CAFSI Comment on PFAS Restriction Proposal

China Association of Fluorine and Silicone Industry（CAFSI）

China Association of Fluorine and Silicone Industry（CAFSI）, a national industry organization on fluorine & silicon chemicals in China, has always guided Chinese fluorochemical industry to fully support and implement international conventions and national regulations, help affiliated enterprises to improve their management on corporate social responsibility including environmental protection.

CAFSI has paid close attention to and carefully studied the content of PFAS restriction proposal prepared by five EU countries. We believe that:

The draft should clarify the scope for management of substances of PFAS, provide clear identification information and list for restricted substances, and should group substances that are not "unacceptable risks", comprehensively evaluate their environment risks so as no to impose "one size fits all" restrictions as such a broad group of substances;

For example, fluoropolymers are unique, stable, and could be regarded as "low concern" polymers under OECD criteria. Especially when taking consideration of the factors such as their irreplaceability in many applications, increasing use of non-fluorinated alternatives of PFAAs, the high efficiency for reclaim and recycle of PFAAs, as well as the development of new technologies that prevent the formation of new PFAAs during the manufacturing and waste incineration of fluoropolymers, and therefore we believe that the lifecycle management will be more appropriate and cost-effective measures to control the emission of these substances.

In addition， as a special substance excluded from PBT, vPvB, or PMT, Trifluoroacetic acid（TFA）has low environmental impact and harm to human health, and shows that it is very unlikely to cause adverse effects at present and in the foreseeable future. We suggest that more studies should be done on assessment for the environmental and socio-economic impact of TFA and keep cautiousness before making any restriction proposals on TFA.

Currently, China becomes the largest in production and export of fluorochemicals in the word. We respect and appreciate the ambitious efforts by the European Union to achieve the goals of a non-toxic environment and zero-pollution. However, we hope that ECHA could fully consider these comments from China. We would like to joint our efforts to ensure the smooth implementation of this proposal as a scientific and practical regulation based on comprehensive assessment of environmental risk and socio-economic impact.

Herein, we intend to present the following views at the public consultation of ECHA on behalf of fluorine industry in China.

Part I: General comments

We believe that it is reasonable to restrict chemicals with Persistent, Bioaccumulative and Toxic (PBT) or very Persistent and very Bioaccumulative (vPvB) characteristics in the PFAS restriction proposal. However, there may be excessive restrictions on all substances that meet the definition of PFAS. On one hand, more than 10,000 substance of PFASs would be subject to restriction, which may hamper the economic development of relevant industry in EU. On the other hand, stringent risk management measures for substances exhibiting only persistence characteristics, similar to PFOS and PFOA listed in the POPs regulation, could contradict the risk management approach of the REACH regulation. In the following are our comments:

I. Defining the Scope of PFAS Substance[1]

Substances listed in the REACH Restriction List or Annex XVII, have explicit identification information. For example, it may refer to a substance, generic substances usually refer to homologous substances or specific chemicals and its related compounds. It may also refer to substances with specific classification. However, such substances were included in corresponding lists with clear identification information.

According to the PFAS restriction proposal, PFASs means substances that contain at least one fully fluorinated methyl (CF3-) or methylene (-CF2-) carbon atom, without any H/Cl/Br/I attached to it. In accordance with Annex XV of REACH Regulation, “The proposal shall include the identity of the substance and the restriction(s) proposed for the manufacture, placing on the market or use(s) and a summary of the justification.” Therefore, it is unreasonable to identify a substance containing a fluorinated methyl (CF3-) or methylene (-CF2-) carbon atom as a PFAS substance. Moreover, supplementary details for this substance, including CAS No, EC No, and substance name, shall be provided.

The United States Environmental Protection Agency announced a framework on PFAS in which the definition of PFAS was given in the following:

PFAS or per- and poly-fluoroalkyl substance means a chemical substance that contains at least one of these three structures:

(i) R–(CF2)–CF(R′)R″, where both the CF2 and CF moieties are saturated carbons;

(ii) R–CF2OCF2–R′, where R and R′ can either be F, O, or saturated carbons; or

(iii) CF3C(CF3)R′R″, where R′ and R″ can either be F or saturated carbons.

PFAS definition by US EPA is much more precise to define hazardous substances since they have a higher possibility of having PBT and vPvB property.

2. PFAS characteristics subject to restriction shall be identified

In accordance with article 68.1 of the REACH regulation:

When there is an unacceptable risk to human health or the environment, arising from the manufacture, use or placing on the market of substances, which needs to be addressed on a Community-wide basis, Annex XVII shall be amended in accordance with the procedure referred to in Article 133(4) by adopting new restrictions, or amending current restrictions in Annex XVII.

Under this provision, the prerequisite of proposing restrictions is the presence of unacceptable risks[2]. PFASs may have an impact on human health including long-range transport potential, mobility, accumulation in plants, bioaccumulation potential, ecotoxicity and endocrine activity because of its persistence. However, for most substances, the data are insufficient. Inputting keywords such as “perfluorooct” or “nonadecafluoro” in the ECHA database (substances restricted under REACH), you will find that most PFAS substances lack persuasive data to prove that whether they exhibit all or some of mentioned properties above. Although some PFAS substances may be identified as concerned substances, there is no evidence to include that all PFAS substances are identified as concerned substances. With over 10,000 substances falling under PFAS definition, they exhibit diverse physicochemical and toxicological properties, including different fate and behavior. Until adequate data are provided to identify the corresponding risk characterization, it is scientifically unfeasible to demonstrate the presence of unacceptable risks in PFASs.

Although some substances have unacceptable risks, such as PFOS and PFOA, it cannot be concluded that all substances meeting the definition of PFAS present unacceptable risks. Substances in same group or category share similar properties but substances in different group or category are

not. The PFAS definition fails to identify the similarity of substances from different groups.

Given the absence of risk assessments for the majority of substances, it is feasible to implement rigorous management measures for specific non-threshold properties, such as EDC, PBT, vPvB, or CMR. This approach also aligns with the current industry understanding of restricted substances.

3. It's not appropriate to manage all PFASs as one category

OECD PFAS definition: Any substance that contains at least one fully fluorinated methyl (CF3-) or methylene (-CF2-) carbon atom (without any H/Cl/Br/I attached to it). In this definition, over 10,000 substances are covered and these substances have differences including in substance structure and hazard.

The question remains: Is it reasonable to classify all substances into one category solely based on CF3- or -CF2-? Has the distinction between the substance's structure and its hazard property been adequately considered?

In OECD PFAS definition, it only considers substance structure but neglects the difference of hazard property. In the Proposal, PFAS is divided into four categories: PFAAS, PolyFAAS, PFAA precursor and other PFASs. Given that polymers typically have high molecular weights, often exceeding tens of thousands, they might exhibit very low bioavailability. The toxicity of polymers can be ignored. Consequently, there exist substantial differences between fluoropolymers and other substances, and categorizing them within the same group is not very accurate. However, even with the category approach outlined in proposal P16, the division of PFAS substances into four categories may not be precise enough. Taking PFAA precursors as an example, the functional groups of perfluoroalkane sulfonyl fluorides and perfluoroalkenes are different. It is advisable to further subdivide these four categories. For instance, the classification of perfluoroalkyl carboxylic acids (PFCAs) is based on homologous compounds. In view of read-across, substances with similar structures show similar properties. They are more suitable to managed with same risk management measures.

Hence, it is strongly advisable to choose a representative substance from a group of similar substances, like selecting one from the PFCAs category, for comprehensive research. Subsequently,

a restriction proposal for a substance should be formulated based on its properties, such as PBT or vPvB characteristics. This approach aligns more closely with the prevailing practices of group or category in the REACH regulation.

4. Lack of scientific grounds

It is not rigorous enough to propose restrictions solely based on the OECD PFAS definition and the presence of (CF3-) or (-CF2-) functional groups. This approach contradicts the principle of risk assessment in chemical management, which is also reflected in the recent restriction intention (https://echa.europa.eu/registry-of-restriction-intentions). In the previous restriction proposal, it had unacceptable risks to human health or the environment such as in paragraph 1, Article 68 of the REACH Regulation. "Unacceptable risks to human health or the environment" is made based on risk assessment, encompassing substance hazard and exposure. The following examples can further elucidate this point: Bisphenols are proposed for restriction due to their endocrine-disrupting properties; MCCP is proposed to restriction due to its PBT or vPvB property; DMAC and NEP have unacceptable risk due to its higher occupational exposure; Terphenyl, hydrogenated has unacceptable risk due to its vPvB property; PAH has unacceptable risk due to its PBT property; DMF has unacceptable risk due to its excessive occupational exposure. All these proposed restrictions are made based on the hazard and exposure of substances, and their unacceptable risks.

For example, PFASs should be treated as non-threshold substances for the purpose of risk assessment in a similar manner to PBT/vPvB substances. Their releases can be accordingly used as a proxy for risk. To minimise the likelihood of adverse effects in the future, all releases should be minimised.

The conclusion in the risk characterization of PFAS is too ambiguous. For example, PFASs should be treated as non-threshold substances for the purpose of risk assessment in a similar manner to PBT/vPvB substances. Their releases can be accordingly used as a proxy for risk. To minimise the likelihood of adverse effects in the future, all releases should be minimised.

Even though PFAS substances are regarded as non-threshold substances, sufficient evidence shall

be provided to demonstrate that PFASs have PBT, vPvB, EDC, or CMR characteristics. If they indeed have these characteristics, it would be reasonable to identify PFASs as non-threshold substances.

