**POSITION PAPER**
18/10/2021 – POS/21/KH/34533

# CropLife Europe - REACH PFAS restriction definition

## Key Messages:

- **Molecules that are considered PFAS in the current proposal because they contain certain small functional groups should be excluded from the REACH PFAS definition because they do not demonstrate the assumed Persistence property.**
- **Data available from the scientific literature and regulatory submissions show:**
  - **Certain -$CF_2$- or -$CF_3$ functional groups cannot be persistent due to chemical reactivity with water e.g. -$OCF_3$, -$NCF_3$**
  - **Certain -$CF_2$- or -$CF_3$ functional groups cannot be assumed to be inherently persistent due to chemical reactivity with water, or other degradation mechanisms.**
- **The primary degradation properties of larger molecules containing these functional groups cannot be uniquely linked to their presence, and thus there is no basis for including these in the restriction scope.**
- **CropLife Europe maintains that for certain single -$CF_2$- or -$CF_3$ functional groups:**
  - **Those which do not demonstrate inherent Persistence should be excluded from the REACH PFAS definition, and thus be of relevance to all industrial sectors.**
  - **Active substances should be derogated such that the relevant vertical legislation (e.g. agrochemical, biocidal, pharmaceutical) can continue to make a more well-informed and detailed case-by-case assessment of the active substance and its potential degradation products.**
- **Alternative property-based PFAS definition proposals developed in other geographies (e.g., USA) aiming at addressing concerns that are identical to those driving the EU restriction initiative, should be evaluated and considered.**

## 1. Introduction

CropLife Europe wishes to provide additional information to the Member States developing the proposed PFAS REACH Restriction. This includes information from the scientific literature which addresses the potential persistence of small PFAS moieties, and as a result contend that these “structural PFAS” should not fall within scope of the broad regulatory Restriction definition. Such functional groups are highly important for tailoring the lipophilicity, metabolism and environmental safety of engineered biologically active molecules in several fields of application (e.g. agrochemical, pharmaceutical and biocidal substances), and must not be unnecessarily lost from the innovation toolbox (Jeschke 2010; Inoue 2020).

Because there is either demonstrably no persistence, or it cannot a priori be reasonably assumed scientifically, the inclusion of these smallest functional groups within scope of a REACH restriction would potentially not be in accordance with the provisions Article 68(1) “unacceptable risk to human health or the environment”.

In light of a risk (rather than structure) related approach to a PFAS definition, CropLife Europe also wants to draw the attention to and encourage consideration of the PFAS working definition set by USEPA (EPA, October 2021). EPA's approach allows to focus attention on the PFAS of concern by considering the structures, the properties and the existing data on PFAS while keeping the number of substances under scrutiny ambitious yet manageable. This approach seems to be in line with the approach advocated by OECD (OECD, 2021) when defining PFAS for regulatory purposes.

CropLife Europe maintains that active substances should be placed outside of the scope of this restriction, as they are already thoroughly risk assessed for human health and the environment, and as well can be removed from the market where appropriate, by the more specific vertical regulation. Leaving these substances under vertical legislation with a case-by-case assessment provides the innovation toolbox with much needed solutions in agrochemical, pharmaceutical and biocidal active substances.

## 2. Definitions and Scope

The term perfluorinated alkyl substances (PFAS) puts structural constraints on what chemicals may be considered to be in scope, and in particular the types of carbon bonding that may be involved: it is not just the number of carbon-fluorine bonds. This is important because the stability and environmental behaviour can be radically affected depending on the carbon atom bonding. The recently published OECD definition for the "universe" of PFAS chemistry is (OECD 2021):

> *"PFASs are defined as fluorinated substances that contain at least one **fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it)**, i.e. with a few noted exceptions, any chemical with at least a perfluorinated methyl group (–$CF_3$) or a perfluorinated methylene group (–$CF_2$–) is a PFAS**."***

The OECD definition goes on to clearly state (page 18) that perfluorinated methylidene carbons (=$CF_2$) should not be considered to be PFAS. Of particular note, the OECD report states of the definition:

> *"This report does not make any recommendation on how working scopes should be set up, in terms of which factors to be considered (which depends highly on specific local context), nor on PFAS grouping. However, when a working scope of PFASs is used, this report highly recommends that users clearly provide the context and rationale for selecting their PFAS working scope in order to provide transparency and avoid confusion by others."*

The stated basis for the REACH restriction is (DS (2021), Chapter III, page 7):

> *"The carbon-fluorine bonds are one of the strongest chemical bonds in organic chemistry. This means substances containing this chemical bond resist degradation when used and also in the environment. All PFASs subject to the description above (as defined in Section II.) are, or ultimately transform into, persistent substances."*

In light of these considerations, CropLife Europe wishes to emphasise that the stated reasons for this restriction proposal are that all molecules meeting the supplied definition are persistent. As a result **it is consistent with the OECD definition to "deselect" individual PFAS moieties which do not demonstrate persistent properties**, and that should not fall within scope of the REACH restriction definition.

As of the second consultation the proposed EU REACH restriction definition is (DS 2021):

> *"X-(-CF2-)n-X' with n ≥ 1 and X, X' not being H (thus including X-CF3) meaning fluorinated substances that contain at least one aliphatic carbon atom that is both, saturated and fully fluorinated, i.e. any chemical with at least one perfluorinated methyl group (-CF3) or at least one perfluorinated methylene group (-CF2-), including branched fluoroalkyl groups and substances containing ether linkages, fluoropolymers and side chain fluorinated polymers."*

To avoid potential confusion, CropLife Europe recommend that the REACH restriction definition be fully aligned with the OECD "PFAS universe" definition (i.e. also excluding Cl, Br, I). The exemptions for X, X' should then be extended to any additional groups that can be reasonably demonstrated to be not persistent on the basis of chemical reactivity.

