Table 3 **Distribution of radioactivity after application of ^{14}C-4-(trifluoromethoxy) benzoic acid on soil LUFA 2.4 and incubation under aerobic conditions [% TAR]**

Days after treatment	Extractable residues			Volatiles		NER	Mass balance
	ACN/H_2O (9/1) 1-3	ACN/H_2O (1/1) + Acetone 1-2	Total extracted	CO_2 [a]	Other		
0	82.2	17.4	99.5	0.0	n.a.	2.3	101.8
0	81.7	17.7	99.3	0.0	n.a.	2.9	102.2
0 mean	**81.9**	**17.5**	**99.4**	**0.0**	**n.a.**	**2.6**	**102.0**
1	59.1	12.5	71.6	7.6	0.00	19.2	98.4
1	58.6	12.6	71.2	8.1	0.00	19.0	98.3
1 mean	**58.8**	**12.5**	**71.4**	**7.8**	**0.00**	**19.1**	**98.3**
2	4.0	1.8	5.8	31.3	0.00	56.2	93.4
2	14.2	3.8	18.0	30.0	0.00	52.8	100.8
2 mean	**9.1**	**2.8**	**11.9**	**30.7**	**0.00**	**54.5**	**97.1**
3	3.0	2.4	5.4	42.2	0.01	45.0	92.7
3	2.0	1.9	3.9	43.2	0.01	47.7	94.8
3 mean	**2.5**	**2.2**	**4.7**	**42.7**	**0.01**	**46.4**	**93.8**
7	0.8	0.2	1.0	54.7	0.00	41.6	97.4
7	0.7	0.6	1.3	56.1	0.00	42.1	99.5
7 mean	**0.7**	**0.4**	**1.1**	**55.4**	**0.00**	**41.9**	**98.4**
10	0.6	0.4	1.1	55.9	0.00	41.6	98.5
10	0.5	0.4	0.9	54.4	0.00	46.2	101.5
10 mean	**0.6**	**0.4**	**1.0**	**55.1**	**0.00**	**43.9**	**100.0**
14	0.5	0.4	0.9	59.3	0.00	37.2	97.4
14	0.5	0.4	0.9	54.4	0.00	39.9	95.3
14 mean	**0.5**	**0.4**	**0.9**	**56.9**	**0.00**	**38.6**	**96.3**
28	0.3	0.3	0.6	61.8	0.00	38.2	100.5
28	0.4	0.3	0.6	61.9	0.00	37.4	99.8
28 mean	**0.3**	**0.3**	**0.6**	**61.8**	**0.00**	**37.8**	**100.2**
56	0.2	0.3	0.4	*53.9*[b]	0.00	31.0	85.4
56	0.2	0.2	0.4	*54.3*[b]	0.00	31.2	85.9
56 mean	**0.2**	**0.2**	**0.4**	***54.1***[b]	**0.00**	**31.1**	**85.6**

TAR = total applied radioactivity (100% = 0.67 mg/kg)
n.a. = not applicable
NER = non-extractable residues
[a] sum of NaOH wash bottles attached during incubation and during drying after extraction
[b] values too low due to insufficient trapping of CO_2

B. Characterization and identification of extractable radioactive residues (ERR)

The identity of the parent substance was confirmed by comparison with the retention time of the ^{14}C-labeled test item and additional mass spectrometric analysis of representative samples. Results are shown in Table 4 to Table 6.

During the course of the study, the amount of parent compound quickly decreased from 97.4 - 102.7% TAR at day 0 to values ≤ 2.0% TAR at 14 DAT (soil Li 10), 6 DAT (soil LUFA 2.2) and 7 DAT (soil LUFA 2.4). Beside the parent compound, a few unknown metabolites were detected, but all below levels of 0.2% TAR.

Table 4 **Composition of radioactive residues of extracts of soil Li 10 after application of ^{14}C-4-(trifluoromethoxy)benzoic acid and incubation under aerobic conditions [% TAR]**

