And 6:2 FTUCA could be transformed to 5:2 ketone, forming perfluorohexanoic acid (PFHxA), PFBA and PFPeA as terminal products. Another defluorination pathway was also revealed where 5:3 FTCA was transformed from 6:2 FTUCA, and generating shorter chain FTCA, FTUCA and PFCA as end products (Kim et al., 2012; Lewis et al., 2016). 6:2 FTCA was reported to be defluorinated by activated sludge to detach at most 2 fluorine from the molecule through same HF elimination and HF exchange reactions as 6:2 FTOH (Fig. S1), and the theoretical fluoride release amounts based on all detected target TPs were only 77 % of released fluoride at most, suggesting unknown defluorination pathway other than one carbon removal pathway (Wu et al., 2024).

Beta-oxidation-like pathways (Fig. 1) were proposed for biodefluorination of short-chain PFAS by aerobic sludge communities according to parent compound removal, transformation product identification, as well as fluoride release (Che et al., 2021). The activation of short-chain PFAS by adding coenzyme A to the molecules initiates biotransformation (Che et al., 2021; Mothersole et al., 2023), followed by beta-oxidation, which shortened the carbon chain for the polyfluorinated compounds. Fluorine on the terminal carbon was removed through oxidative HF elimination and hydrolytic defluorination (Fig. 1a). 3,3,3-trifluoropropanoic acid (3,3,3- TFPA) was almost completely defluorinated (Fig. 1b), while other selected 3-carbon fluorinated carboxylic acids had much less or no defluorination, which possibly resulted from the different degree of fluorine substitution at alpha carbon (Che et al., 2021). 5,5,5-trifluoropentanoic acid was expected to be completely defluorinated based on proposed pathway, however, only 37 % defluorination was also observed, which was likely attributed to non-defluorinating pathways carried out by activated sludge (Fig. 1c). 1:5, 2:4 and 3:3 FTCA could be transformed into FTCA-CoAs by long-chain acyl CoA synthetase obtained from *Gordonia* sp. strain NB4−1Y, supporting the proposed β-oxidation like defluorination pathway which was initiated by CoA activation (Mothersole et al., 2024).

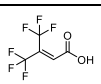
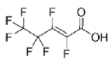
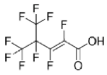
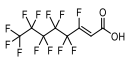
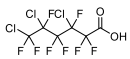
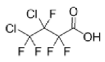
6:2 fluorotelomer sulfonate (FTS) could be aerobically transformed to shorter chain fluorinated carboxylic acid by *Dietzia aurantiaca J3* when fed as the sole sulfur source (Méndez et al., 2022). Similar with the FTOH defluorination pathway, 6:2 FTCA and 6:2 FTUCA are major breakdown products generated from desulfonation and HF elimination, and 4:3 FTCA and PFHpA were produced as deeper defluorination products (Fig. S1b). In total, 2.86 fluoride was released per molecule of 6:2 FTS. Biodefluorination of 6:2 FTS was also reported by *Rhodococcus*

Table 1
Reported degradation of PFAS with significant (>5 %) defluorination. Defluorination degree (%) = released fluoride ion/ (removed PFAS × amount of fluorine per molecule) × 100 %. (*: Incubation time may vary depending on the inoculum used).

Aerobic Condition								
Compound Name	Chemical Formula	Structure	Defluorinating Microorganism(s)/ Community	Maximum Defluorination Degree (%)	Maximum Parent Compound Removal (%)	Test Duration (days)	Reference	Proposed Major Defluorination Pathway
4:2 fluorotelmer alcohol	$C_6H_5F_9O$		*D. aurantiaca J3; P. oleovorans; P. butanovora*	37 %	74 %	4	Bhardwaj et al., 2024; Kim et al., 2012	HF exchange, HF elimination
6:2 fluorotelmer alcohol	$C_8H_5F_{13}O$		*D. aurantiaca J3; P. oleovorans; P. butanovora; augmented Activated sludge*	30 %	100 %	7	Bhardwaj et al., 2024; Lewis et al., 2016; Kim et al., 2012	HF exchange, HF elimination
α,α,α-Trifluorotoluene	$C_7H_5F_3$		*Pseudomonas putida F1*	5 %	N.A.	overnight	Bygd et al., 2022	HF elimination followed by hydrolytic defluorination ($+OH^-$, $-H^+$ $-F^-$)
6:2 fluorotelomer sulfonate	$C_8H_5F_3O_3S$		*Dietzia aurantiaca J3; Rhodococcus jostii RHA1;Gordonia* sp. *NB4–1Y*	22 %	100 %	7	Méndez et al., 2022; Yang et al., 2022; Shaw et al., 2019; Van Hamme et al., 2013	HF elimination following desulfonation
3,3,3-trifluoropropionic acid	$C_3H_3F_3O_2$		Activated sludge	85 %	100 %	3	Che et al., 2021	HF elimination followed by hydrolytic defluorination ($+OH^-$, $-H^+$ $-F^-$)
5,5,5-trifluoropentanoic acid	$C_5H_7F_3O_2$		Activated sludge	37 %	100 %	3	Che et al., 2021	HF elimination and hydrolytic defluorination (+OH-, $-H$+ -F-) following beta-oxidation
6:2 Fluorotelomer carboxylic acid	$C_8H_3F_{13}O_2$		Activated sludge	15 %	43 %	7	Wu et al., 2024	HF exchange, HF elimination
4,5,5-trifluoropent-4-enoic acid	$C_5H_5F_3O_2$		Activated sludge	71 %	30 %	3	Che et al., 2021	HF elimination and hydrolytic defluorination (+OH-, $-H$+ -F-) following beta-oxidation
2-(Trifluoromethyl) acrylic acid	$C_4H_2F_3O_2$		Activated sludge	82 %	100 %	20	Yu et al., 2022b	HF elimination and hydrogenation
4,4,4-Trifluoro-3-(trifluoromethyl) crotonic acid	$C_5H_4F_6O_3$		Activated sludge	77 %	50 %	20	Yu et al., 2022b	removal of fluoromethyl group by oxidation; unknown delfuorination pathways
2H-Perfluoro-2-octenoic acid	$C_8H_2F_{12}O_2$		Activated sludge	10 %	100 %	20	Yu et al., 2022b	Reductive defluorination, HF elimination
3-(trifluoromethoxy) propanoic acid	$C_4H_5F_3O_3$		Activated sludge	86 %	100 %	28	Jin et al., 2023b	ether scission: Spontaneous defluorination of fluoroalchohol TP formed from oxidation and hydrolysis
2-(trifluoromethoxy) acetic acid	$C_3H_3F_3O_3$		Activated sludge	65 %	40 %	28	Jin et al., 2023b	ether scission: Spontaneous defluorination of fluoroalchohol TP formed from oxidation and hydrolysis
2-(perfluoroethoxy) acetic acid	$C_4H_5F_3O_3$		Activated sludge	35 %	90 %	28	Jin et al., 2023b	ether scission: Spontaneous defluorination of fluoroalchohol TP formed from oxidation and hydrolysis
2-(trifluoromethoxy) propanoic acid	$C_4H_5F_3O_3$		Activated sludge	31 %	36 %	28	Jin et al., 2023b	ether scission: Spontaneous defluorination of fluoroalchohol TP formed from oxidation and hydrolysis