## 3. Single $CF_2$ / $CF_3$ moieties which are unstable towards hydrolysis

The -$CF_2$- and -$CF_3$ moieties are the shortest alkyl groups within scope of the proposed REACH PFAS restriction definition. Data from the scientific literature presented here for e.g. the trifluoromethoxy ($CF_3O$-) group shows that should the corresponding alcohol be formed, it will rapidly be hydrolysed. Similarly, simple trifluoromethylamino ($CF_3N$<) groups will directly hydrolyse. As a result, it cannot be justified to claim that all molecules which contain trifluoromethoxy or trifluoromethylamino groups will be persistent purely on the presence in the parent molecule, and these functional groups should be considered for exclusion from the REACH restriction definition.

### 3.1. Trifluoromethoxy groups

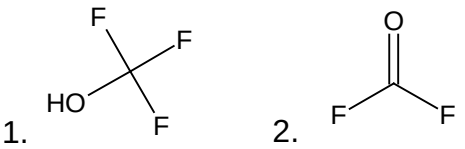



**Figure 1.** Model compounds: 1) trifluoromethanol ($CF_3OH$), and 2) carbonyl difluoride ($CF_2O$).

**Chemical stability of trifluoromethanol towards hydrolysis**

The trifluoromethoxy moiety features the shortest terminal alkyl group (-$CF_3$) within scope of the proposed PFAS restriction definition. Whether the inclusion of larger parent molecules featuring this group on the basis of inherent persistence of metabolites is justified depends on the ultimate stability of the model substance trifluoromethanol. Trifluoromethanol is an unstable substance which is a gas at room temperature. Despite speculation it was too reactive to exist, it was first synthesised in 1977 under completely anhydrous conditions at -120°C (Redwood 1965; Seppelt 1977). With a melting point -82°C, it was described as being unstable towards the elimination of hydrogen fluoride to give carbonyl difluoride (Eqn 1), with thermal degradation under anhydrous conditions already starting slowly at -20°C (corresponding with the estimated boiling point). In a more recent publication, Christie *et al* (2007) similarly state that alcohols possessing a fluorine atom on the α-carbon atom are unstable and undergo facile HF elimination, and performed the synthesis of trifluoromethanol under strictly anhydrous conditions. Supporting this statement, in a similar substance, Østerstrøm *et al* (2019) reported gaseous difluoromethanol to decompose with

a first-order rate coefficient of k = (1.68 x $10^{-3}$) $s^{-1}$, corresponding to an atmospheric half-life of 6.9 min at room temperature.

$CF_3OH$ is strongly acidic and some salt forms have been synthesised under vacuum and rigorously anhydrous conditions, however, these also immediately hydrolyse on contact with water or moist air to give purely inorganic products (Redwood 1965; Klöter 1979).

$$CF_3OH \rightarrow CF_2O + HF \qquad \text{(eqn 1)}$$

Schneider *et al* (1996) investigated the energetics of unimolecular and water-mediated decomposition of $CF_3OH$ into $CF_2O$ and HF. They concluded that the energy barrier to the unimolecular decomposition was large and that at room temperature the rate of the reaction is negligible; however, the presence of water significantly lowers the energy pathway making degradation more favourable. These findings are fully commensurate with experimental findings that have indicated the need for anhydrous conditions in order to isolate trifluoromethanol. Given the potential occurrence of trifluoromethanol in the environmental will not be under anhydrous conditions, decomposition into $CF_2O$ and HF is considered inevitable and rapid.

Carbonyl difluoride does not meet the formal OECD PFAS definition because the carbon is neither methyl nor methylene, but rather methylidene (and for the avoidance of doubt, the OECD definition explicitly excludes this as being termed a PFAS). Carbonyl difluoride also does not meet the EU definition for PFAS being used in the second public consultation, as it is neither methyl nor methylene.

Although not meeting the PFAS structural definition, once formed, carbonyl difluoride additionally does not demonstrate persistent properties. It is known to rapidly hydrolyse in the presence of water:

$$CF_2O + H_2O \rightarrow CF_2(OH)_2 \rightarrow 2HF + CO_2 \qquad \text{(eqn 2)}$$

Although a gaseous substance, Uchimaru *et al* (2004) noted that carbonyl difluoride can react with condensed atmospheric water, and the Henry's law constants and hydrolysis rates lead to partitioning to liquid water. The first order hydrolysis reaction coefficient for carbonyl difluoride has been experimentally determined in liquid water to be $k_{hyd}$ = 4.3 $s^{-1}$, corresponding to a half-life of 1.6 seconds (De Bruyn 1995). Difluoromethanediol is described as a transient intermediate in the rapid reaction of carbonyl difluoride with water which ultimately releases HF and $CO_2$ as depicted in eqn 2. (Science of Synthesis, page 325)

**Examples of trifluoromethoxy degradation from larger molecules**

The following examples are larger molecules containing the trifluoromethoxy groups, which have been shown to undergo degradation in biotic systems. During this process trifluoromethanol is eliminated, and once formed undergoes hydrolysis as described above.