Days after treatment	Total extracted	uk	uk	uk	uk	uk	uk	Parent	uk
	t_R [min]	12.1	26.1	26.8	28.0-28.3	29.7-30.0	31.5-31.6	33.2-33.7	56.9
0	102.8	-	-	-	-	-	-	102.8	-
0	102.7	-	-	-	-	-	-	102.7	-
0 mean	**102.7**	**-**	**-**	**-**	**-**	**-**	**-**	**102.7**	**-**
1	94.7	-	-	-	-	-	-	94.7	-
1	95.6	-	-	-	0.2	0.2	-	95.2	-
1 mean	**95.2**	**-**	**-**	**-**	**0.1**	**0.1**	**-**	**94.9**	**-**
2	74.8	-	-	-	-	-	-	74.8	-
2	74.6	-	-	-	-	-	-	74.6	-
2 mean	**74.7**	**-**	**-**	**-**	**-**	**-**	**-**	**74.7**	**-**
3	60.5	-	-	-	-	-	-	60.5	-
3	53.9	-	-	-	-	-	-	53.9	-
3 mean	**57.2**	**-**	**-**	**-**	**-**	**-**	**-**	**57.2**	**-**
6	9.0	-	-	-	-	-	-	9.0	-
6	6.5	-	-	-	-	-	-	6.5	-
6 mean	**7.8**	**-**	**-**	**-**	**-**	**-**	**-**	**7.8**	**-**
10	8.0	-	0.0	-	0.2	0.2	0.1	7.5	-
10	2.8	0.2	0.1	0.1	0.1	0.1	0.0	2.1	0.1
10 mean	**5.4**	**0.1**	**0.1**	**0.0**	**0.2**	**0.1**	**0.1**	**4.8**	**0.1**
14	2.0	-	-	-	-	-	-	2.0	-
14	1.9	-	-	-	-	-	-	1.9	-
14 mean	**2.0**	**-**	**-**	**-**	**-**	**-**	**-**	**2.0**	**-**
28 [a]	1.3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
28 [a]	1.3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
28 mean	**1.3**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**
57 [a]	0.9	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
57 [a]	0.9	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
57 mean	**0.9**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**

TAR = total applied radioactivity (100% = 0,67 mg/kg)

n.a. = not analyzed
t_R = retention time
uk = unknown
- = not detected
[a] after 14 days, no further HPLC analyses of the pooled soil extracts were carried out since the total extracted radioactivity had dropped to negligible levels.

Table 5 **Composition of radioactive residues of extracts of soil LUFA 2.2 after application of ^{14}C-4-(trifluoromethoxy)benzoic acid and incubation under aerobic conditions [% TAR]**

Days after treatment	Total extracted	uk	uk	Parent	uk
	t_R [min]	26.8-26.9	30.1	32.7-33.7	34.1
0	97.3	-	-	97.3	-
0	97.6	-	-	97.6	-
0 mean	**97.4**	**-**	**-**	**97.4**	-
1	72.8	-	-	72.8	-
1	71.0	-	0.2	70.8	-
1 mean	**71.9**	**-**	**0.1**	**71.8**	-
2	23.0	-	-	23.0	-
2	29.7	-	-	29.7	-
2 mean	**26.4**	**-**	**-**	**26.4**	**-**
3	6.2	-	-	6.2	0.1
3	4.9	-	-	4.9	-
3 mean	**5.6**	**-**	**-**	**5.5**	**0.0**
6	2.2	0.2	-	2.0	-
6	2.1	0.2	-	1.9	-
6 mean	**2.1**	**0.2**	**-**	**1.9**	**-**
10 [a]	1.3	n.a.	n.a.	n.a.	n.a.
10 [a]	1.4	n.a.	n.a.	n.a.	n.a.
10 mean	**1.4**	**n.a.**	**n.a.**	**n.a.**	**n.a.**
14 [a]	1.0	n.a.	n.a.	n.a.	n.a.
14 [a]	1.1	n.a.	n.a.	n.a.	n.a.
14 mean	**1.1**	**n.a.**	**n.a.**	**n.a.**	**n.a.**
28 [a]	0.7	n.a.	n.a.	n.a.	n.a.
28 [a]	0.7	n.a.	n.a.	n.a.	n.a.
28 mean	**0.7**	**n.a.**	**n.a.**	**n.a.**	**n.a.**
56 [a]	0.5	n.a.	n.a.	n.a.	n.a.
56 [a]	0.5	n.a.	n.a.	n.a.	n.a.
56 mean	**0.5**	**n.a.**	**n.a.**	**n.a.**	**n.a.**

TAR = total applied radioactivity (100% = 0.67 mg/kg)

n.a. = not analyzed
t_R = retention time
uk = unknown
t_R = retention time
- = not detected
[a] after 6 days, no further HPLC analyses of the pooled soil extracts were carried out since the total extracted radioactivity had dropped to negligible levels.

Table 6 **Composition of radioactive residues of extracts of soil LUFA 2.4 after application of ^{14}C-4-(trifluoromethoxy)benzoic acid and incubation under aerobic conditions [% TAR]**

Days after treatment	Total extracted	Parent
	t_R [min]	33.1-33.4
0	99.5	99.5
0	99.3	99.3
0 mean	**99.4**	**99.4**
1	71.6	71.6
1	71.2	71.2
1 mean	**71.4**	**71.4**
2	5.8	5.8
2	18.0	18.0
2 mean	**11.9**	**11.9**
3	5.4	5.4
3	3.9	3.9
3 mean	**4.7**	**4.7**
7	1.0	1.0
7	1.3	1.3
7 mean	**1.1**	**1.1**
10 [a]	1.1	n.a.
10 [a]	0.9	n.a.
10 mean	**1.0**	**n.a.**
14 [a]	0.9	n.a.
14 [a]	0.9	n.a.
14 mean	**0.9**	**n.a.**
28 [a]	0.6	n.a.
28 [a]	0.6	n.a.
28 mean	**0.6**	**n.a.**
56 [a]	0.4	n.a.
56 [a]	0.4	n.a.
56 mean	**0.4**	**n.a.**

TAR = total applied radioactivity (100% = 0.67 mg/kg)

n.a. = not analyzed
t_R = retention time
[a] after 7 days, no further HPLC analyses of the pooled soil extracts were carried out since the total extracted radioactivity had dropped to negligible levels.