(*continued on next page*)

Table 1 (*continued*)

Anaerobic Condition								
Compound Name	Chemical Formula	Structure	Defluorinating Microorganism (s)/Community	Maximum Defluorination Degree (%)	Maximum Parent Compound Removal (%)	Test Duration (days)	Reference	Proposed Major Defluorination Pathway
Anaerobic Condition								
Compound Name	Chemical Formula	Structure	Defluorinating Microorganism (s)/Community	Maximum Defluorination Degree (%)	Maximum Parent Compound Removal (%)	Test Duration (days)	Reference	Proposed Major Defluorination Pathway
4,4,4-Trifluoro-3-(trifluoromethyl) crotonic acid	$C_5H_2F_6O_2$		KB-1 enrichment culture	77 %	95 %	35	Yu et al., 2022b	HF elimination; hydrolic defluorination
Heptafluoropent-2- enoic acid	$C_5HF_7O_2$		*Acetobacterium bakii; Clostridium homopropionicum*; KB-1 enrichment culture;	11 %	100 %	49–63*	Yu et al., 2022b; Yu et al., 2024	Reductive defluorination
2-(Trifluoromethyl)acrylic acid	$C_4H_3F_3O_2$		KB-1 enrichment culture	10 %	100 %	35	Y. Yu et al., 2022b	Unknown defluorination pathways
4-(Trifluoromethyl) hexafluoropent-2-enoic acid	$C_6HF_9O_2$		*A. bakii; Acetobacterium woodii; A. paludosum; A. malicum*; KB-1 enrichment culture; Anaerobic activated sludge; Digester sludge; AFFF-impacted soil community; AFFF-impacted groundwater community	11 %	100 %	20–150*	Yu et al., 2020; Yu et al., 2022b, 2024	Reductive defluorination
4,5,5,5-tetrafluoro-4-(trifluoromethyl)-2-pentenoic acid	$C_6H_3F_7O_2$		KB-1 enrichment culture	5 %	91 %	70	Yu et al., 2020	Reductive defluorination
2H-Perfluoro-2-octenoic acid	$C_8H_2F_{12}O_2$		*A. bakii*; KB-1 enrichment culture	17 %	100 %	35–50*	Y. Yu et al., 2022b	Reductive defluorination; HF elimination
3,5,7,8-tetrachloro2, 2,3,4,4,5,6,6,7,8,8-undecafluorooctanoic acid	$C_8HCl_4F_{11}O_2$		Anaerobic activated sludge	77 %	100 %	84	Jin et al., 2023a	Defluorinating triggered by eliminative dechlorination (−ClCl or −ClF) or hydrolytic dechlorination (−Cl, + OH)
2,2-dichloro-3,3,3-trifluoropropanoic acid	$C_3HCl_2F_3O_2$		Anaerobic activated sludge	27 %	100 %	84	Jin et al., 2023a	Defluorinating triggered by eliminative dechlorination (−ClCl or −ClF) or hydrolytic dechlorination (−Cl, + OH)
3,5,6-trichloro-2,2,3,4,4,5,6,6-octafluorohexanoic acid	$C_6HCl_3F_8O_2$		Anaerobic activated sludge	20 %	100 %	84	Jin et al., 2023a	Defluorinating triggered by eliminative dechlorination (−ClCl or −ClF) or hydrolytic dechlorination (−Cl, + OH)
3,4-dichloro-2,2,3,4,4-pentafluorobutanoic acid	$C_4HClF_5O_2$		Anaerobic activated sludge	7 %	100 %	84	Jin et al., 2023a	Defluorinating triggered by eliminative dechlorination (−ClCl or −ClF) or hydrolytic dechlorination (−Cl, + OH)

jostii RHA1 and *Gordonia* sp. NB4–1Y (Van Hamme et al., 2013; Yang et al., 2022), producing 5:3 FTCA as terminal products through desulfonation, oxidation, and HF elimination.

2.2. Ether PFAS

Aerobic biotransformation of ether perfluorinated carboxylic acids was achieved through oxidative and hydrolytic O-dealkylation by activated sludge communities, and it required at least one -CH_2- moiety adjacent to or a C═C bond in the proximity of the ether bond (Jin et al., 2023b). The resulting unstable fluoroalcohol intermediates underwent spontaneous defluorination, forming fluoride and trifluoroacetate as terminal products. Jin et al. demonstrated four out of twelve tested ether PFAS displayed over 20 % defluorination after a 28-day incubation in activated sludge communities (Table 1) (Jin et al., 2023b). 2-(trifluoromethoxy)acetic acid, 2-(trifluoromethoxy)propanoic acid and 3-(trifluoromethoxy)propanoic acid underwent α-oxidation, generating unstable trifluoromethanol as intermediate which underwent