However, this Proposal primarily centers on PFAS hazards. Only persistence property is inadequate to have equivalent concerns with PBT and vPvB, or inadequate to be identified as unacceptable risk. Therefore, it becomes essential to formulate restriction proposals for PFASs based on PBT, vPvB, endocrine-disrupting properties, or equivalent concerns. Nonetheless, this Proposal either lacks information about PFAS properties other than persistence or lacks sufficient evidence to validate properties like PBT or equivalent concerns. As a result, it is not persuasive.

5. Data lacking

It mentioned in the Proposal, considering the increasing lines of evidence from modelling, laboratory and monitoring studies, there is a justified concern for a subset of PFASs being bioaccumulative while large uncertainties remain for the majority of compounds due to lack of data. As to bioaccumulation in the PFAS restriction proposal: Any substance that contains at least one fully fluorinated methyl (CF3-) or methylene (-CF2-) carbon atom (without any H/Cl/Br/I attached to it). The large number of different substances with heterogenous properties (e.g. due to different functional groups) in the group of PFASs makes the assessment of their ecotoxicity very complex.

Regarding the correlation between bioaccumulation and octanol-water partition coefficient, a higher octanol-water partition coefficient might indicate the potential for bioaccumulation. Consequently, certain substances may have bioaccumulation property. However, relying on data from a limited number of substances is inadequate to identify substances with PBT or equivalent concerns.

Given the substantial variations in PFAS functional groups, inherent differences in properties are likely to arise. In the absence of sufficient data, it becomes impossible to conduct hazard assessment, exposure evaluation, or risk characterization. Consequently, the ability to identify unacceptable risks is compromised. Under such circumstances, it is necessary to introduce some tools, including read-across or group/category, or QSAR to predict the properties such as bioaccumulation and mobility of specific sub-group. This strategy would provide information on sub-category substances.

Subsequently, you can compare this information with data from registered PFAS substances published by ECHA. This approach could curtail the proposal of invalid PFAS restrictions, thereby reducing the risk of inaccurate representation of unacceptable risks. For instance, the group approach could potentially encompass MCCP within the restriction scope.

Table 7. Congener groups concluded as PBT and/or vPvB

Number of chlorine atoms and Carbon chain length	Cl_1	Cl_2	Cl_3	Cl_4	Cl_5	Cl_6	Cl_7	Cl_8	Cl_9	Cl_{10}	Cl_{11}	Cl_{12}	Cl_{13}	Cl_{14}	Cl_{15}	Cl_{16}	Cl_{17}
C_{14}	-	-	**vPvB**	**vPvB PBT**	**vPvB PBT**	**vPvB PBT**	**vPvB PBT**	**vPvB PBT**	**vPvB**	**vPvB**	**vPvB**	-	-	-			
C_{15}	-	-	**vPvB**	**vPvB**	**vPvB PBT**	**PBT**	**PBT**	**PBT**	-	-	-	-	-	-	-		
C_{16}	-	-	**vPvB**	**vPvB**	**vPvB PBT**	**PBT**	**PBT**	**PBT**	-	-	-	-	-	-	-	-	
C_{17}	-	-	-	-	-	**PBT**	**PBT**	**PBT**	**PBT**	-	-	-	-	-	-	-	-

Source: Conclusions on the P, B and T properties in (ECHA, 2021a)

Part II: Fluoropolymers should be excluded from the PFAS restriction proposal

We oppose the inclusion of fluorinated polymers as a whole under the PFAS restriction proposal. We also hold opposing views on certain aspects related to fluorinated polymers in the proposal, and believe that the proposal fails to consider all relevant facts in presenting these viewpoints, leading to evident logical gaps. Evidences as follows support that fluoropolymers should excluded from the PFAS restriction proposal.

1. Fluorinated polymers constitute a distinct and highly specialized category within PFAS substances. PFAS can be categorized into polymers and non-polymers. Within the polymer category, there are three subtypes, including: fluoropolymers (with only C-C bonds in the main chain), perfluoropolyethers (with C-O bonds in the main chain), and fluorinated side-chain polymers.

Despite sharing the characteristic molecular structure defined by PFAS, their properties markedly differ from other PFAS substances. They typically have a much larger molecular weight, far exceeding that of PFOA and PFOS with long carbon chains. Additionally, their immense molecular weight prevents them from crossing cell membranes, rendering them non-bioaccumulative. Furthermore, fluorinated polymers lack mobility and toxicity, placing them in the "Low Concern" category according to the OECD's Composite Polymer Category (CPC) definition.

For instance, while the basic chemical structure of PTFE is -O3SO(CF2)n, which is identical to PFOS in structural definition, their vastly different molecular weights (with n value over 100 for PTFE compared to 8 for PFOS) result in drastically distinct water solubilities. PFOS exhibits high water solubility, whereas PTFE is entirely insoluble in water. Consequently, the issues of bioaccumulation, toxicity, and mobility associated with solubility are entirely different. In comparison to PFOS, PTFE is a specialized polymer material that poses no harm to living organisms and can be used for surface coatings in implanted medical devices[3].

Following the OECD's definition of "Low Concern" substances, fluorinated polymers fall under the category of Polymer of Low Concern (PLC). The specific criteria for this designation are as follows:[4]

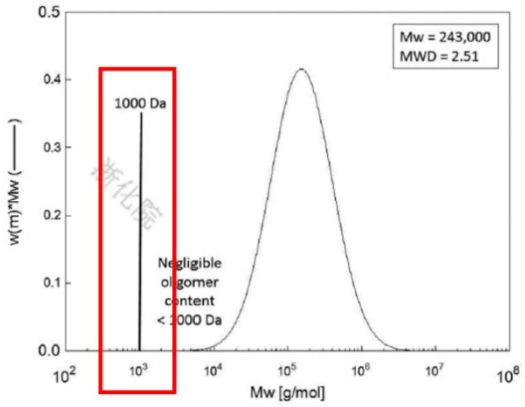
序号	Project	PLC Criteria	Fluorinated Polymer Characteristics
1	Polymer Composition	lements connected to C include: H, N, O, Si, S, F, Cl, Br, or I	Elements connected to C are F or Cl
2	Molecular Weight/Molecular Weight Distribution	Molecular weight greater than 1000 g/mol	Much greater than 1000 g/mol, [Using PTFE as an example, molecular weight ranges from 520,000 to 4,500,000 g/mol, see Example 1]
3	Oligomer Content	<1%	Negligible [Example 2][Example 3, using PVDF as an example, GPC molecular weight slice shows

			Mw>25,000 g/mol, with only 0.5% content] Charge Neutral, charge is related to toxicity Neutral, no charge
4	Charge Neutral	charge is related to toxicity Neutral	no charge
5	Reactive Functional Groups	Contains highly reactive functional groups, such as acrylic acid, methyl acrylic acid, isocyanate, etc.	None
6	Relative Molecular Weight of Reactive Groups	Larger relative molecular weight indicates weaker reactivity	Very large, relative molecular weight exceeds 105~106 [Example 4]
7	Low Molecular Weight Leachables	No organic/inorganic leachables	Negligible
8	Water solubitlity	Saturated concentration <10 mg/L	10^{-6} mg/L
9	Particle size	>5 μm	>50 μm[Example 5, using PTFE as an example, particle size ranges from 100 to 500 μm]
10-13	Physicochemical Stability	Stability Physical, chemical, and biological stability	All stable

Example 1: Molecular Weight and Distribution of Various Fluorinated Polymers[5]

	Fluoropolymers			
	PTFE	ETFE	FEP	PFA
(M_n > 1000 Da and oligomer content < 1%)	520 000–45 000 000[bd]	530 000–1 200 000[ef]	241 000–575 000[eg]	200 000–450 000[eh]
Wt % oligomer (see Figure 2)	Negligible	Negligible	Negligible	Negligible

Example 2: Molecular Weight and Molecular Weight Distribution of FEP[3]



Example 3: GPC Molecular Weight Slicing[2]

PVDF（Mw *10⁴）	占比
>200	6.4%
150-200	6.2%
100-150	13.0%
80-100	8.5%
60-80	11.5%
40-60	15.7%
20-40	21.0%
10-20	11.3%
5-10	4.4%
2.5-5	1.6%
<2.5	0.5%
合计	100%

Example 4: Relative Molecular Weight of Reactive Groups in Various Fluorinated Polymers[2]

	Fluoropolymers			
	PTFE	ETFE	FEP	PFA
FGEW[k] (typical value) (the lower the FGEW, the more reactive the polymer and the higher the potential for health and environmental impact)	$>10^5$–10^7	$>10^5$–10^6	$>10^5$	$>10^5$

Example 5: Particle Size of Various Fluorinated Polymers[2]

	Fluoropolymers			
	PTFE	ETFE	FEP	PFA
Particle size (median mass aerodynamic diameter, MMAD, should be >5 μm)	100–500 μm (powders)	50–250 μm (powders)	50–250 μm (powders)	50–250 μm (powders)
	—	2–4 mm (pellets)	2–4 mm (pellets)	2–4 mm (pellets)

Conclusion: Fluorinated polymers fully comply with the OECD's PLC criteria, indicating that they do not pose a risk to human health or the environment. This contradicts and conflicts with the restrictions stipulated in Article 68(1) of the REACH regulation.