C. CHARACTERIZATION OF NON-EXTRACTABLE RESIDUES (NER)

No further NER characterization was carried out.

D. PROPOSED DEGRADATION PATHWAY

The only transformation reactions of 4-(trifluoromethoxy)benzoic acid observed were the release of carbon dioxide and the formation of non-extractable residues. The high amounts of CO_2 formed from the OCF_3-group demonstrate that along with the degradation of the molecule, the OCF_3-group is rapidly and largely mineralized, with the process of mineralization continuing even after the radioactivity was part of the non-extractable residues. The carbon mineralization from the OCF_3-group is an indirect proof that also the organically bound fluorine is fully mineralized, i.e. it ends up as inorganic fluoride in soil.

The proposed degradation pathway of 4-(trifluoromethoxy)benzoic acid in soil under aerobic conditions is presented below.

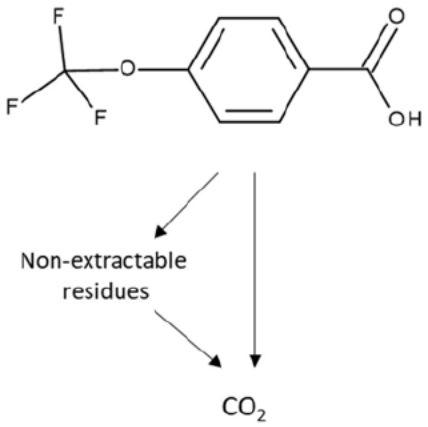


Figure 1 Proposed route of degradation for 4-(trifluoromethoxy)benzoic acid in soil

E. KINETIC EVALUATION

Kinetic evaluation and calculation of $DegT_{50}$ and $DegT_{90}$ values (trigger endpoints) for 4-(trifluoromethoxy)benzoic acid was performed following the recommendations of the FOCUS Kinetics workgroup [Ref. 1]. The obtained $DegT_{50}$ and $DegT_{90}$ values are given below. For details see Table 7 - Table 9.

Trigger endpoints of 4-(trifluoromethoxy)benzoic acid at 20 °C

Soil	Kinetic model	χ^2 error [%]	$DegT_{50}$ [d]	$DegT_{90}$ [d]
Li 10	HS	5.46	3.14	5.68
LUFA 2.2	SFO	17.9	1.15	3.82
LUFA 2.4	HS	3.70	1.19	2.13

To derive trigger endpoints at 12 °C, the correction for temperature was conducted using the Q_{10} approach according to FOCUS [Ref. 1] considering SFO kinetics for all three soils. The respective temperature correction factor (f_{temp}) and trigger endpoints at 12 °C are summarized below.

Estimation of trigger endpoints for 4-(trifluoromethoxy)benzoic acid at 12 °C

Soil	Kinetic model	χ^2 error [%]	$DegT_{50}$ [d] at 20 °C	$DegT_{90}$ [d] at 20 °C	Correction factor* (f_{temp})	$DegT_{50}$ [d] at 12 °C	$DegT_{90}$ [d] at 12 °C
Li 10	SFO	13.9	2.67	8.86	2.13	5.70	18.9
LUFA 2.2	SFO	17.9	1.15	3.82	2.13	2.45	8.15
LUFA 2.4	SFO	23.6	0.97	3.22	2.13	2.07	6.87

* based on a Q_{10} correction factor of 2.58

Table 7 Statistical and visual assessment of different kinetic models tested for degradation of ^{14}C-trifluoromethoxybenzoic acid in soil Li 10

Kinetic model	Visual assessment	χ^2 error [%]	Kinetic parameters	Prob>t	DegT$_{50}$ [d]	DegT$_{90}$ [d]
SFO	acceptable	13.9	M_0: 112.6 k: 0.26	NA <0.001	2.67	8.86
FOMC	acceptable	15.1	M_0: 112.6 α: 2.82E+006 β: 1.09E+007	NA NA* NA*	2.67	8.86
DFOP	acceptable	16.6	M_0: 112.6 k_1: 0.26 k_2: 0.0129 g: 1.00	NA <0.001 nd NA	2.67 (overall)	8.86 (overall)
HS	good	5.46	M_0: 104.9 k_1: 0.1512 k_2: 0.6328 t_b: 2.6810	NA <0.001 <0.001 NA	3.14 (overall)	5.68 (overall)

⇨ SFO kinetic model provides a visually acceptable fit; although the initial concentration is overestimated and the residuals show some systematic deviation, the overall decline pattern is well represented by the SFO model; χ^2 error is <15%; k is significantly different from zero (p-value <0.001).