Dihel *et al* (2009) describe the *in vivo* metabolism of a development pharmaceutical proceeding via CYP-mediated oxidative displacement of the trifluoromethoxy group (-$OCF_3$), with the resulting formation of $CF_3OH$, which rapidly degrades to form carbonyl difluoride at room temperature (Eqn2).

Consistent with this, a survey conducted by Pfizer scientists published in 2015, found no consistent improvement in metabolic stability for trifluoroanisoles (Ar-$OCF_3$) compared to anisoles (Ar-$OCH_3$) across a series of 439 mixed matched pairs (Xing 2015; Johnson 2020).

Complete biomineralization has been described for a model substance featuring a trifluoromethoxy group, 10-trifluoromethoxy-decane-1-sulfonate (Peschka 2008; Frömel 2010). Analysis of fluoride ions over the course of the degradation process indicated a rapidly increasing concentration between 3 and 17 days, which slowed and then reached a plateau between 63 and 87 days. The favoured biotransformation pathway (90%) started with desulfonation and oxidation to a carboxylic acid. The alkyl carbon chain was then shortened by successive β-oxidation to finally yield trifluoromethanol, which was stated to be unstable in water, and to degrade abiotically. A second less favoured pathway (10%) was also described which ultimately led to trifluoromethanol, and once formed, underwent mineralisation. As a result, virtually complete mineralization was demonstrated.

Considering the use pattern of most agrochemicals the key compartments of interest where degradation of the substance to trifluoromethanol and subsequently to carbonyl difluoride will take place are likely to be soil (and associated pore water reservoirs) and surface water. Such environments are considered highly conducive to the degradation of carbonyl difluoride as Uchimaru *et al* have shown that having an excess of water molecules in the system reduces the energy barriers to the reaction with water leading to the formation of carbon dioxide and hydrogen fluoride.

## 3.2. Trifluoromethylamino groups

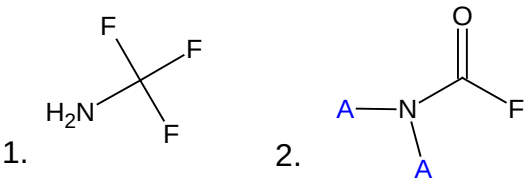



**Figure 2.** Model compounds: 1) trifluoromethylamine ($CF_3NH_2$), 2) carbamoyl fluoride (A,A'-NCOF).

**Chemical stability of trifluoromethylamine towards hydrolysis**

The trifluoromethylamine moiety features the shortest terminal alkyl group (-$CF_3$-) within scope of the proposed PFAS restriction definition. Whether the inclusion of larger parent molecules featuring this group on the basis of inherent persistence of metabolites is justified, depends on the stability of the model substance trifluoromethylamine. Klöter *et al* (1977) synthesised the trifluoromethylamine using similar approaches to trifluoromethanol, under strictly anhydrous conditions, with spontaneous decomposition increasing above -21°C to form a mixture of compounds (Klöter, 1979).