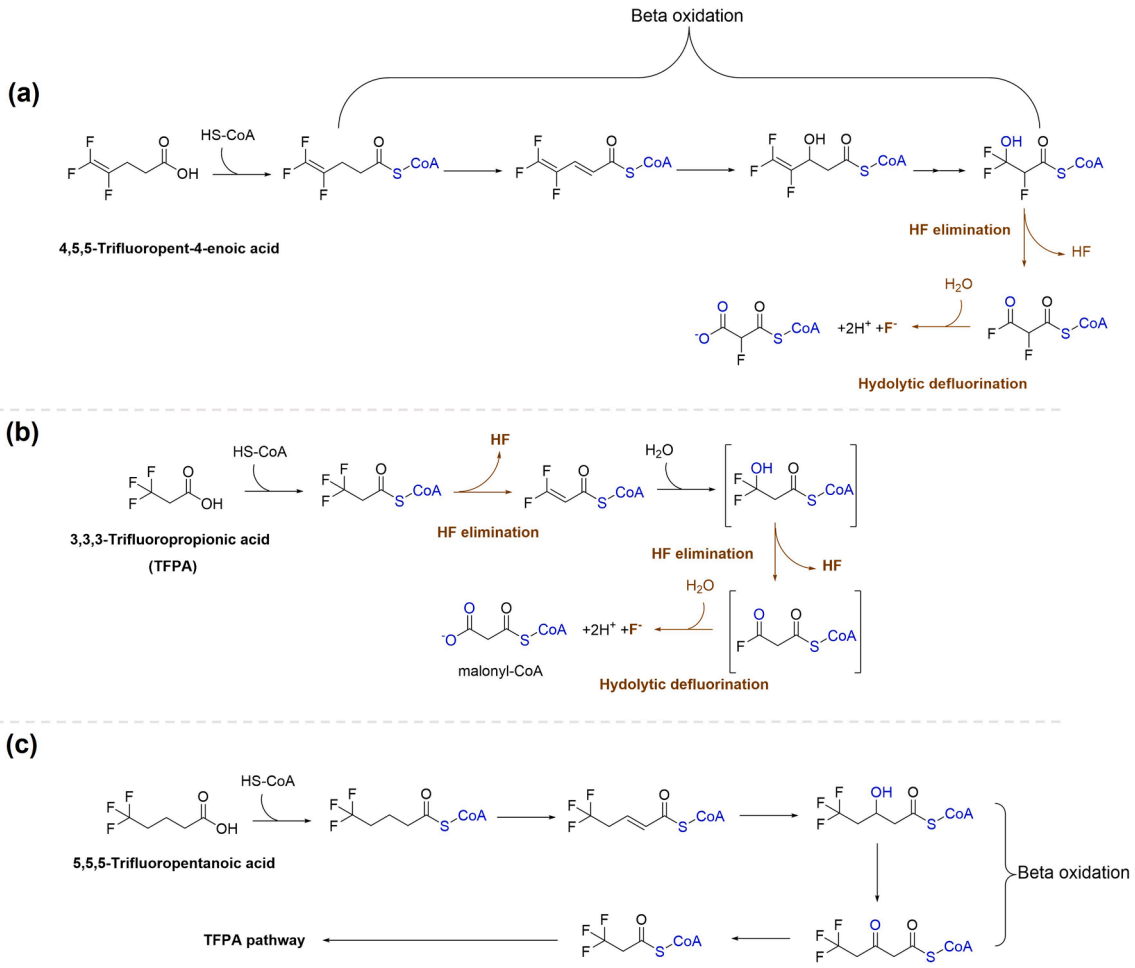


Fig. 1. Biotransformation pathway for fluorotelomer structures: (a) 4,5,5-trifluoropent-4-enoic acid, (b) 3,3,3-trifluoropropionic acid (TFPA), and (c) 5,5,5-trifluoropentanoic acid. Pathways are adapted from Che et al. (2021), with a focus on defluorination steps and redrawn for clarity.

spontaneous defluorination and released fluorine (Fig. 2a). The methyl group on the α-carbon hindered the transformation of 2-(trifluoromethoxy)propanoic acid, resulting in 34 % lower defluorination than 2-(trifluoromethoxy)acetic acid (Table 1). 3-(trifluoromethoxy) propanoic acid was proposed to be defluorinated through the same beta-oxidation pathways as short-chain PFAS (Fig. 2b) (Che et al., 2021), which was followed by similar hydrolysis and spontaneous defluorination. Di(polyfluoroether thioether(*S*)-oate) sulfonate (diFESOS), a PFAS containing ether and thioether insertions, could be degraded to 2-((1,1,2-trifluoro-2-(heptafluoropropyloxy)ethyl)thio)ethan-1-ol and 2-((1,1,2-trifluoro-2-(heptafluoropropoxy)ethyl)thio)acetic acid (FESCA) by activated sludge in a sulfate-free defined medium (Joudan and Mabury, 2022). Defluorination was proposed to occur through sequential HF elimination reactions on carbon alpha following the desulfonation of FESCA (Fig. 2c), while defluorination degree was not available due to the low parent compound concentration and detection limit of ion chromatography.

2.3. Unsaturated per- and polyfluorinated carboxylic acids

The critical role of $C = C$ double bonds in the biotransformation of per- and polyfluorinated carboxylic acids was illustrated with activated sludge communities (Y. Yu et al., 2022b). First, no biotransformation of any unsaturated perfluorinated compounds was observed during the aerobic incubation using activated sludge. For unsaturated polyfluorinated carboxylic acids, biodefluorination was observed to varying degrees depending on the position and substitution of the double bond. For instance, 4,5,5-trifluoropent-4-enoic acid with a terminal $C = C$ bond exhibited 30 % aerobic removal with ~80 % defluorination of the removed portion via a 2-F release pathway (Fig. 1a) (Che et al., 2021; Yu et al., 2022b). 2-(Trifluoromethyl)acrylic acid showed complete aerobic removal within 24 h and complete defluorination within two weeks. The elucidated biotransformation pathways indicated that for 2-(trifluoromethyl)acrylic acid, the reaction started with parent compound hydrogenation, followed by HF elimination (Fig. S2a) (Yu et al., 2022b). 4,4,4-Trifluoro-3-(trifluoromethyl)crotonic acid underwent 50 % parent compound degradation after 21 days with a defluorination degree of 82 %. While hydrogenation was confirmed for 4,4,4-trifluoro-3-(trifluoromethyl)crotonic acid, the exact defluorination pathways remain unclear due to the lack of detected intermediates (Fig. S2b). It is noteworthy that alpha and beta unsaturated fluorinated chemicals, when both positions were substituted with H or -CH_3, underwent nearly complete hydrogenation. 2H-Perfluoro-2-octenoic acid, with a beta carbon position substituted with fluorine, showed 10 % biodefluorination which was achieved through HF elimination and reductive defluorination (Table 1) (Yu et al., 2022b).