⇨ FOMC kinetic model provides a visually acceptable fit (very similar to SFO fit); the goodness-of-fit is not improved since the χ^2 error is slightly increased compared to the SFO kinetic model; the estimated values for α and β are very large, indicating that degradation is close to first-order kinetics.

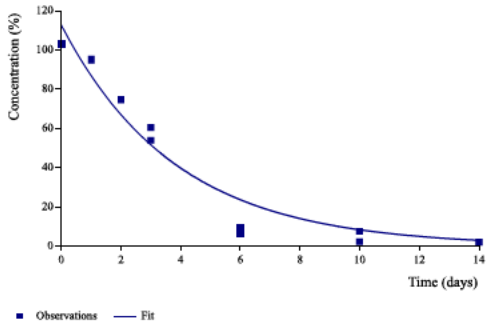
⇨ DFOP kinetic model provides a visually acceptable fit (very similar to SFO fit), but no improvement over SFO and FOMC; the χ^2 error is higher than for SFO and FOMC; the parameter g is estimated as 1 indicating that degradation is close to first-order kinetics.

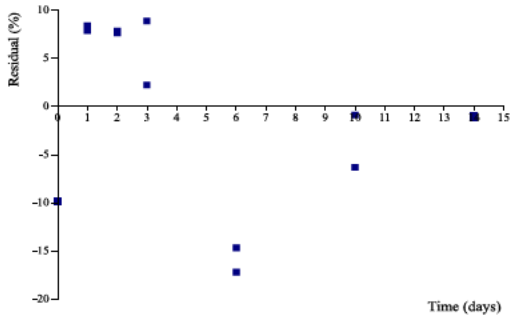
⇨ HS kinetic model improved the visual and statistical fit compared to SFO, FOMC and DFOP models. HS model provides a visually good fit; the fitted initial concentration matches well and the overall decline pattern is well represented, with no systematic deviations; χ^2 error is lower than for SFO kinetics; k_1 and k_2 are significantly different from zero (p-value <0.001).

⇨ **Conclusion: HS** model is considered the best-fit model appropriate to derive trigger endpoints for ^{14}C-trifluoromethoxybenzoic acid: DegT$_{50}$ = 3.14 d, DegT$_{90}$ = 5.68 d.

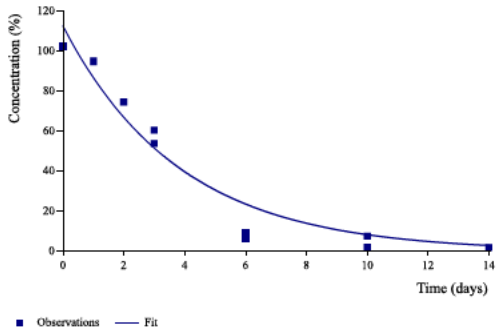
NA = Not applicable.
nd = Not determined. "Statistics may be missing because the covariance matrix could not be fully calculated. This may be because the higher-order model fitted is close to an SFO fit: g_Parent is approximately 1"
* Since α and β are no rate constants, t-test results were not reported.