**Examples of trifluoromethylamine degradation from larger molecules**

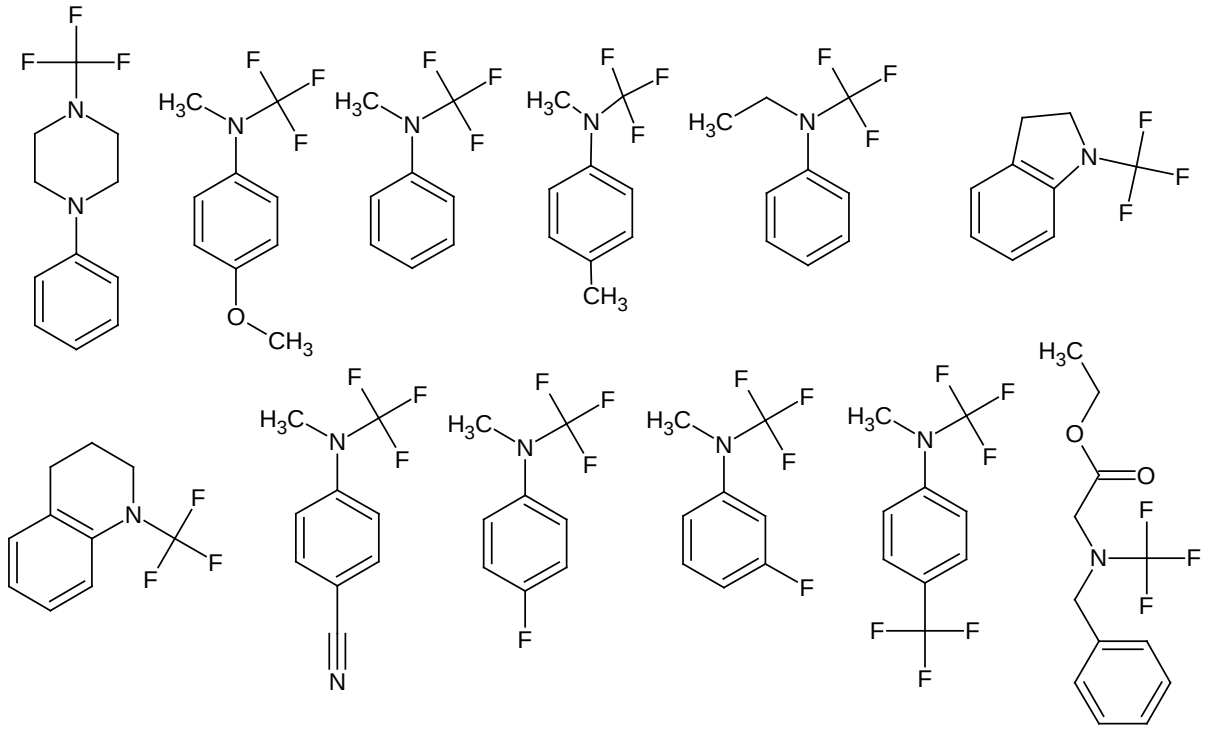


**Figure 3.** Model trifluoromethylamine compounds demonstrating hydrolysis within 72 hours (Schiesser et al (2020).

Schiesser *et al* (2020) synthesised 12 model trifluoromethylamine derivatives which very rapidly hydrolysed (within 72 hours) to give a carbamoyl fluoride, A,A'-NCOF, eliminating 2HF in the process. The carbamoyl fluoride metabolites cannot be considered to be PFAS (methylidene carbon, and single fluorine bond), and hence nor should any parent trifluoromethylamines for the purpose of the REACH restriction.

Unlike simpler amines, *N*-trifluoromethylazoles on the other hand, were stable towards hydrolysis *on the timescale of the experiment* (72 hours). Never-the-less, further investigations in regulatory hydrolysis studies or biodegradation in environmental media could also demonstrate consistent degradation for this functional group.

## 4. Single $CF_2$ / $CF_3$ moieties which demonstrate variable degradation in biotic systems

The -$CF_2$- and -$CF_3$ moieties are the shortest alkyl groups within scope of the proposed PFAS restriction definition. Data from the scientific literature are presented here which shows that the functional groups difluorodioxo (O-$CF_2$-O), trifluoromethylphenyl (Ar-$CF_3$), difluoroethoxy (-$OCF_2CH_3$), and difluoromethylene (C-$CF_2$-C) groups degrade, or have the potential to degrade, without forming persistent PFAS metabolites.

Given these functional group's potential to degrade, sectors which typically engineer highly specialized molecules should be excluded from the scope of the restriction (e.g. plant protection products, pharmaceuticals, biocides, etc), and the appropriate vertical legislation allowed to distinguish those molecules that need to be removed from the market on a case-by-case basis. REACH substance evaluation could also be considered for those only within the scope of REACH.

## 4.1. Difluorodioxo groups

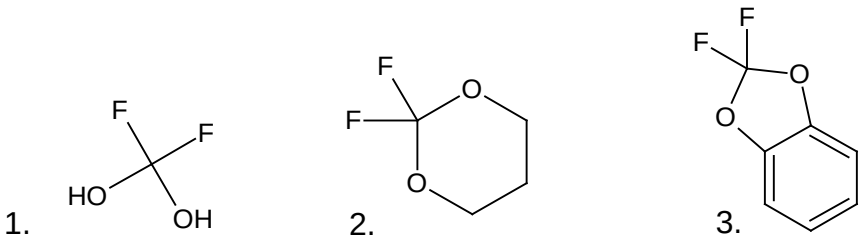



**Figure 4.** Model substances: 1) difluoromethanediol, 2) difluorodioxane and 3) difluorobenzodioxole.

**Chemical stability of difluoromethanediol towards hydrolysis**

The difluorodioxo moiety features the shortest alkyl group (-$CF_2$-) within scope of the proposed PFAS restriction definition. Whether the inclusion of larger parent molecules featuring this group on the basis of inherent persistence of metabolites is justified, depends on the stability of the model substance difluoromethanediol. Very little scientific literature exists for this compound, and it does not appear to be commercially available, often an indication of chemical instability. Difluoromethanediol is the gem-diol form of carbonyl difluoride, and reversible equilibrium between gem-diols and ketones is very well established. Given that carbonyl difluoride is known to rapidly hydrolyse in water, and it has been stated that difluoromethanediol is a transient intermediate in the hydrolysis of carbonyl difluoride (eqn 2), it is equally expected that difluoromethanediol behaves similarly in condensed environmental media with decomposition to HF and $CO_2$ (Science of Synthesis, page 325).

**Examples of difluorodioxo degradation from larger molecules**

There is no identified experimental evidence that difluoromethanediol forms in the metabolism of difluorodioxo groups. However, there are some examples of environmental and mammalian metabolism leading to defluorination *via* carbonyl difluoride.

Minor biotransformation in humans of fluorinated benzodioxoles has been reported for the pharmaceutical Lumacaftor (FDA 2014). The biotransformation was not elaborated on in the regulatory document, but potential degradation pathways were recently proposed, both relying on arene oxidation followed by extrusion of carbonyl difluoride (Johnson 2020, see scheme 39). In juxtaposition, the same group appears to be conserved in the available mammalian metabolism data for Fludioxonil. This again demonstrates how the stability of a parent molecule is dependent on far more than the simplistic presence or absence of a single functional group. This is further exemplified by Alexandrino *et al* (2020), who demonstrated that environmental microbial communities enriched from estuarine and agriculture ecosystems were capable of completely removing and defluorinating Fludioxonil at concentrations up to 10 mg $L^{-1}$, in a period of 21 days, under the experimental conditions of the study. The presence or absence of the difluorodioxo group does not define the overall characterisation for persistence of the parent molecule, and further detailed experimental work is needed to establish this in practice.