2.4. Polyfluorinated aromatic compounds

Pseudomonas species have versatile metabolic functions, among which defluorination capacities were revealed by recent studies on polyfluorinated aromatic compounds (Bygd et al., 2021; Bygd, 2022). A Rieske dioxygenase possessed by *Pseudomonas putida* F1 enabled rapid defluorination of 2,2-fluoro-1,3-benzodioxole (DFBD) moiety (Fig. S3a).

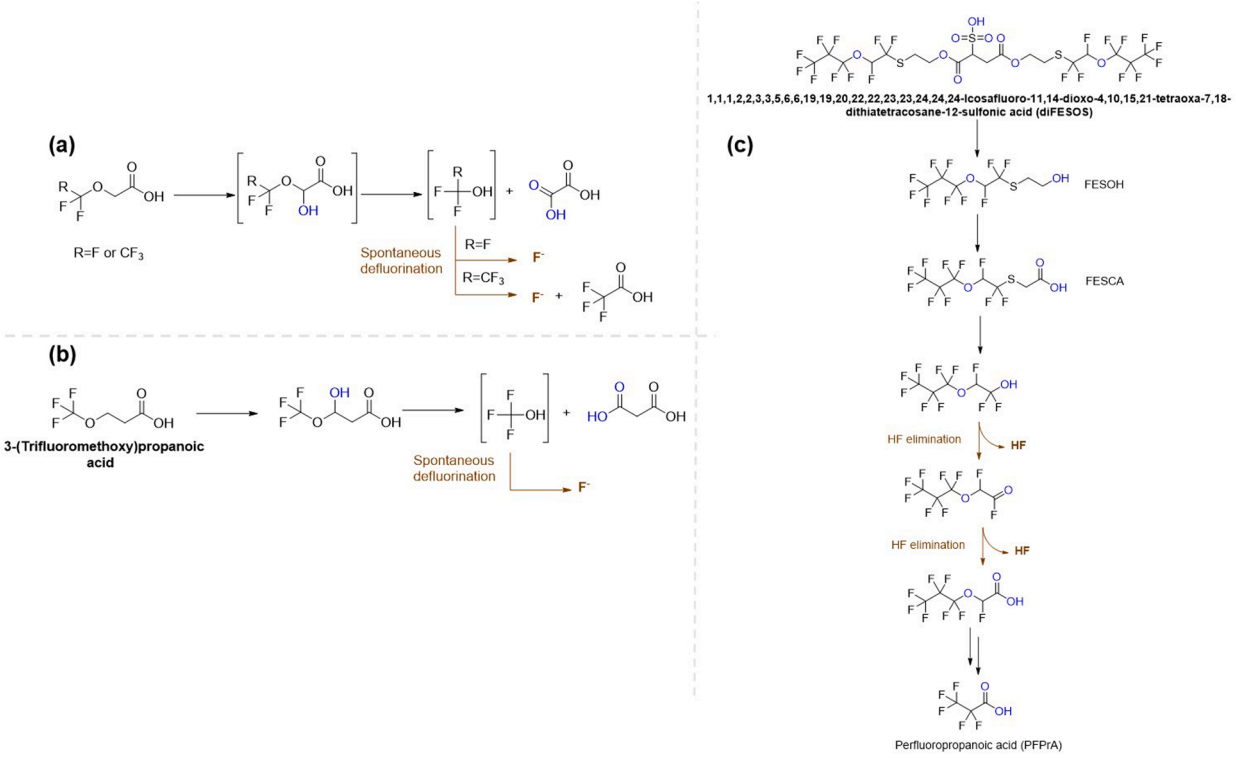


Fig. 2. Proposed ether PFAS aerobic biotransformation pathways for (a) 2-(trifluoromethoxy)acetic acid and 2-(perfluoroethoxy)acetic acid; (b) 3-(trifluoromethoxy) propanoic acid; and (c) di(polyfluoroether thioether(*S*)-oate) sulfonate (diFESOS). Pathways are adapted and redrawn from Jin et al. (2023b) and Joudan & Mabury (2022).

The resultant trihydroxy compound from the initial oxidation reaction was proposed to go through C—O breaking, rearomatization, and opening the ring of the five-membered 1,3-dioxole (Bygd et al., 2021). Inspired by the finding, a following microwell fluoride screen study revealed microbial defluorination capacity of *P. putida* F1, in which the -CF_3 group on trifluoromethylphenyl (-C_6H_6—CF_3) compounds (e.g., 4-fluorobenzotrifluoride in Fig. S3b) went through HF elimination to form a double bond and, following hydrolytic defluorination to release the other two fluorine, while the fluorine at the para position remains in the terminal products 4-fluorosalicylate and 4-fluoro-2,3-dihydroxy benzoic acid (Bygd et al., 2022). In addition, nine aromatic compounds with difluoromethoxy (-O-CHF_2) or trifluoromethoxy (-O-CF_3) moiety were defluorinated by the F1 strain, which likely went through a similar defluorination reaction as 2,2-difluoro-1,3-benzodioxole (Fig. S3a).