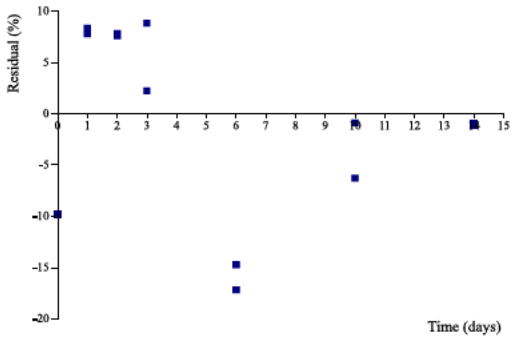
SFO



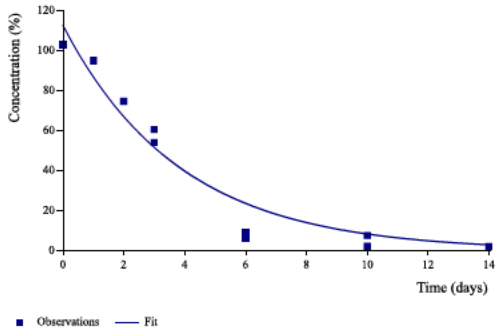


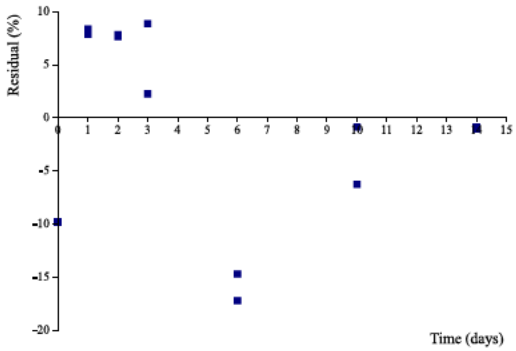
FOMC


Concentration (%)
Time (days)
Observations
Fit

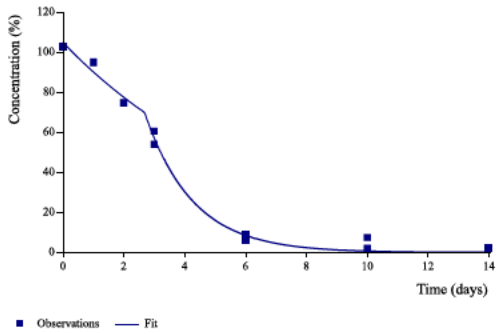

Residual (%)
Time (days)

DFOP


Concentration (%)
Time (days)
Observations
Fit


Residual (%)
Time (days)

HS


Concentration (%)
Time (days)
Observations
Fit

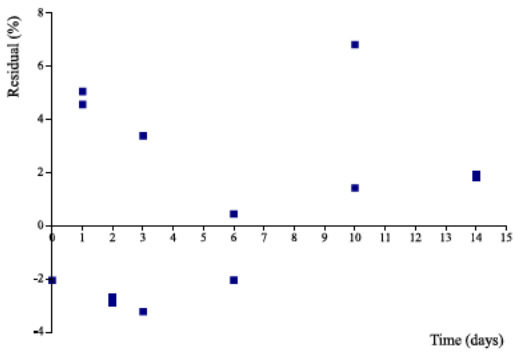

Residual (%)
Time (days)

Table 8 **Statistical and visual assessment of different kinetic models tested for degradation of ^{14}C-trifluoromethoxybenzoic acid in soil LUFA 2.2**

Kinetic model	Visual assessment	χ^2 error [%]	Kinetic parameters	Prob>t	$DegT_{50}$ [d]	$DegT_{90}$ [d]
SFO	acceptable	17.9	M_0: 103.1 k: 0.6031	NA <0.001	1.15	3.82
FOMC	acceptable	20.4	M_0: 103.1 α: 6.38E+003 β: 1.06E+004	NA NA* NA*	1.15	3.82
DFOP	acceptable	25.5	M_0: 103.1 k_1: 0.6031 k_2: 0.0153 g: 1.00	NA <0.001 nd NA	1.15 (overall)	3.82 (overall)
HS	acceptable	25.5	M_0: 103.1 k_1: 0.603 k_2: 0.009 t_b: 7.331	NA nd nd NA	1.15 (overall)	3.82 (overall)

⇨ SFO kinetic model provides a visually acceptable fit; although the residuals show some systematic deviation, the overall decline pattern is well represented by the SFO model; χ^2 error is above 15%; k is significantly different from zero (p-value <0.001).

⇨ FOMC kinetic model provides a visually acceptable fit (very similar to SFO fit); the goodness-of-fit is not improved since the χ^2 error is increased compared to the SFO model; the estimated values for α and β are very large, indicating that degradation is close to first-order kinetics.

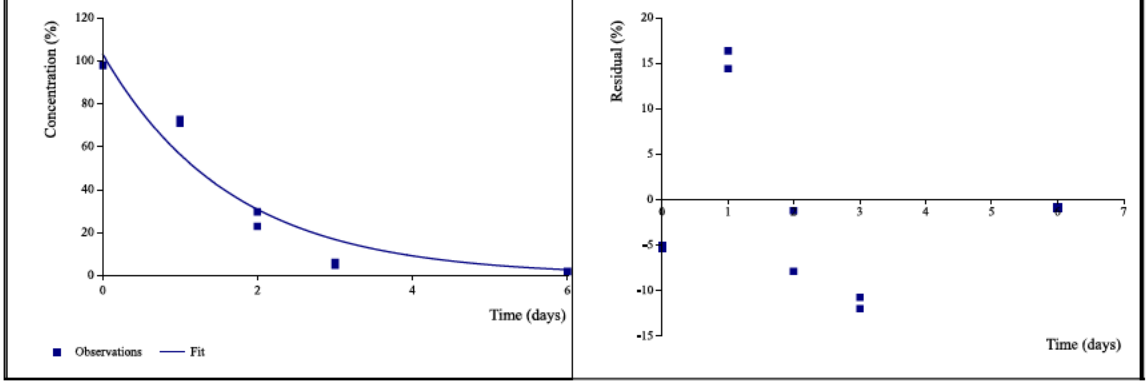
⇨ DFOP kinetic model provides a visually acceptable fit (very similar to SFO fit), but no improvement over SFO and FOMC; the χ^2 error is higher than for SFO and FOMC; the parameter g is estimated as 1 indicating that degradation is close to first-order kinetics.