## 4.2. Trifluoromethylphenyl groups

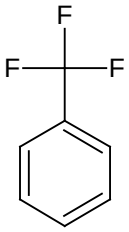


**Figure 5.** Model compound: (trifluoromethyl)benzene.

### Chemical stability of trifluoromethylphenyl groups

No data on the chemical stability of the model compound (trifluoromethyl)benzene has been identified in the literature. Instead examples are presented of observed biotic degradation of -$CF_3$ groups bonded to aryl carbons, as opposed to alkyl carbon chains.

### Examples of trifluoromethyl degradation from larger molecules

Sakai & Santi (1971, 1973) describe the mechanism of elimination of single fluoride ions influenced by a conjugated π-system (Figure 6). This reaction was demonstrated among others for o- and p-trifluoromethylphenol, finally ending up in o- or p-hydroxybenzoic acid.

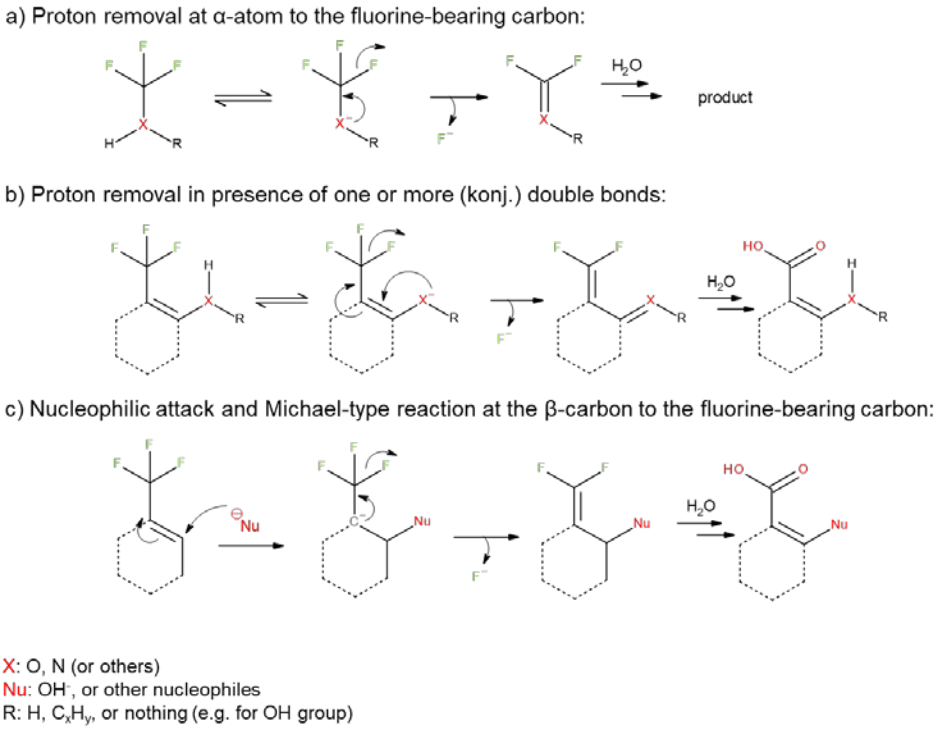
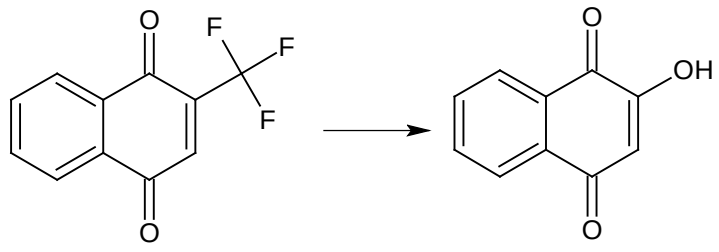



**Figure 6.** Schematic reaction mechanism as described by Sakai & Santi (1973). Especially reaction c) is described for enzymatic degradation in Trifluoromethyl uracil derivates.



1. 2.

**Figure 7.** 1) trifluoromenadione, 2) lawsone.

Additionally, it has been reported that trifluoromenadione (Figure 7) can undergo a vinylogous haloform-type reaction that leads to elimination of $CF_3$ (Lanfranchi 2012, Johnson 2020).

The mechanisms described above can explain why some trifluoromethylphenyl- containing substances (U-$^{14}$C-labelled in the phenyl ring) did not show the high stability often assumed for classical PFAS and, in addition, do not always show formation of the metabolite trifluoroacetic acid (Figure 8).

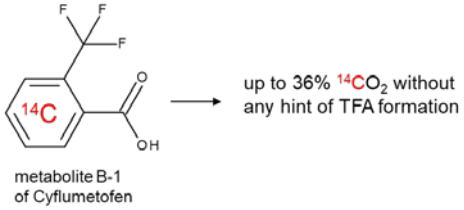



**Figure 8.** Soil degradation of 2-(trifluoromethyl)benzoic acid (metabolite B-1) of Cyflumetofen (data based on public version of *Cyflumetofen renewal dossier 2021*). Range of metabolite B-1 soil DT50s = 6.3 - 36.3 days (n=7).

From soil metabolism data with specifically $^{14}$C-labelled substances (Figure 9) it can be shown that rather than the formation of trifluoroacetic acid, the $^{14}$C-labelled C-atom next to the $CF_3$ group was mineralized to $^{14}CO_2$. This is only possible if the stepwise loss of fluoride took place or if the $CF_3$ group was lost by forming trifluoromethanol. As described above, trifluoromethanol would then be mineralized (Peschka *et al* 2008).