3. Anaerobic biodefluorination of PFAS

Considering that PFAS degradation pathways can vary substantially under different redox conditions, it is critical to explore the biodefluorination pathways of emerging PFAS under anaerobic conditions. Anaerobic removal of legacy PFAS (e.g., PFCAs, C_7—C_{10}) catalyzed by microorganisms has been reviewed in a recently published study (Smorada et al., 2024) and will not be the focus of this review. Significantly less attention has been given to the biotransformation of emerging PFAS compared to their legacy counterparts. Such insights are complimentary information to aerobic biotransformation data for designing effective bioremediation strategies and for the development of fluorinated alternatives with improved degradability.

3.1. Unsaturated per- and polyfluorinated carboxylic acids

Complete biodegradation of 4-fluoroaromatics to CO_2 and HF was achieved by the denitrifying *Thauera aromatica* via activation to a CoA ester, followed by oxygen-independent arylic C–F bond cleavage catalyzed by an ATP-dependent enzyme (Tiedt et al., 2016). Even though 4-fluoroaromatics could not be considered as PFAS (Wang et al., 2021), the discovery of the defluorinating enzyme as well as proposed reductive arylic C-F bond cleavage via Birch reduction-like mechanism shed lights on comprehension of PFAS biodefluorination (Rabideau and Marcinow). Using the KB1 (https://www.siremlab.com/) enrichment culture, a comprehensive analysis was conducted on 16 structurally diverse PFAS (Yu et al., 2022b; Yu et al., 2020), including a broad range of commercially available unsaturated fluorinated carboxylic acids. Compounds with α, β-unsaturation (–C═C–COOH) displayed nearly complete removal, suggesting that α, β-unsaturated C═C bonds play a critical role in initiating anaerobic microbial biotransformation (Yu et al., 2022b). This process appears unaffected by the degree of fluorine substitution or whether the structures are linear or branched. The transformation of α, β-unsaturated fluorinated carboxylic acids primarily undergoes two pathways: reductive defluorination and hydrogenation (Fig. 3a). The preference for defluorination or hydrogenation is influenced by the substitution pattern on the C═C bond. For compounds with both α-, and β-carbons substituted with fluorine, the reaction predominantly underwent reductive defluorination. When these positions were substituted with hydrogen, hydrogenation became more favorable. For instance, in 4-(trifluoromethyl)hexafluoropent-2-enoic acid, where both α- and β-carbons are substituted with fluorine, reductive defluorination is the predominant reaction (Fig. 3b). However, when these positions are substituted with hydrogen, as seen in 2H-perfluoro-2-octenoic acid (Fig. 3c), hydrogenation becomes more favorable. In the most recent study, *Acetobacterium* spp. were found capable of unsaturated fluorinated carboxylic acids biotransformation and biodefluorination (Yu et al., 2024). Reaction stoichiometry elucidated using ^{19}F-NMR showed that 82 % of the perfluorinated unsaturated carboxylic acid (i.e., PFMeUPA) underwent reductive defluorination, while only 18 % underwent hydrogenation, which aligns with findings from the community study (Yu et al., 2020). Furthermore,

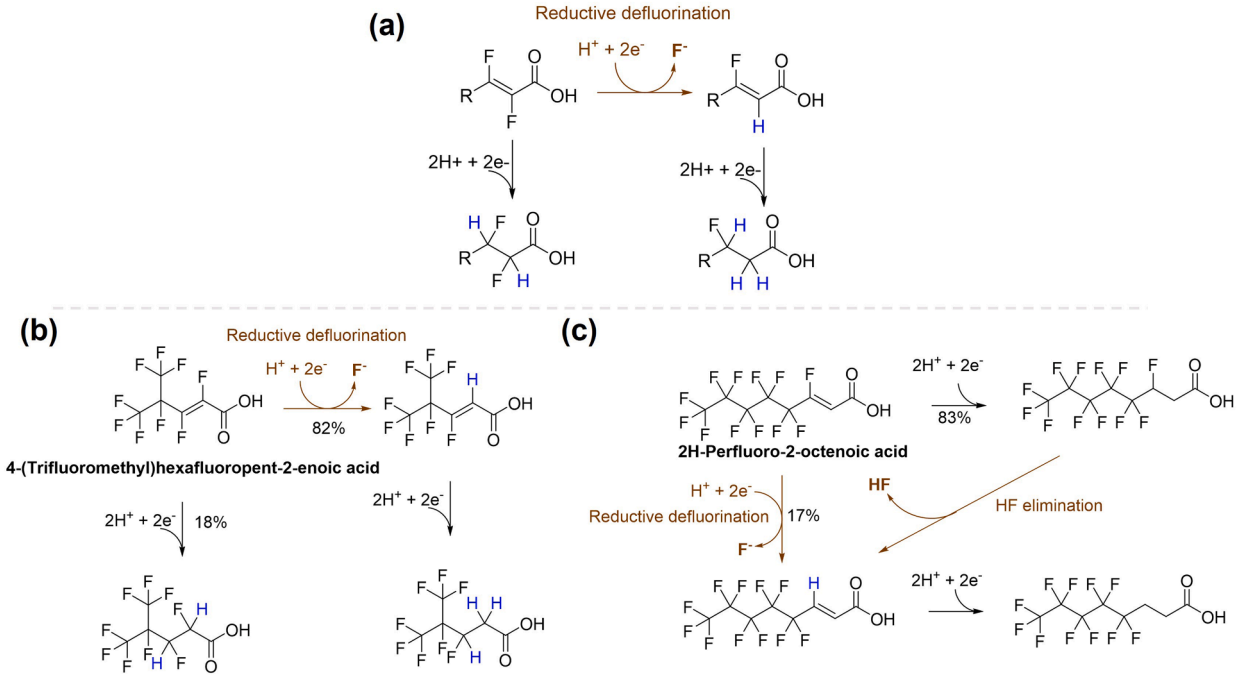


Fig. 3. (a) Schematic anaerobic biotransformation of α, β-unsaturated acids with both α and β carbon position substituted with F; (b) biotransformation pathways of 4-(trifluoromethyl)hexafluoropent-2-enoic acid; and (c) biotransformation pathways of 2H-Perfluoro-2-octenoic acid. Percentages indicate the proportion of parent compound undergoing each reaction pathway. Pathways adapted and redrawn from Yu et al. (2020, 2022b, 2024).

for the anaerobic biodefluorination of unsaturated fluorinated carboxylic acids, enzymes involved in fluoride detoxification and the flavin-based electron-bifurcating caffeate reduction pathway are proposed to drive the defluorination reaction (Yu et al., 2024). A global survey of wastewater metagenomes implicates the widespread distribution of the defluorination capability (Yu et al., 2024). Although the defluorination process was incomplete, it represents a critical first step and highlights the potential for harnessing microbial processes to treat fluorinated contaminants with specific structures. Future studies could build on these findings by screening more environmentally relevant microorganisms to achieve broader, faster, and more efficient PFAS biotransformation.