2. Fluorinated polymers play an irreplaceable role in specialized applications. They are the only materials that combine heat resistance, weather resistance, chemical resistance, hydrophobicity, lubricity, and unique optical or electrical properties[6]. Fluorinated polymers are indispensable key materials in various fields such as new energy (fuel cells, lithium-ion batteries, photovoltaic panels), semiconductors (clean components), electrical and electronic communication (wire coatings and liquid crystal materials), transportation (automobiles, airplanes, railways, marine), medical (tubing, protective clothing), and environmental protection (coatings, membrane products) [7].

The proposal document suggests alternative materials for fluorinated polymers, such as PEEK, PDMS, PMMA, PAA, and HNBR. However, we believe these alternatives have the following drawbacks:

PEEK (engineering plastic):

1. Poor processability: PEEK has a compact molecular structure, making it difficult to process using conventional methods like cutting and drilling. Special tools and techniques such as ultrasonic processing and electrical discharge machining are needed, which increases manufacturing costs and time.
2. Poor oxidation resistance: PEEK is prone to oxidation reactions at high temperatures. This leads to the formation of an oxide film on the surface, reducing its physical properties and chemical stability.

Limited UV resistance: While PEEK exhibits good chemical and heat resistance, its resistance to UV light is relatively poor. Under sunlight exposure, PEEK gradually yellows and loses its original color and gloss, affecting its performance and appearance quality.

3. Unsuitable for long-term exposure to acidic environments: PEEK may experience structural damage when exposed to acidic environments for extended periods, leading to a decrease in mechanical properties and chemical stability.

PDMS (gas separation membrane):

1. Susceptible to expansion and deformation under high pressure differentials due to its rubbery nature.
2. Difficult to prepare ultra-thin films when used as a separation membrane.

PMMA (membrane coating):

Compared to PVDF coating, the major drawbacks of PMMA resin are:

1. Lower melting temperature.
2. Higher swelling in electrolytes.
3. Poor electrochemical stability.

PAA (positive electrode binder):

Compared to PVDF binders, the main drawbacks of lithiated PAA are:

1. Poor processability, only suitable for the lithium iron phosphate system.
2. Lower flexibility.
3. Inferior cycling performance.
4. Lower energy density.

HNBR (positive electrode binder):

Compared to PVDF binders, the major drawbacks of HNBR are:

1. Poor cycling performance.
2. Higher cost.
3. Lower energy density.

3. Zero Emissions of PFAAs in the Manufacturing Process of Fluorinated Polymers

The proposal document in Annex B repeatedly mentions the critical role of PFAA surfactants such as HFPO-DA, DONA, 9Cl-PF3ONS, PFOA, PFOS, PFECHSP, etc., in the synthesis process of fluorinated polymers. These additives exhibit significant toxicity, mobility, and bioaccumulation. Moreover, residents in countries where fluorinated polymers are manufactured have been found to have these surfactants in their bodies. However, these are not the only facts.

Non-PFAA additives have begun industrial application internationally. Most fluorinated polymer manufacturers worldwide are actively researching and developing new surfactants to avoid the use of PFAA-like compounds. For example, companies like Arkema[8] and Solvay[9] have announced the cessation of PFAA additive use in the production of fluorinated polymers. Arkema employs Pluronic 31R1 as an additive to produce fluorocarbon coatings, lithium battery binders, and other emulsion products. Solvay uses water-soluble cellulose ethers and other dispersants in suspension polymerization processes for fluorinated polymer production.

Novel alternatives to PFAAs are continuously under development. Over the past decade, numerous patents have reported the use of non-fluorinated surfactants, such as copolymeric monomers, polyacrylic acid, polysiloxane, polyether, and glycosides, for emulsion polymerization of fluorinated monomers like VDF, TFE, HFP, CTFE, etc. (see Figure 1).

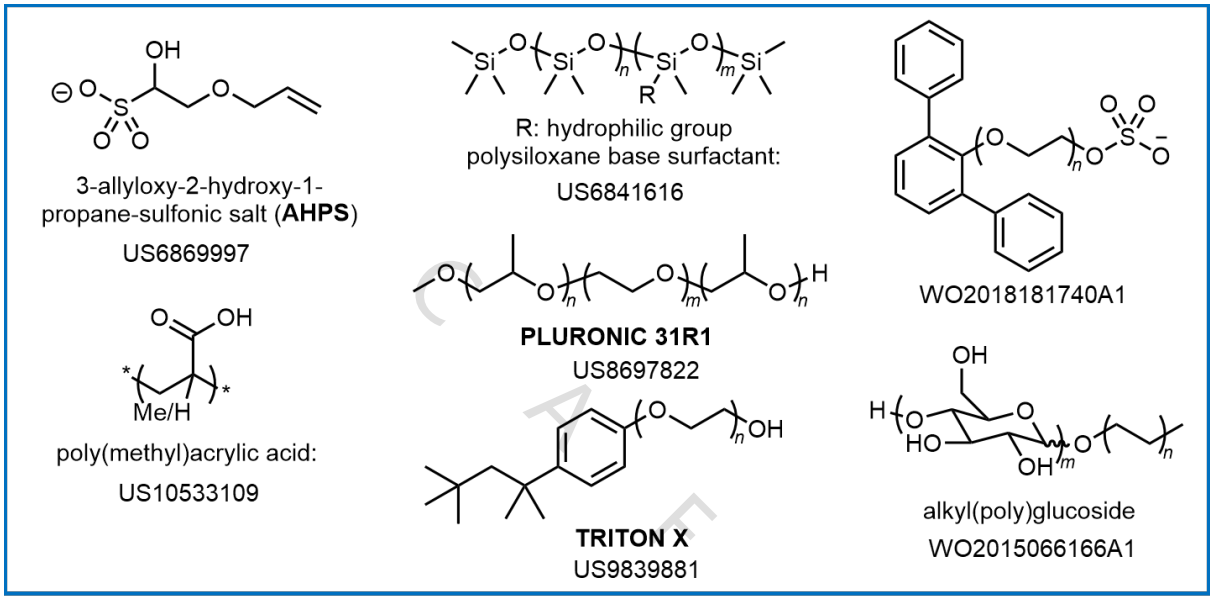


Figure 1, Patented alternatives to PFAAs.

New recycling technologies enable effective recovery of PFAAs. While the use of PFAA additives may currently be considered irreplaceable in specific product manufacturing processes, technologies for the recovery and degradation of PFAA additives are continuously evolving. In recent years, a series of new PFAA adsorbents have been reported, such as polycyclic aromatic hydrocarbons[10], cyclodextrins[11], and porous organic frameworks[12]. These novel adsorbents can effectively detect and remove PFAA molecules from production wastewater. For instance, a new porous organic framework can reduce the concentration of PFOA in wastewater to 0.1 ppb within ten minutes, essentially meeting the standards for drinking water purification. Additionally, as this material does not require the use of rare elements, cost reduction can be achieved as the technology matures and production capacity increases. This means that zero emissions of PFAAs can be achieved even under conditions where PFAAs must be used in the process.

Harmless treatment technologies ensure zero emissions of PFAAs in the fluorinated polymer manufacturing process. Dichtel and colleagues reported a method of alkaline hydrolysis to degrade PFAA molecules at low temperatures (120 degrees Celsius) into inorganic substances like fluoride ions and trifluoroacetic acid.[13] Kumar and others summarized the progress made over the past decade in electrochemically oxidizing PFAA molecules, with most reports achieving over 95% degradation in less than three hours.[14] Additionally, in a 2019 study, Zhang Yan proposed a novel reaction pathway for degrading PFAAs using persulfates under acidic conditions[15]. Persulfates are commonly used inexpensive oxidants in industrial wastewater treatment, and this route has shown high technical feasibility.

In conclusion, while the synthesis of certain fluorinated polymers for specific applications still requires the use of PFAAs as additives, it is foreseeable that with the widespread application of non-PFAA additives, the continuous development of novel PFAA alternatives, and the maturation of PFAA recovery and treatment technologies, it is entirely possible to fully replace PFAAs in the future and achieve the goal of zero emissions of PFAAs.

4. The Manufacturing Process of Fluorinated Polymers Can Avoid the Generation of New PFAAs

In the proposal document, Annex B, on pages 154 to 155, it is mentioned that in the emulsion polymerization process of PCTFE, when persulfate is used as the initiator, trimeric and tetrameric oligomers of PFAAs are produced during polymerization. However, the proposal also explicitly states that there is currently no evidence, aside from PCTFE, to prove the formation of similar toxic oligomers in the synthesis process of other fluorinated polymers.[16]

Under appropriate polymerization conditions, PCTFE oligomers will not be generated. An unmentioned fact in the proposal is that in the manufacturing process of fluorinated polymers, including PCTFE, non-water-soluble initiators are commonly used to reduce the impact of persulfate end groups on product performance.[17] Even if oligomers are formed under such reaction conditions, they would be non-water-soluble due to the lack of hydrophilic end groups. The toxicity, mobility, and bioaccumulation of such oligomers significantly differ from PFAAs. These oligomers, lacking water-soluble end groups and being difficult to dissolve in conventional organic solvents, exist as greasy substances at room temperature and pressure. They are widely used as solvent-resistant, high-temperature lubricants.[18]

The synthesis of fluorinated polymers other than PCTFE does not lead to the formation of new PFAAs. Annex B of the proposal document cites the viewpoint from a paper published by Lohmann et al. in 2020 on page 99, suggesting that in the production of fluorinated polymers, especially PVDF, oligomers with fewer than 100 repeat units are generated, which are leachable and eventually released into water and the atmosphere. Another unmentioned fact in the proposal is that the homopolymerization reactivity of CTFE is significantly lower than other fluorinated monomers like VDF and TFE. Therefore, based on the polymer chain length dynamic formula, the probability of PVDF, PTFE, and other fluorinated polymers generating oligomers is much lower than that of PCTFE. In fact, for PVDF, the molecular weight of commercial products generally ranges from 200,000 to 1,500,000. According to existing formula derivations and actual test data, oligomers below 1000 g/mol cannot be detected by SEC (Size Exclusion Chromatography) (see Figure 2).