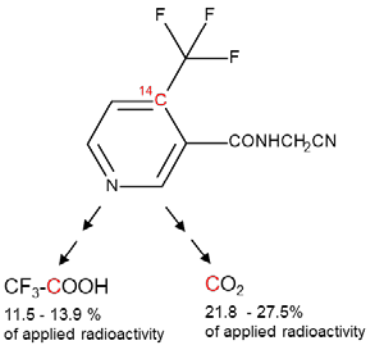



**Figure 9.** Soil degradation of insecticide Flonicamid (data based on public version of *Flonicamid renewal dossier 2020*). Range of Flonicamid soil DT50s = 0.3 – 1.9 days (n=4).

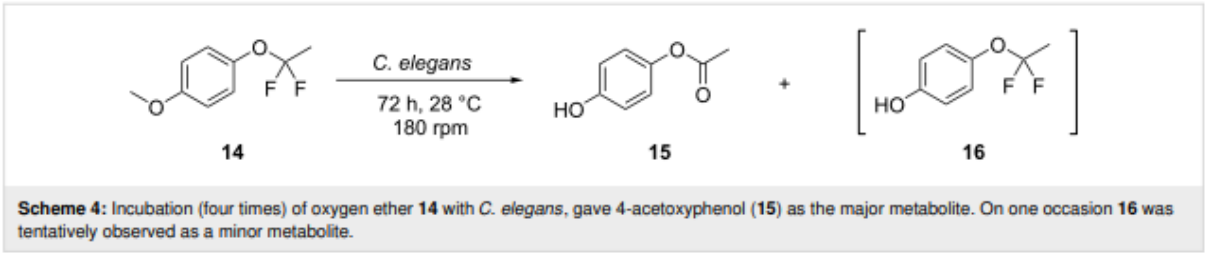
These findings show that (1) it is not the single $CF_3$-group which defines the potential persistence of a parent compound and (2) not every -$CF_3$ group results in formation of trifluoroacetic acid.

Trifluoromethylphenyl substituents have also been shown to undergo photochemical degradation to acyl fluorides and carboxylic acids. As an example, the pharmaceutical fluoxetine was found reactive in sunlight surface waters and proved to degrade to the corresponding carboxylic acid with a half-life of 55.2 h under simulated conditions. (Lam 2005)

While some parent molecules are known to degrade to form stable metabolites containing the conserved trifluoromethyl moiety (e.g. trifluoroacetic acid), the above examples clearly

show that exceptions occur, and these should not be included within the scope of the proposed REACH restriction. From a regulatory perspective, the simplest resolution for these cases is to exclude active substances from well-regulated vertical legislation (e.g. plant protection, pharmaceuticals, etc), and for those regulations to be allowed to assess in detail the full degradation and metabolite behaviour.

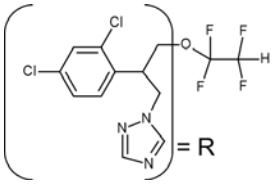
## 4.3. Difluoroethoxy groups




**Scheme 4:** Incubation (four times) of oxygen ether **14** with *C. elegans*, gave 4-acetoxyphenol (**15**) as the major metabolite. On one occasion **16** was tentatively observed as a minor metabolite.

**Figure 10.** Rodil et al (2019) metabolism of a difluoromethoxy ether.

Rodil et al (2019) describe the metabolism of a difluoromethoxy ether, proceeding via hydrolysis of -$OCF_2CH_3$ with the resulting formation of an acetoxy-phenol as main metabolite at 28°C by *c. elegans.*




Tetraconazole

**Figure 11.**

Degradation of a similar ethoxy functional group but with a higher degree of fluorination, has been observed in Tetraconazole (Figure 11). The soil metabolism under natural sunlight conditions of Tetraconazole showed a stepwise attack at the tetrafluoroethoxy- group (see the proposed degradation pathway of tetraconazole in soil in the public version of *Tetraconazole renewal dossier 2019*). The most plausible reaction pathway leading to the detected metabolites M14360-DFA and M14360 alcohol is shown in Figure 12. The final degradation product of the tetrafluoroethoxy-group after having lost all fluoride ions is oxalic acid.

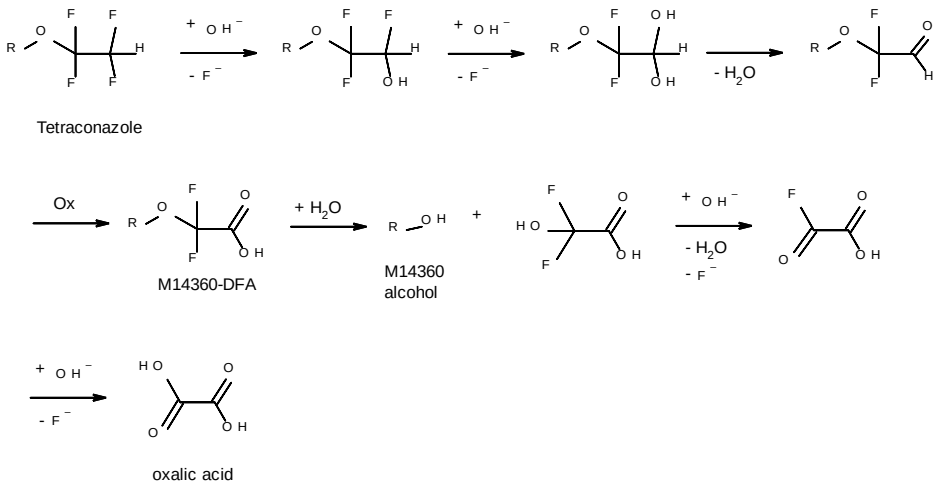


**Figure 12.** Reaction mechanisms at the tetrafluoroethoxy-group leading to the Tetraconazole metabolites M14360-DFA and M14360 alcohol in soil under photolytic conditions

The fluoride-free metabolite M14360 alcohol is oxidized to the M14360 acid (not shown here), which then undergoes further transformation. This shows that also fluoride containing moieties like tetrafluoroethoxy-groups are in principle degradable and do not qualify for being classified as a "forever chemical".