3.2. *Chlorinated PFAS*

Chloro-fluorochemicals represent a class of PFAS that have been systematically studied due to their significant biodegradability and intriguing reaction mechanisms. Recent research highlights that defluorination of polychlorofluorocarboxylic acids is primarily triggered by anaerobic microbial dechlorination processes (Jin et al., 2023a). Among these, chlorotrifluoroethylene (CTFE) oligomer carboxylic acids (Table 1), such as CTFE2, CTFE3, and CTFE4, have been investigated for their defluorination pathways (Fig. 4a). The CTFE oligomers undergo multiple biotransformation pathways, including reductive dechlorination, hydrolytic dechlorination, and eliminative dechlorination (Fig. 4a). Reductive dechlorination, characterized by the substitution of

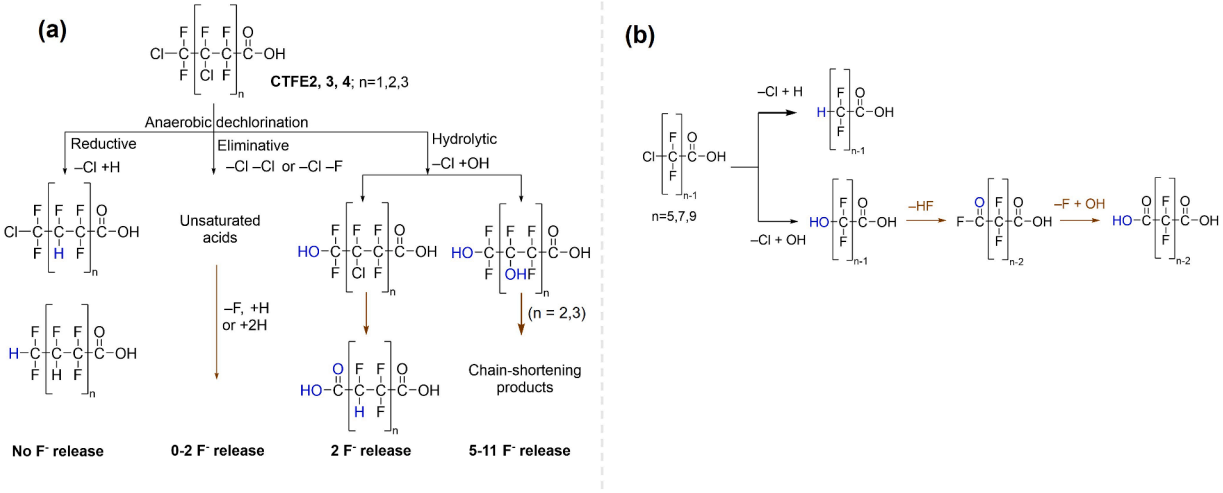


Fig. 4. Anaerobic biotransformation mechanisms of (a) chlorotrifluoroethylene and (b) Cl-terminal chloro-fluorochemicals. Pathways are adapted and redrawn from Jin et al. (2023a).

chlorine with hydrogen (-Cl, +H), does not release fluoride ions (F^-). However, eliminative dechlorination, which removes -ClF or -ClCl, produces unsaturated TPs releasing a small amount of fluoride ions through slower reductive defluorination. The most significant defluorination occurs through hydrolytic dechlorination, which produces fluoroalcohol moieties leading to spontaneous HF elimination. For CTFE2, 3, and 4, the degree of defluorination increases from <10 % for CTFE2 to approximately 80 % for CTFE4 after 84 days of incubation, correlating with an increase in chlorine substitutions. This trend highlights the role of chlorine in enhancing defluorination degree.

In addition, Cl-terminal and ultra-short-chain structures also exhibit varied biotransformation and defluorination performances. Cl-terminal polyfluorocarboxylic acids (PFCAs), such as Cl-C_5, Cl-C_7, and Cl-C_9, primarily undergo reductive dechlorination and hydrolytic dechlorination (Fig. 4b). While the reductive pathway predominantly leads to non-defluorinating transformation products, the hydrolytic pathway contributes to defluorination (Fig. 4b). The biotransformation efficiency is generally lower for monochlorinated and ultra-short-chain PFCAs, but significant defluorination was observed with chlorinated structures compared to their non-chlorinated counterparts. The enhanced biodegradability observed in these chlorinated PFAS emphasizes the potential for designing more readily degradable and less persistent fluorochemicals. Furthermore, *Desulfovibrio aminophilus* and *Sporomusa sphaeroides*, two closest genomes to the dominant species in the highly enriched defluorinating culture were further identified after cultivation, both exhibited active defluorination of CTFE tetramer acid.

4. Framework of investigating the biodefluorination of PFAS

To effectively address the PFAS issue, international cooperation is crucial in environmental monitoring, research, technology development, as well as regulation. For research on PFAS biotransformation and biodefluorination, data transparency paves the way for global collaboration. Thus, we propose the general workflow for PFAS biotransformation study, which integrates the testing conditions (i.e., aerobic and anaerobic), the analysis of fluoride release, the removal of parent compound, and the identification of transformation products (Fig. 5a).

OECD 301–311 provide guidelines for biodegradability tests of organic chemicals under aerobic and anaerobic conditions, respectively (OECD, 2017). However, the characterization mostly relies on the measurement of total dissolved carbon, oxygen demand, and release of carbon dioxide, which are not suitable for chemicals at trace concentrations or contaminants undergoing cometabolic biotransformation pathways. To address these limitations, we propose that the defluorination degrees should be a direct and efficient parameter for PFAS degradability evaluation.