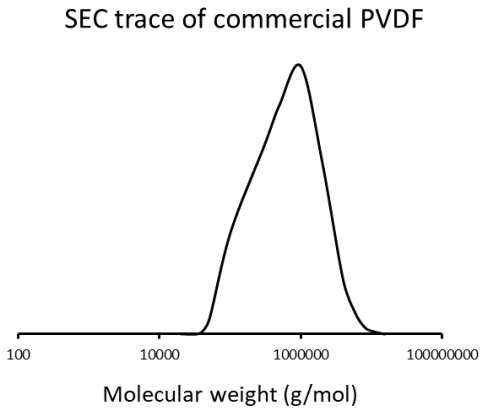


Figure 2, GPC test results for commercial PVDF products.

The non-PCTFE oligomers currently detected are not generated during the production process. The paper by Lohmann et al. published in 2020 only references partial data from a paper

by Newton et al. published in 2017[19] . While the presence of carboxylic acid compounds with repeat units from fluorinated monomers like VDF was indeed observed in the paper, the authors also pointed out that the synthesis of these compounds not only required compounds containing iodine atoms as chain transfer agents but also required the conversion of end groups under strong oxidation conditions with SO3 and H2SO4. We believe that such synthesis conditions do not involve these substances in the reaction, and therefore, are not representative of the conditions for synthesizing the majority of fluorinated polymers.

In summary, we believe that factors other than the use of PFAA additives do not lead to the emission of other PFAA compounds in the manufacturing process of fluorinated polymers.

5. Fluorinated Polymer Particles are Non-Toxic and Pose Less Harm to Organisms Compared to Non-Fluorinated Polymers.

Furthermore, the proposal references a study by Lohmann et al. published in 2020, suggesting that fluorinated polymer particles can enter cell membranes and cause biological toxicity.[20] However, this viewpoint is based on small-sized non-fluorinated polymers, such as polystyrene particles smaller than 100 nm, which can enter cell membranes through phagocytosis.[21] This extrapolation is made to fluorinated polymer particles without concrete evidence in the article. In reality, the particle size of fluorinated polymers generated in the production process typically ranges from 100 to 300 nm (see Figure 3), which is not conducive to cellular phagocytosis. Moreover, the lower surface energy of fluorinated polymers further discourages cellular phagocytosis. Therefore, fluorinated polymers do not enter the intracellular environment to induce biological toxicity.

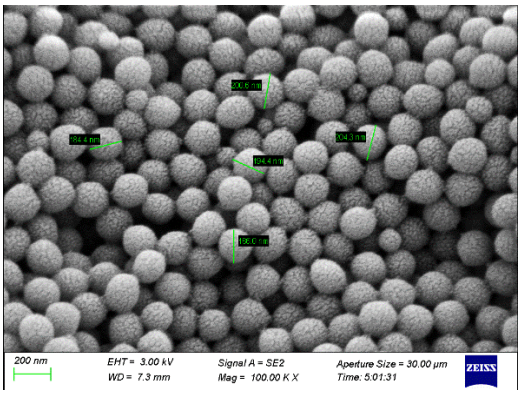


Figure 3, SEM magnified image of commercial PVDF products.

The proposal document in Annex B also cites the fact that fluorinated polymer particles have been detected in the bodies of deep-sea fish on pages 220 to 221, aiming to demonstrate the bioaccumulation of these particles. However, it is worth noting that the specific details mentioned in the proposal are related to PTFE particles larger than 500 micrometers, detected using FTIR. These particles far exceed the size of biological cells, and therefore, do not induce biological toxicity by entering the intracellular environment. The proposal also mentions that these particles are generated during processing and use, and currently, there is no data proving that these particles have issues with leaching PFAAs. Furthermore, due to their excellent chemical stability, fluorinated polymers find wide applications in implantable medical devices. Thus, even if these polymer particles exhibit bioaccumulation, they do not result in biological toxicity.

More importantly, the issue of polymer particles is a challenge faced by all polymers, not exclusive to fluorinated polymers. Considering that the usage of fluorinated polymers is much lower than that of non-fluorinated polymers, the proposal should not singularly prohibit the production and use of fluorinated polymers for this reason. The proposal also points out the fact that in the Han River in South Korea, PTFE particle content is only 16%, much lower than that of PE (40%) and PP (23%). Coupled with the superior chemical stability of fluorinated polymers and their lack of any biodegradability, they do not produce toxic leachables with bioaccumulation.

Therefore, we contend that there is no direct or indirect evidence indicating that fluorinated polymer particles pose an unacceptable harm to human health. Moreover, non-fluorinated polymers have a more significant impact on this issue. Therefore, fluorinated polymers should not be singled out for prohibition based on this rationale, while excluding non-fluorinated polymers.

6. Due to the definition of persistence, non-fluorinated polymers also exhibit high persistence. Therefore, we believe that prohibiting the use of fluorinated polymers based on their high persistence is inappropriate.

Fluorinated polymers, as a high-cost, high-value-added industry, owe their stable market presence and ability to survive in intense competition to their outstanding persistence, particularly in specialized applications where non-fluorinated polymers are unable to provide a substitute. Moreover, in terms of the definition of persistence, non-fluorinated polymers like PE and PP, with degradation cycles exceeding 1000 years, should also be classified as persistent compounds.[22] If fluorinated polymers were replaced with non-persistent alternatives, it could potentially lead to higher carbon emissions and increased environmental pollution in human society.

7. Under appropriate conditions, the incineration of fluorinated polymers does not lead to the emission of greenhouse gases and small-molecule PFAS.

The proposal, in Annex B from page 209 to 210, cites Huber et al.'s 2009 study, reporting the generation of fluorinated greenhouse gases such as CF4 (PFC-14), CHF3 (HFC-23), and C2F6 (PFC-116) during the incineration of PTFE. Additionally, it references Stoiber et al.'s 2020 perspective, suggesting that incinerating fluorinated polymers produces toxic gases and greenhouse gases. Based on this, it is argued that fluorinated polymers inevitably emit greenhouse gases throughout their life cycle, holding them accountable for climate change impacts.

We find that this viewpoint involves a generalization error in its derivation. Firstly, the facts presented in Huber et al.'s 2009 paper only pertain to the controlled incineration of PTFE at temperatures between 700-1050 degrees Celsius, producing fluorinated greenhouse gases.[23] Furthermore, Stoiber et al.'s 2020 reference to toxic gas generation from incinerating fluorinated polymers is derived from Ellis et al.'s 2003 data, which demonstrated the gradual breakdown of PTFE at around 360 degrees Celsius, releasing primarily toxic molecules like TFA and HFP.[24]

Under appropriate conditions, fluorinated polymers can be decomposed into harmless compounds. It is worth noting that there are various types of fluorinated polymers, and their decomposition products can vary significantly under different conditions. Améduri et al.'s 2023

paper summarizes the decomposition products of different fluorinated polymers at different temperatures. It is reported that even PTFE, when decomposed at an appropriate temperature (e.g., 450 degrees Celsius), yields only harmless HF and COF2 (Figure 4).[25] Additionally, it has been documented that commercially mature incineration techniques and equipment can effectively convert fluorinated polymers into HF and CO2 products (Figure 5).[26]

Polymer	T (°C)	Main products
PTFE	450	COF_2. HF
	400–500	TFE, HFP, PFIB
	500	HFP, TFA
	530	CF_4 (PFC-14), C_2F_6 (PFC-116), TFE, HFP, c-C_4F_8 (c-OFB) (PFC-318)
	550	CF_2O, C_2F_6, CF_3CFO, C_5F_4, CF_3CF_2CFO, $(CF_2)_3O_2$
	600–700	TFE, OFCB) (PFC-318)
	750–800	HFP
	850–900	PFIB
	800 °C	CF_4 (PFC-14)
	>900 °C	C_2F_6 (PFC-116)
	850	HFP, TFE
	750–1050	C_2F_6 (PFC-116), CF_4 (PFC-14)
ETFE	350	COF_2, PFBE, TFE, CO
ECTFE	500	TFA, CDFA
FEP	400	COF_2, CHF_3 (HFC-23), HFP, TFE, PFIB
PFA	400	COF_2
PEEPE	500	TFA
CPTFE/PCTFE	500	CPFP, CDFA
PTFE/PFA + PTFE/FEP	800	CH_4, CHF_3 (HFC-23), C_2F_6 (PFC-116)

Figure 4, Summary of decomposition products of different fluorinated polymers at different temperatures.