### 4.4. Difluoromethylene groups

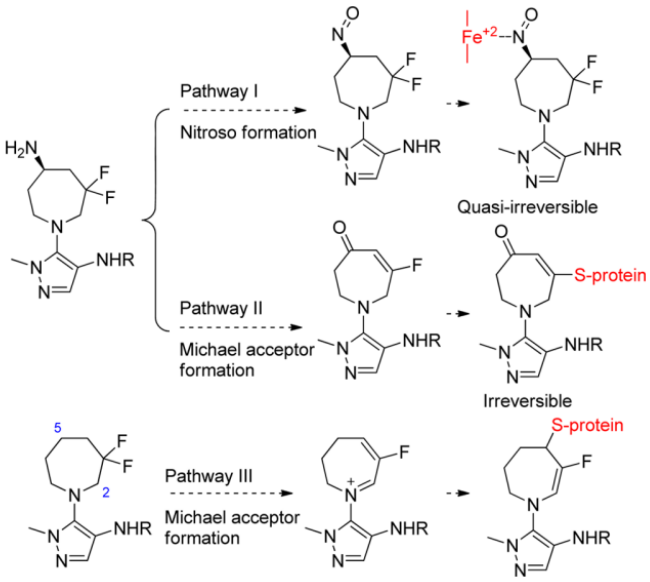



Figure 2. Proposed mechanisms of action.

**Figure 13.** Wang *et al* (2015) describe a metabolic displacement of a difluoromethylene group.

Wang *et al* (2015) describe a metabolic displacement of a difluoro-methylene group adjacent to methylene groups by cytochrome peroxidases. The fluorine atoms are eliminated and replaced to yield non fluorinated metabolites.

## 5. Conclusion

To avoid confusion in terminology with the “PFAS label”, the REACH definition for PFAS substances should fully align with the OECD **structural** PFAS definition (i.e. also excluding Cl, Br, I), before focusing on those molecules demonstrating the properties intended to be regulated.

Given the demonstrated instability of trifluoromethanol and “non-PFAS” metabolite carbonyl difluoride towards hydrolysis, the central property being used to define the PFAS group for the REACH restriction, namely *“All PFASs subject to the description above (as defined in Section II.) are, or ultimately transform into, persistent substances.”*, does not hold for the trifluoromethanoxy (-$OCF_3$) or trifluoromethylamino ($CF_3N<$) moieties. Similarly for difluorodioxo (O-$CF_2$-O), difluoroethoxy (-$OCF_2CH_3$), difluoromethylene (C-$CF_2$-C) and trifluoromethylphenyl (Ar-$CF_3$) groups clear examples of full or partial degradation can be shown warranting either complete exclusion from the restriction, or case-by-case

assessment under more appropriate vertical legislation or regulatory mechanisms such as REACH substance evaluation.

**The degradation properties of parent molecules containing these functional group cannot be uniquely linked simply to their presence in the molecule, and as such there is no justifiable basis for including all $CF_2$ / $CF_3$ molecules in the restriction scope.**

**CropLife Europe maintains that for single -$CF_2$- or -$CF_3$ functional groups:**

- **Those which do not demonstrate inherent Persistence should be excluded from the REACH PFAS definition, and thus be of relevance to all industrial sectors.**
- **Active substances should be derogated such that the relevant vertical legislation (e.g. agrochemical, biocidal, pharmaceutical) can continue to make a more well-informed and detailed case-by-case assessment of the active substance and its potential degradation products.**

## 6. References

Alexandrino, D.A.M et al. (2020) Microbial degradation of two highly persistent fluorinated fungicides epoxiconazole and fludioxonil. J. Haz. Mat.; 394: 122545. https://doi.org/10.1016/j.jhazmat.2020.122545

Christe, K.O. et al. (2007) Convenient Access to Trifluoromethanol. Angewandte Chemie; 46(32): 6155-6158. https://onlinelibrary.wiley.com/doi/full/10.1002/anie.200701823

De Bruyn, W.J. et al. (1995) Uptake of haloacetyl and carbonyl halides by water surfaces. Environ. Sci. Technol.; 29: 1179-1185. https://pubs.acs.org/doi/pdf/10.1021/es00005a007

Dihel, L. et al. (2009) Oxidative metabolism of the trifluoromethoxy moiety of OSI-930. Drug Metab. Drug Interact. 24, 95−121. https://pubmed.ncbi.nlm.nih.gov/20408495/

DS (2021) Information Document accompanying the 2nd Stakeholder Consultation on a Restriction for PFAS, July 2021. https://www.reach-clp-biozid-helpdesk.de/media/Helpdesk/download/Supplementary-Document-to-CfE.pdf

US Environmental Protection Agency, October 2021; National PFAS Testing Strategy: Identification of candidate Per-and Poly-fluoroalkyl Substances (PFAS) for Testing