Fluoride quantification is crucial for assessing biodefluorination efficiency and analyzing corresponding pathways, however, there is a significant methodological gap in measuring fluoride in complex matrix such as wastewater and biological media, as organics and anionic ions could severely impact the analysis of fluoride (Kontozova-Deutsch et al., 2011; van den Hoop et al., 1996). Ion chromatography (IC), ion-selective electrode (ISE) and colorimetric assays are the predominant methods used for fluoride measurement in PFAS biodefluorination experiments (Bhardwaj et al., 2024; Bygd et al., 2022; Che et al., 2021; Jin et al., 2025; Probst et al., 2024; Yu et al., 2022b). Briefly, IC is a widely used technique for fluoride detection due to its precision, reproducibility, and ability to handle complex matrices. However, it has limitations, particularly when applied to environmental samples like wastewater. Co-existing anions such as formate, acetate, and chloride can interfere by overlapping with the fluoride peak, affecting quantification accuracy (Kontozova-Deutsch et al., 2011). While IC offers a relatively low detection limit, it may not be sufficient for trace-level detection compared to potentiometric methods. Accurate results also depend on optimized ion separation.

Compared to IC, ISE is widely used for rapid fluoride quantification due to their ease of use and real-time measurement capabilities. However, similar to IC, a major limitation of ISE is interference from co-existing ions (Borjigin et al., 2009; Harwood, 1969). To minimize such interference, sample preparation with Total Ionic Strength Adjustment Buffer is often required. Previous studies have shown that cross-validation between IC and ISE offers comparable and reliable defluorination results (Che et al., 2021; Yu et al., 2020). Future studies should take these considerations into account and incorporate matrix-matched calibration.

Colorimetric assays detect fluoride based on a visible color change

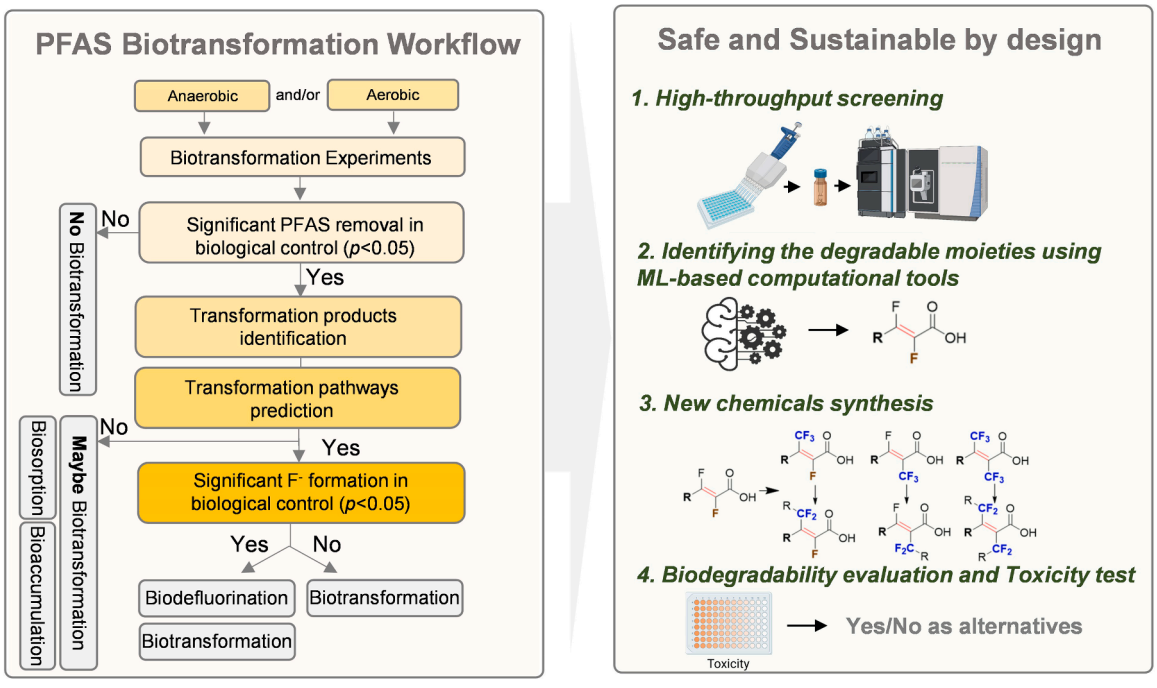


Fig. 5. Proposed (a) PFAS biotransformation workflow and (b) flowchart for the safe-and-sustainable-by-design development of fluorinated chemicals.

resulting from the reaction between fluoride ions and specific reagents, allowing for visual or spectrophotometric measurement (Bygd et al., 2022; Probst et al., 2024). While these assays are simple, low-cost, and provide rapid results, they also have limitations, including a relatively narrow detection range and high susceptibility to interference from co-existing anions and dissolved organics (Bygd et al., 2022; Probst et al., 2024). Therefore, colorimetric assays might be best suited for low reaction volume, high-throughput screening experiments (e.g., using a 96-well plate setup) to quickly assess defluorination activity.

Besides fluoride ion quantification, it is also important to note that the transformation products may have toxicity levels comparable to, or even higher than, the parent compounds (Trojanowicz et al., 2020). Therefore, identifying the transformation products, typically via high-resolution mass spectrometry remains crucial (Liu et al., 2019).

Complex microbial communities are capable of diverse metabolisms for organic contaminants (Che and Men, 2019). As mentioned in OECD 301, inoculum could be derived from a variety of sources, including activated sludge, sewage effluent, surface water, and soils. Once biodefluorination of specific PFAS is observed, the identification of functional microorganisms and enzymes can be further carried out.