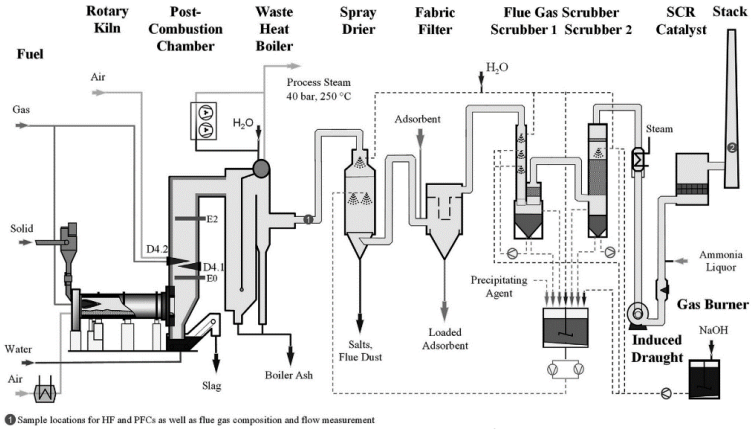


Figure 5, Commercial fluorinated organic compound incineration equipment.

Fluorinated compounds generated under unsuitable incineration conditions can be efficiently recovered using inexpensive adsorbents. In recent years, novel fluorinated gas adsorbents have seen significant development, exhibiting marked improvements in adsorption capacity and selectivity. For instance, the use of novel amorphous carbon[27] or MOF materials[28] Among them, MOF materials reported to use inexpensive formic acid as a ligand have achieved over 300 times higher gas adsorption selectivity under nitrogen atmospheres, representing a highly promising commercial prospect for fluorinated gas adsorption materials.

Apart from incineration, there are more energy-efficient methods for polymer degradation. The C-F bonds in fluorinated polymers are resistant to oxidation but susceptible to reduction. Utilizing high-reducing photoredox catalysts[29] or reducing minerals[30] can facilitate the environmentally benign degradation of fluorinated polymers at lower energy consumption. For example, WO3 can effectively reduce the CF2 carbene generated during the incineration of fluorinated polymers to carbon dioxide, simultaneously producing harmless WFxOy inorganic

minerals. This scheme represents an inexpensive method for treating fluorinated polymer incineration exhaust gases.

Fluorinated polymers containing hydrogen elements, such as PVDF and ETFE, can be harmlessly degraded with alkaline substances. Ameduri et al. reported that in the presence of strong alkalis like KOH or Ca(OH)2, hydrogen-containing fluorinated polymers like PVDF and ETFE can be degraded at 4 MPa and 250 degrees Celsius into fluoride salts and carbon dioxide, with the generated TOC byproduct being less than 2%.[31] For hydrogen-containing fluorinated polymers, degradation conditions are gentler, and synthetic fluorite minerals can be produced for the synthesis of new fluorinated chemicals, greatly promoting the industrialization of fluorinated polymer recovery.

Lifecycle management is the most cost-effective way to control the environmental risks of fluorinated polymers. In reality, there is currently no data supporting the extent of greenhouse gas and toxic molecule emissions from the improper incineration of fluorinated polymers. Therefore, we believe that focusing on the recycling management of fluorinated polymers and developing appropriate post-treatment technologies is a more suitable solution to the issue of incineration emissions.

PART III Trifluoroacetic acid (TFA) should be excluded from the PFAS restriction proposal

1. TFA is not PBT, vPvB or PMT, although it is persistent.

According to the REACH registration dossier and the Chemical Safety Report (CSR), TFA is a persistent because it does not meet the criteria either for toxicity or for bioaccumulation in REACH Annex XIII (Table 1). As can be seen in Table 1, the log Pow value of TFA is 0.5, which is lower than the judgement criterion value of REACH of 4.5, and its NOEC value is greater than 2.5mg/L, which is much higher than the judgement standard set by REACH. Therefore, TFA should be a non-bioaccumulative and non-toxic substance. ECHA has reviewed and evaluated the TFA dossier and concluded that there is no need to take further regulatory action[32].

Table 1 Identification of PBT toxicity and bioaccumulation for TFA[33][34]

		bioaccumulation（B）	toxicity（T）
criteria[2]		log Pow>4.5，and BCF>2000	Aquatic chronic toxicity (algae, Daphnia magna, fish)NOEC<0.01mg/L
TFA	properties[3]	log Pow=0.5	NOEC>2.5 mg/l
	result	Non-bioaccumulative substances	Non-toxic substance

Note: TFA data from Appendix Table 1 of Reference 2, P161

2. TFA has completely different toxicological properties from other PFAAs, has a low environmental impact and should not be classified with other PFAAs.

2.1 The toxicological properties of TFA are different from those of PFAAs with long carbon chains.

(1) Page 5 of Rest_pfas_annex_b suggests that TFA which has been demonstrated to be a persistent substance with harmful properties in a comparable way as other PFASs with longer fluorinated alkyl chains, while it is not correct. p278 of the EEAP-2022 report clearly states that these longer chain PFAS have key chemical, physical, and biological properties that become quite different with increasing length of the carbon-chain. For example (see Table 2), log K_{OW} (a measure of partitioning between lipids in organisms and water); Henry's Law Constant (a measure of partitioning between water and air); K_{OC} (a measure of adsorption to soil and sediment); and the half-life in humans (related to chronic exposure and chronic toxicity) all vary with changes in the length of the carbon chain.

Table 2 Key physical, chemical, and biological properties of the linear perfluorinated carboxylic acids from 2-8 carbons[3]

Property	Trifluoro-acetic acid	Perfluoro-propanonic acid	Perfluoro-butanoic acid	Perfluoro-pentanoic acid	Perfluoro-hexanoic acid	Perfluoro-heptanoic acid	Perfluoro-octanoic acid
Abbreviation	TFA	PF TFA	PFBA	PFPeA	PFHxA	PFHpA	PFOA
Number of carbon atoms	2	3	4	5	6	7	8
Log K_{OW}	0.5	1.5	2.43	3.262	3.48	5.024	5.905
Henry's Law Constant (atm m^{-3} mol^{-1})	1.1×10^{-7}	4.43×10^{-6}	0.0051	0.029	0.174	1.521	3.044
K_{OC} (L kg^{-1})	0.17-20	12.7	58	270	1247	5761	30440
Half-life in humans	16h	NA	72-81h	NA	14-49d	1.2-1.5yr	2.1-10yr

These relationships are well recognized as they are important drivers of adsorption, distribution,

and excretion in animals, which are major determinants of adverse effects. Regulating TFA in a chemical group of PFAS would be inconsistent with the risk assessment of TFA. The EEAP-2022 report explicitly cites the consensus of the majority of experts that a majority of a panel of experts agreed that "all PFAS should not be grouped together, persistence alone is not sufficient for grouping PFAS for the purposes of assessing human health risk, and that the definition of appropriate subgroups can only be defined on a case-by-case manner." In addition, the majority opinion with respect to toxicology was that "it is inappropriate to assume equal toxicity/potency across the diverse class of PFAS". The UNEP[4-5][35][36] reports that, based on the available studies, unlike PFOS and PFOA, TFA presents a minimis risk to human and environmental health.

(2) Rest_pfas_annex_b page 5 suggests that TFA has been shown to be a persistent substance with harmful properties. However, recent reports such as the following suggest that the proposal is wrong. As the German UBA 2021 report[37] and the Norwegian Environment Agency 2017 report[38] show that the risk of toxicity of TFA to organisms and human beings is low and that the toxicity of TFA has been tested on a wide range of aquatic and terrestrial species and can be assessed as low. It also shows that TFA has no health effects at measured concentrations and is not harmful to ecosystems according to available studies.

Wolfgang Dekant et al[39] reviewed mammalian toxicity and human exposure to TFA and the results of their study showed that: (i) the potential of TFA to induce acute toxicity is very low; (ii) oral repeated dose studies in rats have identified the liver as the target organ with mild liver hypertrophy as the lead effect; (iii) biomarker analyses showed that TFA is a weak peroxisome proliferator in rats; and (iv) administration of TFA to rats did not induce adverse effects in an extended one-generation study and in a developmental toxicity study or induce genotoxic responses; all above suggest that TFA has very low toxic effects on mammals.

Wolfgang Dekant et al also mentioned that the NOAEL of 10 mg/ kg bw/day for TFA in rats was obtained from 90-day experimental data, which led to a tolerable daily intake (TDI) of 0.018 mg/kg bw in humans, and a study of the maximum daily exposure of humans to TFA based on the concentrations of TFA detected in various environments, as well as on the maximum daily exposure of TFA obtained from the results of the EFSA and Euratom studies (Table 3). Food Safety Authority (EFSA) studies to obtain the maximum measure of TFA to which humans are exposed on a daily basis, and the relevant data were used to assess the exposure boundary value (MoE) for human

intake of TFA from the environment (Table 3). The results showed that the majority of people had exposure boundary values (MoE) ranging from 4,000 to 476,000. MoEs for human exposures to TFA are well above 100, indicating that no health risk exists. This indicates that the levels of TFA in the environment are several orders of magnitude lower than those considered toxic.