FDA (2014) Clinical Pharmacology Lumacaftor/Ivacaftor, page 117. Accessed online: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/0206038Orig1s000ClinPharmR.pdf

Frömel T. & Knepper T.P. (2010) Biodegradation of Fluorinated Alkyl Substances. In: De Voogt P. (eds) Reviews of Environmental Contamination and Toxicology Volume 208. Reviews of Environmental Contamination and Toxicology (Continuation of Residue Reviews), vol 208. Springer, New York, NY. https://doi.org/10.1007/978-1-4419-6880-7_3

Inoue, M. (2020) Contribution of Organofluorine Compounds to Pharmaceuticals. ACS Omega; 5(19): 10633–10640. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7240833/

Jeschke, P. (2010) The unique role of halogen substituents in the design of modern agrochemicals. Pest Manag. Sci.; 66: 10-27. https://onlinelibrary.wiley.com/doi/10.1002/ps.1829

Johnson B.M. et al. (2020) Metabolic and Pharmaceutical Aspects of Fluorinated Compounds. J. Med. Chem.; 63: 6315−6386. https://pubs.acs.org/doi/pdf/10.1021/acs.jmedchem.9b01877

Klöter, G. et al. (1977) Trifluormethylamin, CF3NH2. Angew. Chem.; 89(10): 754. https://onlinelibrary.wiley.com/doi/pdf/10.1002/ange.19770891027

Klöter, G. et al. (1979) Trifluoromethanol (CF3OH) and T rifluoromethylamine (CF3NH2). J. Am. Chem. Soc., 101: 347. https://pubs.acs.org/doi/pdf/10.1021/ja00496a012

Lam, M. W. et al. (2005) Aqueous photochemical reaction kinetics and transformations of fluoxetine. Environ. Sci. Technol., 39, 513−522. https://doi.org/10.1021/es0494757

Lanfranchi, D. A. et al. (2012) Exploring the trifluoromenadione core as a template to design antimalarial redox-active agents interacting with glutathione reductase. Org. Biomol. Chem., 10, 4795−4806. https://doi.org/10.1039/C2OB25229E

OECD (2021) Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance, Series on Risk Management No.61, ENV/CBC/MONO(2021)25. https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/CBC/MONO(2021)25&docLanguage=en

Østerstrøm et al. (2019) Mechanistic study of the reaction of CH2F2 with Cl atoms in the absence and presence of CH4 or C2H6: decomposition of CHF2OH and fate of the CHF2O radical. Phys.Chem.Chem.Phys.; 21: 9376-9383. https://doi.org/10.1039/C8CP06425C

Peschka, M, et al. (2008) Synthesis and analytical follow-up of the mineralization of a new fluorosurfactant prototype. Chemosphere; 72(10), 1534-1540. https://doi.org/10.1016/j.chemosphere.2008.04.066

Redwood, M.E. et al. (1965) Fully fluorinated alkoxides part I. Trifluoromethoxides of alkali metals. Can. J. Chem.; 43(7): 1893. https://cdnsciencepub.com/doi/pdf/10.1139/v65-251

Rodil, A. et al. (2019) Fluorine-containing substituents: metabolism of the α,α-difluoroethyl thioether motif. Beilstein J. Org. Chem. 2019, 15, 1441−1447. https://www.beilstein-journals.org/bjoc/articles/15/144

Sakai T.T. & Santi, D.V. (1973) Hydrolysis of Hydroxybenzotrifluorides and fluorinated uracil derivatives. A general Mechanism for Carbon-Fluorine Bond Labilization. Journal of Medicinal Chemistry, Vol.16, No. 10, 1079 – 1084. https://pubmed.ncbi.nlm.nih.gov/4749467/

Santi, D.V. & Sakai, T.T. (1971) Thymidylate Synthetase. Model Studies of Inhibition by 5-Trifluoromethyl-2'-deoxyuridylic Acid. Biochemistry, Vol. 10, No. 19, 3598 – 3607. https://pubs.acs.org/doi/pdf/10.1021/bi00795a018

Schiesser, S. et al. (2020) N-Trifluoromethyl Amines and Azoles: An Underexplored Functional Group in the Medicinal Chemist's Toolbox. J. Med. Chem.; 63: 13076−13089. https://pubs.acs.org/doi/pdf/10.1021/acs.jmedchem.0c01457

Schneider, W.F. et al. (1996) Energetics and Mechanism of Decomposition of CF3OH. J. Phys. Chem.; 100: 6097-6103. https://pubs.acs.org/doi/pdf/10.1021/jp952703m

Science of Synthesis (2014): Houben-Weyl Methods of Molecular Transformations, Vol. 18: Four Carbon-Heteroatom Bonds

Seppelt, K. (1977) Trifluoromethanol. Angew. Chem.; 89(5): 325. https://doi.org/10.1002/ange.19770890509

Uchimaru, T. et al. (2004) Ab initio study of the hydrolysis of carbonyl difluoride (CF2O): importance of an additional water molecule. Chem. Phys. Lett.; 396: 110–116. https://www.sciencedirect.com/science/article/pii/S0009261404012035

Wang, X. et al. (2015) Probing Mechanisms of CYP3A Time-Dependent Inhibition Using aTruncated Model System, ACS Med. Chem. Lett. 6, 925 – 929. http://dx.doi.org/10.1021/acsmedchemlett.5b00191

Xing, L. et al. (2015) Fluorine in drug design: a case study with fluoroanisoles. ChemMedChem, 10, 715−726. https://doi.org/10.1002/cmdc.201402555