Additionally, several key factors must be carefully considered when conducting PFAS biotransformation tests. First, non-biological removal pathways may contribute to the apparent loss of parent compounds through adsorption to reactor surfaces or biomass, or through volatilization (Milinovic et al., 2016; Zhang et al., 2013). Therefore, including abiotic and adsorption controls is critical to accurately attribute PFAS removal to biotransformation. Second, impurities in test compounds must be accounted for, as commercially available PFAS often have purities ranging from 95 % to 99 %. Previous studies have shown that observed biodefluorination may be due to these impurities rather than the parent compound itself (Yu et al., 2022b). It is essential to confirm true biodegradability and defluorination by tracking the removal of the parent compounds and identifying any resulting transformation products.

For transformation products identification, online platforms, such as enviPath (https://envipath.org/), have proven to be invaluable tools for predicting microbial biotransformation pathways of organic environmental contaminants under various conditions (e.g., cell cultures, activated sludge, and soil) (Hafner et al., 2024; Wicker et al., 2015; Zhang and Fenner, 2023). However, as highlighted in the recent study where enviPath was combined with non-targeted screening to identify PFAS transformation products, a critical limitation persists in PFAS biotransformation predictions: the lack of curated PFAS-specific biotransformation pathways and reaction rules (Geng and Helbling, 2024). Therefore, it is crucial to integrate existing knowledge of PFAS degradation pathways and associated enzyme data (Wackett and Robinson, 2024) into platforms like enviPath (Schmid and Fenner, 2021) to pave the way for machine learning-based tools designed specifically for fluorinated chemicals. By accounting for the unique structure-biodegradability characteristics of PFAS, such tools could greatly enhance the accuracy of predicting biodefluorination products, thereby advancing both the fundamental understanding of PFAS biodefluorination and the practical strategies for their remediation.

Furthermore, successful prediction of PFAS biodefluorination reactions is limited by insufficient experimental data, given that only a few structures have been found to be biodefluorinated by microorganisms. Considering the large number of PFAS, it is essential to develop high-throughput screening assays for generating larger datasets. These comprehensive datasets on the biodefluorination reactions can help refine predictive models and strengthen environmental monitoring systems. High-throughput assays also allow for the evaluation of structure-specific biotransformation, bioaccumulation, and toxicity across entire groups of PFAS, ideally before these chemicals enter the market or the environment. This proactive approach helps ensure that only safer and more environmentally friendly PFAS alternatives are developed and deployed.

5. Environmental implications: efforts toward the design of environmental-friendly PFAS

Recent regulatory actions in Europe and the United States have intensified efforts to phase out all PFAS from commercial products, driven by their significant threats to public health and ecosystems (ECHA, 2023). However, achieving a complete replacement for all PFAS in a short term is challenging due to their crucial roles in various industries, including coatings, paints, varnishes, and food packaging, where suitable fluorine free alternatives are not yet available (Ateia and Scheringer, 2024; OECD, 2022a; Bygd, 2022b). The transition away from PFAS requires balancing feasibility, economic costs, and thorough evaluations of replacement chemicals (Ateia and Scheringer, 2024). This necessitates cooperation among stakeholders, governments, manufacturers, and scientists to ensure a smooth and effective phase-out process.

To support sustainable development and mitigate the ecological risks associated with emerging chemicals, it is crucial to focus on designing environmentally friendly PFAS. While there is a significant push towards developing fluorine-free alternatives to address PFAS-related concerns entirely, we must also prioritize creating PFAS compounds that are less persistent and more degradable. This involves leveraging biodefluorination-structure relationships to design new compounds that maintain the beneficial properties of legacy PFAS while reducing their negative impacts. Studies on short-chain, unsaturated, chlorinated, and aromatic fluorinated compounds offer valuable insights into developing fluorinated structures with enhanced degradability. Ongoing research efforts are closing the gap between PFAS structures and their reactivities (Che et al., 2021; Jin et al., 2023a, 2023b, 2025; Yu et al., 2022b). By combining established PFAS biotransformation mechanisms with artificial intelligence (Yang et al., 2024), it becomes possible to generate new PFAS structures that are more readily degradable and have a lower environmental footprint.

Future fluorinated alternatives should maintain the beneficial physicochemical properties of legacy PFAS yet minimize ecological and human health risks, all while remaining cost-effective for industry. Additionally, the toxicity evaluation should not only be conducted on the alternatives themselves but also on their degradation products to thoroughly assess their impact on humans and ecosystems.

Inspired by the principles of green chemistry, biodefluorination results can guide the design of new chemical structures with higher biodegradability and lower toxicity (Fig. 5b). A careful evaluation of biodegradability, bioaccumulation, and toxicity is required for introducing PFAS alternatives in commercial products to avoid repeating past mistakes of contamination and replacement cycles (Hernández et al., 2020; Hetzer et al., 2014; Yu et al., 2022a). Future studies should focus on investigating three types of fluorinated chemicals: currently used PFAS, fluorine-free alternatives, and newly designed biodegradable PFAS.

By prioritizing these areas, we can work toward the development of safer, more sustainable chemical alternatives. Collaboration among researchers, industry stakeholders, and regulatory agencies will be essential in ensuring that these new compounds meet safety standards and are economically feasible. Ultimately, integrating scientific innovation with efforts from various sectors will pave the way for a healthier environment and a more sustainable future.

6. Conclusions

- Certain PFAS structures exhibit promising higher degradability and defluorination capabilities, indicating the potential to achieve better PFAS biotransformation through proper structure design.
- Comprehensive analysis of fluoride release, parent compound degradation, and transformation product identification is essential for evaluating PFAS biodegradability and understanding defluorination mechanisms.

- Combining biotransformation insights with computational approaches can facilitate not only the design of degradable fluorinated chemical alternatives but also aid in establishing a digital early warning system to predict the environmental fate of PFAS.
- Despite their essential roles in industrial production due to unique physicochemical properties, the degradability and toxicity of newly designed PFAS must be carefully evaluated to avoid introducing greater contamination than legacy PFAS.

CRediT authorship contribution statement

Shun Che: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis. **Huaqing Liu:** Writing – review & editing, Visualization, Investigation. **Shucai Zhang:** Writing – review & editing, Supervision. **Yaochun Yu:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.wroa.2025.100356.

Data availability

No data was used for the research described in the article

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