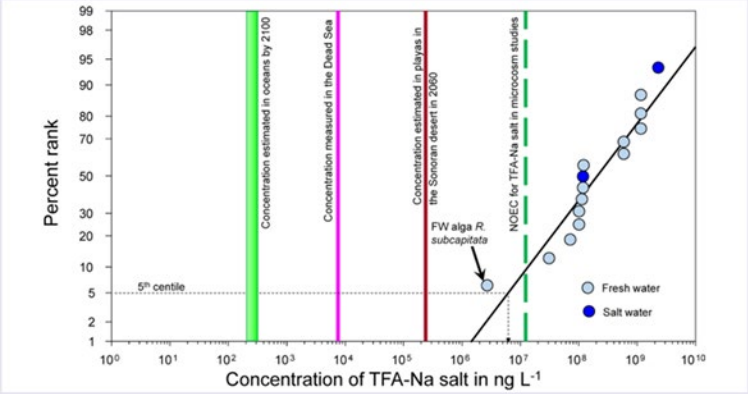
Table 3 Margin of exposure assessment for human exposures to TFA from environmental sources based on a NOAEL of 10 mg TFA/kg bw/day from a 90-day oral study in rats

Source of human exposure	Dose received (water consumption of 2 L/day, body weight of 60 kg)	Margin of exposure to NOAEL of 10 mg/kg bw/day in rats
Drinking water, based on the highest concentration (4.8 µg TFA/L) detected in environmental water samples taken from 2014 to 2022	0.16 µg/kg bw/day	62,500
Drinking water, based on the highest concentration (0.63 µg TFA/L) used by EFSA	0.021 µg/kg bw/day	476,190
Diet, based on the assessment of dietary exposure to TFA by EFSA in 2014	2.5 µg/kg bw/day	4000

The EEAP-2022 report demonstrates that “TFA is of low toxicity to mammals” and “TFA in beer and tea is a trace residue of low risk to humans”.

2.2 Environmental impacts of TFA are minimal.

The effects of TFA on aquatic organisms are described on page 290 of the EEAP-2022 report (Figure 1), a no observed effect concentration (NOEC) of 2.5 mg a.e. L^{-1} (2,500,000 ng L^{-1}) was reported based on inhibition of growth. B The margin of exposure between the distribution of NOECs and the observed and expected concentrations in the oceans and endorheic basins is several



orders of magnitude and is indicative of *de minimis* risk.

Fig. 1 A log-probability cumulative frequency plot of no observed effect concentrations (NOEC) of trifluoroacetic acid salt compared to various environmental concentrations in water. The dashed vertical green line indicates the NOEC for TFA-Na salt in microcosms is a toxicology-based criterion

The results of the above studies have proved that TFA has characteristics that are particularly different from those of long-chain PFAS such as PFOA and PFOS, which are now restricted, which means TFA should be studied as a separate substance. At present, the research on the various toxicological, biological and environmental effects of TFA is not sufficient, and further relevant studies are needed before deciding on specific control measures.

3. Environmental concentrations of TFA that are unlikely to cause adverse effects now and in the certain future.

Page 6 of proposal annex_b suggests that TFA concentrations in municipal and tap water have been increasing over the last decades. The EEAP-2022 report concluded that although releases will add to the existing load of TFA in the environment but predicted amounts are well below the threshold for concern with respect to human and environmental health .The results from Wolfgang Dekant et al[8] who provided presence of TFA in water of different origins (Table 4), show that the current maximum presence of TFA in rainwater is 4.78 μg/L, in tap water is about 0.4 μg/L, in surface water is 1.1 μg/L, and in spring water is 1.8 μg/L, 59 μg/L in leachate and effluents from waste disposal sites, and 2.4 μg/L in soil; these presence of TFA are well below $5.6x10^2$ μg/L (According to the ecotoxicity data related to TFA documented in the REACH registry dossier, the lowest Predicted Non-Effective Concentration (PNEC) of TFA for freshwater is $5.6x10^2$ μg/L[40]), also indicating that the current concentration of TFA in the environment is well below the concentration that constitutes a hazard.

Table 4 Presence of TFA in water of different origins

Source	Sampling period	Concentration of TFA [μg/L]	Source	Sampling period	Concentration of TFA [μg/L]
Rainwater/snow			Spring water		
Germany	2018-2020	0.028-4.78 (min.-max. values)	Germany	1995–1996	<0.01-0.32 (min.-max. values)

China	2016	0.0088-1.8 (min.-max. values)	China	2016	1.8 (mean)
Tab water			Leachates and effluents from waste disposal sites		
USA	1995-1996	0.041-0.15 (min.-max. values)	China	2016	2-59 (median: 17)
China	2016	0.384 (mean)	Soil		
Germany	2016	0.310(median)	Germany	2017/2019	<0.2-2.4 (min.-max. values)
Surface water			China	2016	0.06-2.08 (min.-max. values)
Germany	2017	0.35-0.51 (min.-max. values)	Beverages		
USA	2021	0.102-0.714 (mean values)	Beer	ns	<0.100-51 (min.-max. values)
China	2016	0.5-1.1(min.-max. values)	Tea	n.s	0.390-13 (min.-max. values)

Artificially sourced TFA is mainly formed as a result of atmospheric degradation of some HFCs and HFOs. For most HFC/HFO refrigerants, degradation rates/yields into TFA are small. Only a few commercialized fluorinated gases decompose into fractions of TFA over 30% (including, HFO-1234yf, HFC-227ea, HFC-134a). Refrigerant degradation products would only result in a slight increase in total TFA concentrations compared to pre-existing TFA concentrations. The maximum potential amount of TFA generated by refrigerants (the two refrigerants that have the greatest impact on TFA emissions) was examined in the EEAP-2022 report, p. P282 (Table 5), indicating that TFA, a product of degradation of refrigerants, is likely to accumulate in some bodies of water, and it is unlikely to have a negative impact until 2100. The 1234yf EIS[41] also suggests that although TFA concentrations have increased in water bodies, they are far from the concentration levels that would be harmful to aquatic organisms, and that TFA concentrations in other environmental media are hardly likely to be harmful to organisms.

Table 5 Projected global yields of TFA from HFC-134a and HFO-1234yf and total deposition between 2020 and 2100

	HFC-134a	HFO-1234yf	Sum
Annual formation of TFA (a.e., acid equivalents)			
2020	0.01–0.03 Tg yr^{-1}	0.03–0.03 Tg yr^{-1}	0.04–0.06 Tg yr^{-1}
2050	0.02–0.05 Tg yr^{-1}	0.34–0.49 Tg yr^{-1}	0.36–0.54 Tg yr^{-1}

2100	0.01–0.02 Tg yr^{-1}	0.63–1.03 Tg yr^{-1}	0.64–1.05 Tg yr^{-1}
Sums of deposited TFA (a.e.)			
2020–2050	0.5–1.5 Tg	5.3–6.6 Tg	5.8–8.1 Tg
2020–2100	1.0–2.9 Tg	30.5–49.0 Tg	31.5–51.9 Tg
Concentration of TFA as the sodium salt in the oceans in		2050	244–246 ng L^{-1}
		2100	266–284 ng L^{-1}

4. Inclusion of TFA in the PFAS could impede the implementation of the Kigali Amendment to the Montreal Protocol and seriously undermine global efforts to combat climate change.

The TEAP-May2023 Progress Report[42]states that refrigerants currently used in refrigeration, air conditioning and heat pump (RHVAC) applications include hydrofluorocarbons (HFCs) substances and blends such as HFC-134a, R410A, and R407C. From a global climate/warming perspective, these F-gases with high global warming potential (GWP) are one of the major contributors to global warming. For this reason, the international community reached the Kigali Amendment to the Montreal Protocol in 2016, which requires countries to progressively reduce the production and consumption of HFCs, with the European Union (EU) expected to reduce its consumption of HFCs to 80% of its baseline by 2045. Successful implementation of the Kigali amendment is projected to reduce global warming by 0.4 °C by the end of the century.

Low GWP alternatives to HFCs such as HFOs, HCFOs, etc. have now become mainstream alternatives to HFCs due to their good environmental and application performance, e.g., HFO-234yf has been widely used as a replacement for HFC-134a in automotive air conditioning, and HCFO-233zd is used as a polyurethane blowing agent as a replacement for HFC-245fa. However, in accordance with the PFAS Restriction Proposal definition of PFAS, these alternatives to HFCs are also included in the definition of PFAS. This has caused considerable distress in the selection of alternatives to HFCs globally, with the concern that the proposed PFAS regulation may result in some or all fluorinated alternatives being unavailable, resulting in some application industries for alternatives to HFCs delaying the selection of alternatives to HFCs and related investment decisions. Since it generally takes about 10 years for a new alternative to go from development to commercial application, once low GWP alternatives to HFCs such as HFOs, HCFOs, etc. are restricted, the global compliance process for the Kigali Amendment will be seriously affected. The TEAP-

May2023 Progress Report analyses the possible consequences of the PFAS restriction on the RACHP market. A broad-ranging PFAS restriction, if finalised, for the RACHP market would likely (i) slow the uptake of low GWP alternative refrigerants (which is crucial to meet HFC phase-down targets), (ii) limit the energy efficiency of medium sized RACHP systems and (iii) slow the roll-out of heat pumps (which are much needed to decarbonise heating). These three issues could likely lead to an increase in greenhouse gas emissions from the RACHP sector.

The PFAS restriction proposal will affect the implementation of the Montreal Protocol, whose Kigali amendment is to require global HFCs reduction to achieve the 0.4 °C reduction target, and to achieve the reduction of HFCs, it is necessary to have low GWP alternatives, and HFOs, perfluorinated ketones, etc., are one of the mainstream alternatives at present, and they are difficult to be replaced in many occasions (refrigeration, fire extinguishing). Therefore, if TFA is banned as PFAS, it means that the use of low GWP alternatives such as HFOs, HCFOs, perfluoroketones, etc. is banned, which leads to difficulties in substitution, thus affecting the process of HFCs reduction.