⇨ HS kinetic model provides a visually acceptable fit (very similar to SFO fit), but no improvement over SFO and FOMC; The parameter t_b is not adequately inside the observation range.

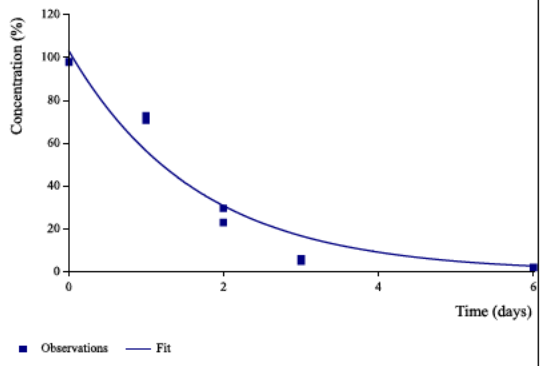
⇨ **Conclusion: SFO** model is considered the best-fit model appropriate to derive trigger endpoints for ^{14}C-trifluoromethoxybenzoic acid: $DegT_{50}$ = 1.15 d, $DegT_{90}$ = 3.82 d.

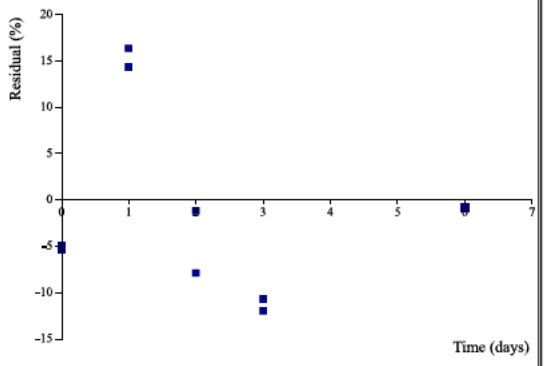
NA = Not applicable.
nd = Not determined "Statistics may be missing because the covariance matrix could not be fully calculated. This may be because the higher-order model fitted is close to an SFO fit: g_Parent is approximately 1"
* Since α and β are no rate constants, t-test results were not reported.

SFO

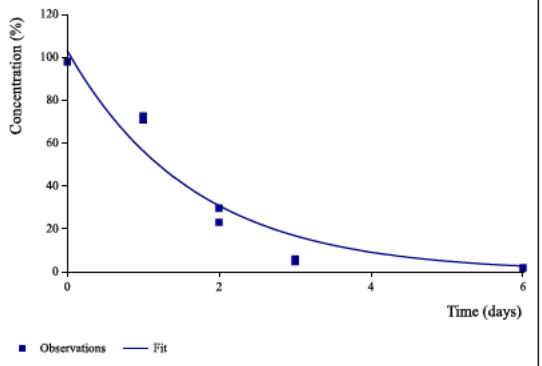


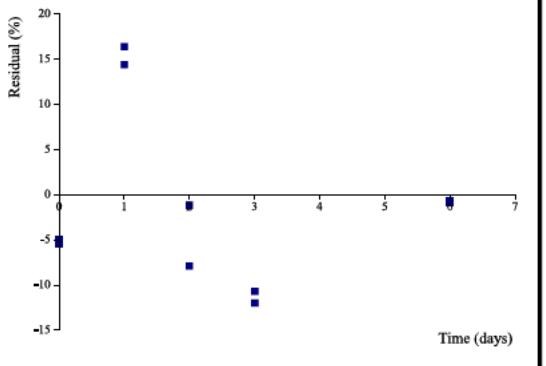
FOMC


Concentration (%)
Time (days)
Observations
Fit

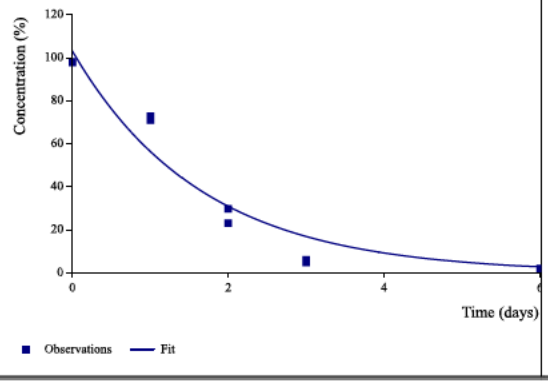

Residual (%)
Time (days)

DFOP


Concentration (%)
Time (days)
Observations
Fit


Residual (%)
Time (days)

HS


Concentration (%)
Time (days)
Observations
Fit

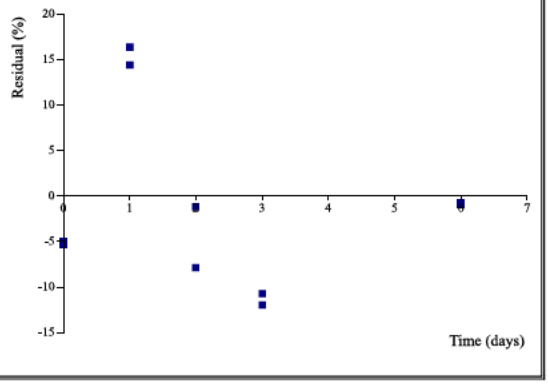

Residual (%)
Time (days)

Table 9 **Statistical and visual assessment of different kinetic models tested for degradation of ^{14}C-trifluoromethoxybenzoic acid in soil LUFA 2.4**

Kinetic model	Visual assessment	χ^2 error [%]	Kinetic parameters	Prob>t	DegT$_{50}$ [d]	DegT$_{90}$ [d]
SFO	acceptable	23.6	M_0: 107.1 k: 0.7153	NA <0.001	0.97	3.22
FOMC	acceptable	27.0	M_0: 107.1 α: 3.10E+006 β: 4.34E+006	NA NA* NA*	0.97	3.22
DFOP	acceptable	33.7	M_0: 107.1 k_1: 0.7153 k_2: 0.0135 g: 1.00	NA <0.001 nd NA	0.97 (overall)	3.22 (overall)
HS	good	3.70	M_0: 102.1 k_1: 0.36 k_2: 1.72 t_b: 1.00	NA >0.1 >0.1 NA	1.19 (overall)	2.13 (overall)

⇨ SFO kinetic model provides a visually acceptable fit; although the residuals show some systematic deviation, the overall decline pattern is still acceptable; χ^2 error is above 15%; k is significantly different from zero (p-value <0.001).

⇨ FOMC kinetic model provides a visually acceptable fit (very similar to SFO fit); the goodness-of-fit is not improved since the χ^2 error is increased compared to the SFO kinetic model; the estimated values for α and β are very large, indicating that degradation is close to first-order kinetics.

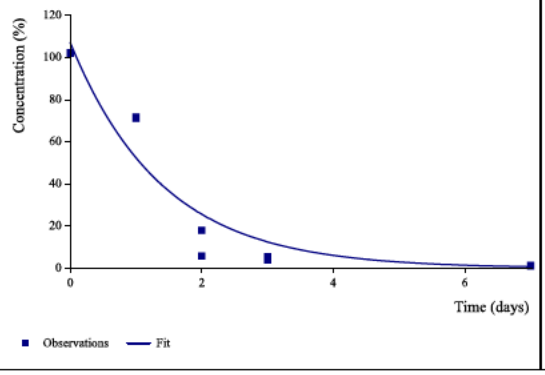
⇨ DFOP kinetic model provides a visually acceptable fit (very similar to SFO fit); but no improvement over SFO and FOMC; the χ^2 error is higher than for SFO and FOMC; the parameter g is estimated as 1 indicating that degradation is close to first-order kinetics.

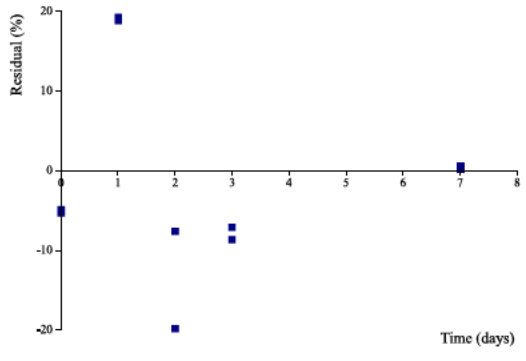
⇨ HS kinetic model improved the visual and statistical fit compared to SFO and other bi-phasic models. HS model provides a visually good fit; the fitted initial concentration matches well and the overall decline pattern is quite well represented with no systematic deviation; χ^2 error is <15% and is lower than for SFO, FOMC and DFOP kinetics.