5. The source of TFA is uncertain.

Rest_pfas_annex_b, p. 5-6, suggests that most of the TFA in the oceans is from natural origin, whereas in the atmosphere, sediments, freshwater, and needles of conifers, TFA is likely to come from anthropogenic sources. The reason for this is that the total amount of TFA present in the global environment greatly exceeds the expected contribution from various industrial sources. Recently, however, evidence for natural TFA has been examined and a different conclusion has been reached on the origin of TFA in the oceans, concluding that the presence of TFA in the deep sea and the lack of a closed TFA budget do not provide sufficient evidence that TFA occurs naturally, especially in the absence of a plausible mechanism for its formation.

The conclusions given in Annex B of the proposal proved that the submitters of the proposal had not clearly identified the source of TFA, indicating that TFA was a substance of uncertain origin and not suitable for outright prohibition.

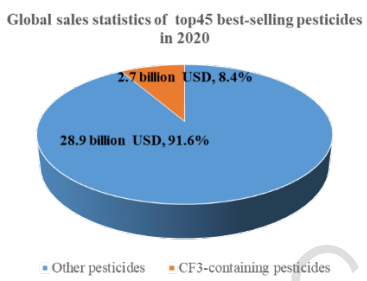
6. TFA has played an irreplaceable role in the production process of pharmaceutical and pesticides.

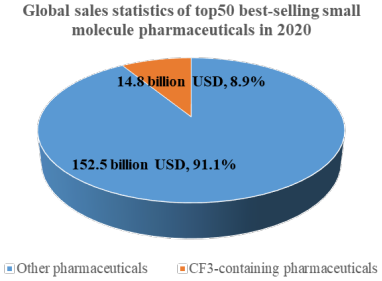
There are two reasons to support this view. Firstly, the Dossier Submitter of PFAS Proposal

from five national authorities consider that the derogation covers all preceding steps that are necessary to produce the product, including pharmaceuticals and pesticides that complied with relevant EU regulations. But there is no specific definition of necessary production. As all know, CF_3-containing pharmaceuticals and pesticides play a critical role in global market. Currently, the main raw materials for large-scale production of CF_3-containing aliphatic and heteroaromatic products are TFA and related downstream compounds (ethyl trifluoroacetate, trifluoroethanol, ethyl 4,4,4-trifluoroacetoacetate, trifluoroacetylacetone, 4-ethoxy-1,1,1-trifluoro-3-buten-2-one, etc.), which are difficult to replace with other raw materials or synthesis methods. In addition, TFA could also be used as reaction solvent, analytical reagent, protective reagent, and deprotective reagent, which are widely used in production of pharmaceuticals and pesticides. Therefore, TFA should be considered as part of necessary production and excluded from the production of pharmaceuticals and pesticides. Secondly, although the CF_3-containing pharmaceuticals and pesticides are excluded from the proposal, the fact of their degradation products contain TFA is obviously existence. If TFA cannot be excluded from the proposal, it will have a serious impact on the development of new CF_3-containing products and even the whole industry of pharmaceuticals and pesticides.

6.1 TFA should be considered as part of necessary production and excluded from the production of pharmaceuticals and pesticides.

CF_3-containing pharmaceuticals and pesticides play a critical role in human health and food safety. According to statistical data from Jon T. Njardarson group[43], there were five CF_3-containing products with a total sale of 14.8 billion USD and a proportion of 8.9%, among the top50 small molecule pharmaceuticals by retail sales in 2020, including enzalutamide, sitagliptin, sitagliptin/metformin combination, teriflunomide, and nilotinib. According to statistical data from Phillips McDougall[44], there were also five CF_3-containing products with a total sale of 2.7 billion USD and a proportion of 8.4%, among the top45 pesticides (fungicides, insecticides, herbicides) by sales in 2020, including trifloxystrobin, picoxystrobin, cyhalothrin, fipronil, and bifenthrin.

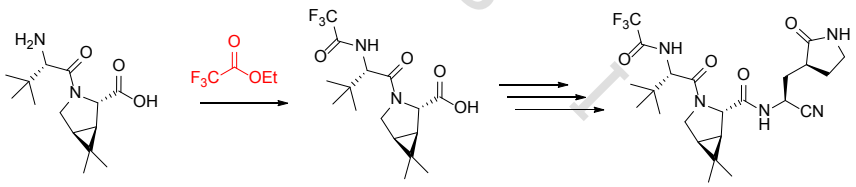




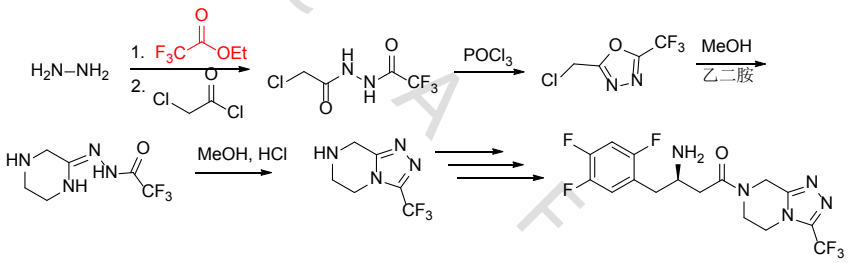
In the production process of pharmaceuticals and pesticides, there are three main methods for introducing trifluoromethyl into molecules. The first one is chlorination and then fluorination of methyl on molecules. This method has limitations such as use of toxic gases (Cl_2 and HF), high requirements for equipment, and low chemical selectivity. The second method is using trifluoromethylation reagents such as halogenated trifluoromethane, $TMSCF_3$, Togni reagent, Langlois reagent, and Umemoto reagent. This method can regioselectively introduce trifluoromethyl into molecular, but there are limitations such as expensive reagents, poor atomic economy, harsh reaction conditions, and difficulty in large-scale production. The third method is using TFA and related downstream compounds as raw materials to construct target molecules through functional group conversion or carbon-carbon bond formation. This method has the advantages of good selectivity, mild conditions, high yield, and low cost. It is currently the main method for large-scale production of CF_3-containing aliphatic and heteroaromatic products, which is difficult to be replaced by other raw materials or synthesis methods. There are several typical examples as follows:

6.1.1 Pharmaceutical production

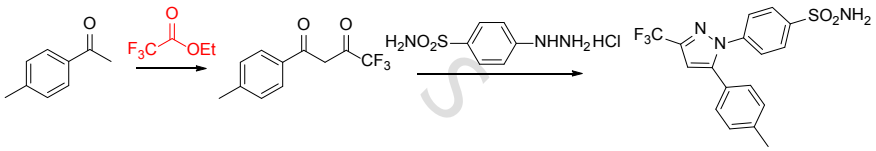
Nirmatrelvir is one of active ingredients in the anti COVID-19 drug Paxlovid, which was approve by EMA in 2022[45]. In the same year, the global sale of Paxlovid is 18.9 billion USD, ranking 1st in global best-selling small molecule pharmaceuticals. The patented synthesis route of nirmatrelvir is to first construct a trifluoroacetamide group using ethyl trifluoroacetate (downstream compound of TFA) as the raw material, and then synthesize the target molecule through multi-step reactions[46]. There is no industrialized alternative route so far.



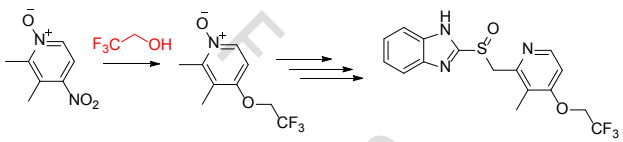
Sitagliptin is a commonly used diabetes drug authorized by HMA[47]. In 2022, the global sale of sitagliptin is 2.8 billion USD, ranking 23rd in global best-selling small molecule pharmaceuticals. The patented synthesis route of sitagliptin is to first construct trifluoromethyl oxadiazole intermediate using ethyl trifluoroacetate as raw material, and then synthesize the target molecule through multi-step reactions[48]. There is no industrialized alternative route so far.



Celecoxib is a non-steroidal anti-inflammatory drug authorized by HMA. In 2022, the global sale of celecoxib is 0.34 billion USD, ranking 191st in global best-selling small molecule pharmaceuticals. The patented synthesis route of celecoxib is to first construct trifluoroacetyl ketone intermediate using ethyl trifluoroacetate as raw material, and then synthesize the target molecule through multi-step reactions[49]. There is no industrialized alternative route so far.



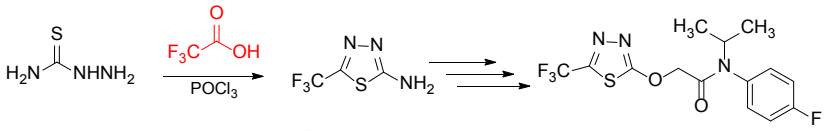
Lansoprazole is an anti-ulcer drug, authorized by HMA. In 2022, the global sale of lansoprazole is 0.51 billion USD, ranking 148th in global best-selling small molecule pharmaceuticals. The patented synthesis route of lansoprazole is to first construct trifluoroethyl ether intermediate using trifluoroethanol (downstream compound of TFA) as raw material, and then synthesize the target molecule through multi-step reactions[50]. There is no industrialized alternative route so far.



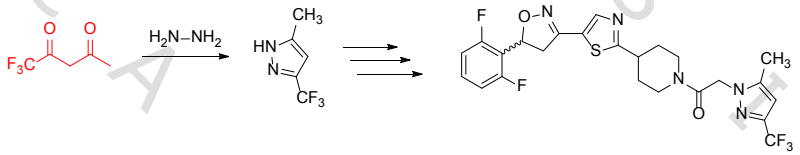
6.1.2 Pesticide production

Flufenacet is a herbicide developed by Bayer and authorized by the European Commission[51]. The global sale is 0.25 billion USD in 2019. Flufenacet is widely used in many countries all over the world, including the EU. The patented synthesis route of flufenacet is to first construct

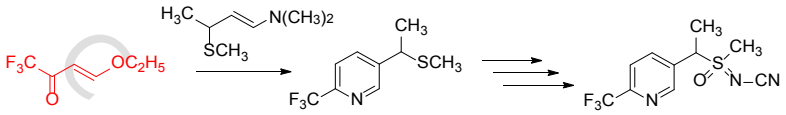
trifluoromethyl thiadiazole intermediate using TFA as raw material, and then synthesize the target molecule through multi-step reactions[52]. There is no industrialized alternative route so far.



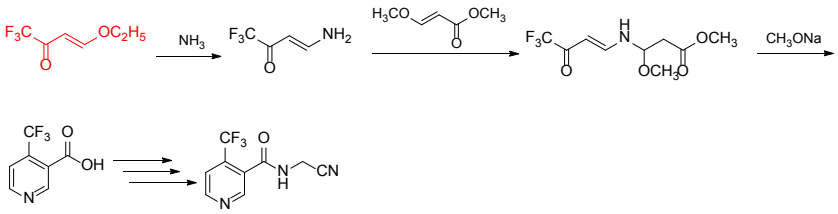
Oxathiapyrolin is a fungicide developed by Corteva and Syngenta and authorized by the European Commission. The global sale is 55 million USD in 2019. Due to its novel mechanism of action, oxathiapyrolin has specific effects on downy mildew and late blight. The patented synthesis route of oxathiapyrolin is to first construct trifluoromethyl pyrazol intermediate using trifluoroacetylacetone (downstream compound of TFA) as raw material, and then synthesize the target molecule through multi-step reactions[53]. There is no industrialized alternative route so far.



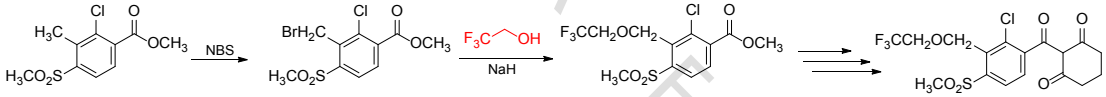
Sulfoxaflor is a neonicotinoid insecticide developed by Corteva and authorized by the European Union. The global sale is 0.19 billion USD in 2019. Sulfoxaflor has become an alternative product of traditional neonicotinoid insecticides due to low bee toxicity. The patented synthesis route of sulfoxaflor is to first construct trifluoromethyl pyridine intermediate using 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (downstream compound of TFA) as raw material, and then synthesize the target molecule through multi-step reactions[54]. There is no industrialized alternative route so far.



Flonicamid is an insecticide developed by ISK and authorized by the European Union. The global sale is 0.12 billion USD in 2021. Due to its unique mechanism of action and low bee toxicity, flonicamid has a good market prospect. The patented synthesis route of flonicamid is to first construct trifluoromethyl pyridine intermediate using 4-ethoxy-1,1,1-trifluoro-3-buten-2-one as raw material, and then synthesize the target molecule through multi-step reactions[55]. There is no industrialized alternative route so far.



Tembotrione is a herbicide developed by Bayer and authorized by the European Union. The global sale is 0.25 billion USD in 2019. Trifluoroethanol is used as raw material in the patented synthesis route of tembotrione[56]. There is no industrialized alternative route so far.



6.1.3 Other application

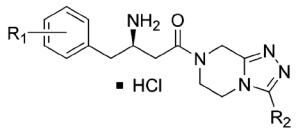
In the production process of pharmaceuticals and pesticides, TFA could not only be used as the raw material, but also as reaction solvent, analytical reagent (such as HPLC mobile phase), deprotection reagent for protective groups, and protective reagent for amino groups. It is widely used in the synthesis of complex molecules such as amino acids, peptides, and steroids.

6.2 Due to the serious impact on the development of new CF_3-containing products and even the whole industry of pharmaceuticals and pesticides, TFA should be excluded from the proposal.

Trifluoromethyl functional group is widely used in the design and development of pharmaceuticals and pesticides due to its strong electron withdrawing ability, which can change the charge distribution and configuration of molecules, thereby affecting their physical and chemical properties and enhancing biological activity. In the field of drug development, trifluoromethyl is often used to improve the cell membrane permeability and pharmacokinetic properties of drugs, such as increasing oral bioavailability and reducing liver metabolism. The interaction between drug molecule and target enzyme could be enhanced, while the activity and selectivity of drug improved by introducing trifluoromethyl[57].

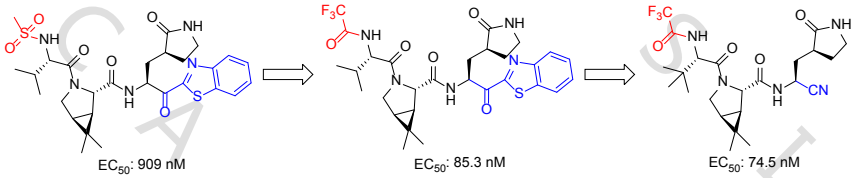
For example, during the discovery of sitagliptin, when the substituent R_2 is trifluoromethyl, its activity is significantly higher than H, ethyl, perfluoroethyl and other substituents[58].

Table 6 Inhibitory activity of sitagliptin derivatives on target enzymes

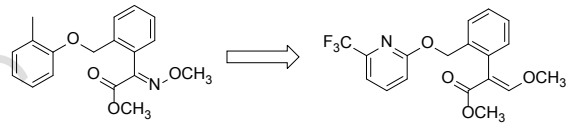


compd	R1	R2	DPP-IV IC_{50} (nM)	QPP (nM)	DPP8 (nM)	DPP9 (nM)
22	3,4-di-F	H	455	>10000	38000	>100000
23	3,4-di-F	Et	231	64000	45000	>100000
24	3,4-di-F	CF_3	128	98000	46000	>100000
25	2,5-di-F	CF_3	27	>100000	69000	>100000
1	2,4,5-tri-F	CF_3	18	>100000	48000	>100000
26	2,4,5-tri-F	H	68	>10000	72000	>100000
27	2,4,5-tri-F	CF_2CF3	71	78000	80000	>100000
28	2,5-di-F	CH_2CF_3	103	>100000	35000	>100000

Another example is the discovery of nirmatrelvir. The antiviral activity has been significantly improved by 10 times by the replacement of the methanesulfonyl with trifluoroacetyl on the amino group[59].



In the field of pesticide development, trifluoromethyl is often used as a bioisostere of halogen, cyano, and short chain alkyl groups in the molecular design to enhance the activity and persistence[60]. For example, the fungicide picoxystrobin is optimized based on the structure of kresoxim-methyl. By replacing phenyl with trifluoromethyl pyridine group, the internal absorption, fluidity, and metabolic stability of pesticides could be improved, thereby showing better activity against bacteria[61].



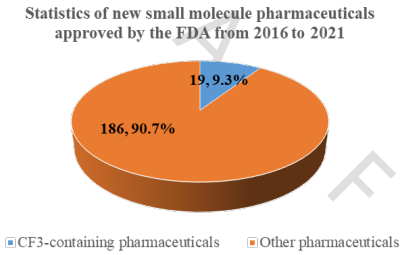
Kresoxim-methyl Picoxystrobin

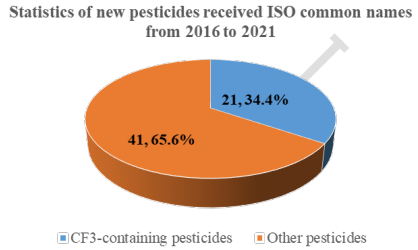
Table 7 Redistribution properties of kresoxim-methyl and picoxystrobin

	Kresoxim-methyl	Picoxystrobin
Fluidity in leaf	low	medium
Metabolic stability in leaf	low	stable
Transfer fluidity	low	medium
Internal absorption in xylem	×	√
Internal absorption in new leaf	×	√
Fluidity in phloem	×	×

Due to the unique properties of trifluoromethyl, CF_3-containing pharmaceuticals and pesticides have become an important direction for new product development. According to statistical data from

FDA[62], there are 19 new CF_3-containing products with a proportion of 9.3%, among 205 new small molecule pharmaceuticals approved by the FDA from 2016 to 2021. According to statistical data from the British Crop Protection Council (BCPC)[63], there are 21 new CF_3-containing products with a proportion of 34.4%, among the 61 new pesticides that received ISO common names from 2016 to 2021. Moreover, there are still many new CF_3-containing pharmaceuticals and pesticides in the product development pipeline, while companies have invested a lot of manpower and resources in the early stage. Although the CF_3-containing pharmaceuticals and pesticides are excluded from the proposal, the fact of their degradation products contain TFA is obviously existence. If TFA cannot be excluded from the proposal, it will bring great risks to the approval of new products in the EU, thereby having a serious impact on the development of new CF_3-containing products and even the whole industry of pharmaceuticals and pesticides.





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