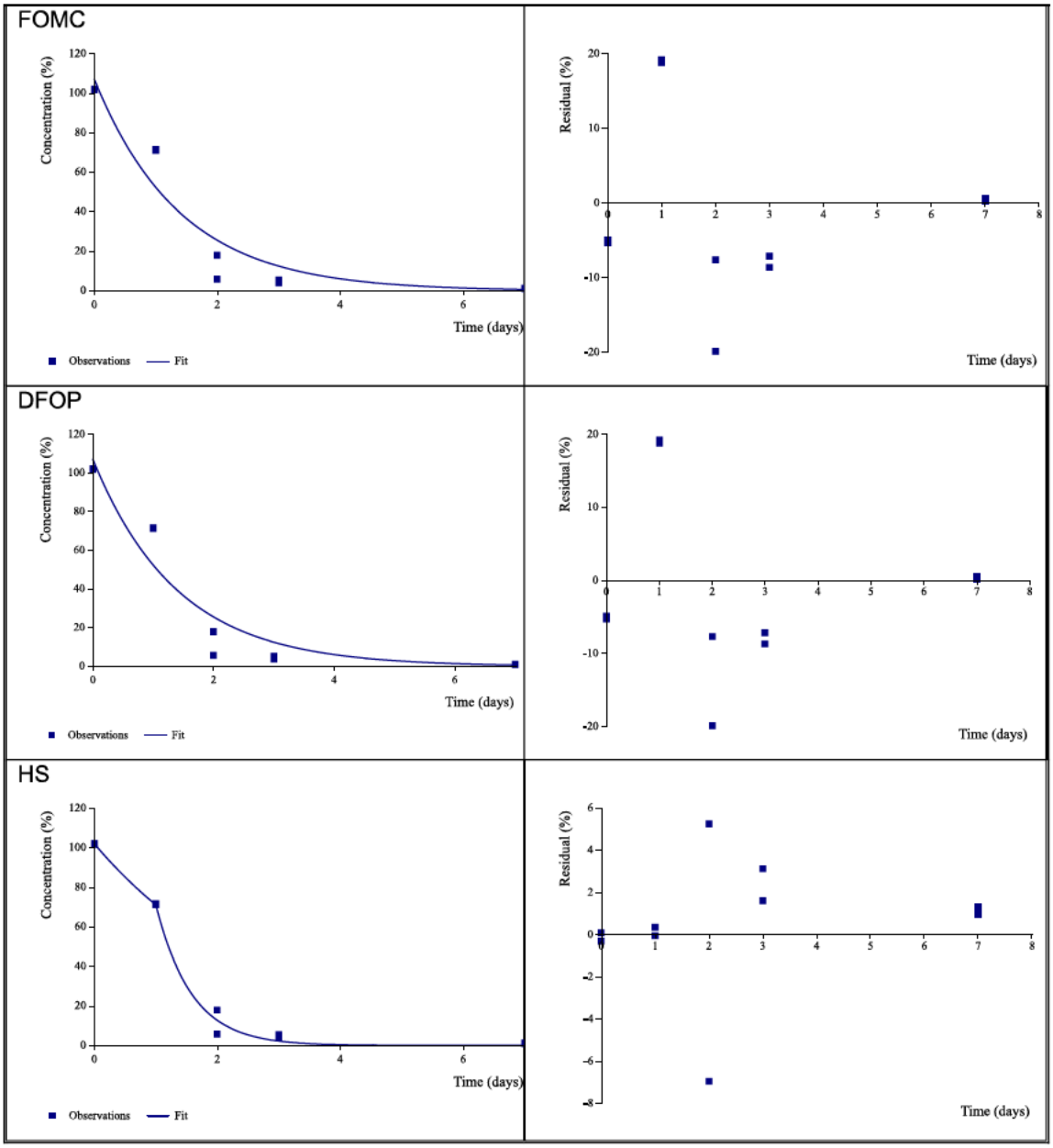
⇨ **Conclusion: HS** model is considered the best-fit model appropriate to derive trigger endpoints for ^{14}C-trifluoromethoxybenzoic acid: DegT$_{50}$ = 1.19 d, DegT$_{90}$ = 2.13 d.

NA = Not applicable.
nd = Not determined "Statistics may be missing because the covariance matrix could not be fully calculated. This may be because the higher-order model fitted is close to an SFO fit: g_Parent is approximately 1"
* Since α and β are no rate constants, t-test results were not reported.

SFO






FOMC
Concentration (%)
Time (days)
Observations
Fit
Residual (%)
Time (days)
DFOP
Concentration (%)
Time (days)
Observations
Fit
Residual (%)
Time (days)
HS
Concentration (%)
Time (days)
Observations
Fit
Residual (%)
Time (days)

III. CONCLUSION

The model compound 4-(trifluoromethoxy)benzoic acid degraded quickly under aerobic conditions and was last observed after 6 - 14 days of incubation. The kinetic evaluation resulted in $DegT_{50}$ values of 1.2 to 3.1 days at the temperature at 20 °C. Normalized to 12 °C by using the Q_{10} temperature correction factor of 2.58, the $DegT_{50}$ values increased to 2.1 – 5.7 days.

The only transformation reactions observed were the formation of carbon dioxide (up to 61.8 -72.7 % TAR) and of non-extractable residues (22.9 - 31.1% TAR at study end). The high amounts of CO_2 formed from the OCF_3-group demonstrate that along with the degradation of the molecule, the OCF_3-group is rapidly and largely mineralized, with the process of mineralization continuing even after the radioactivity was part of the non-extractable residues. The carbon mineralization from the OCF_3-group is an indirect proof that also the organically bound fluorine atoms are fully mineralized in soil, ending up as inorganic fluoride.

Overall, the experimental data show that the presence of an OCF_3-group does not automatically leave a molecule persistent in the environment or lead to persistent degradation products.

IV. REFERENCES

[Ref. 1] FOCUS (2006) "Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration" Report of the FOCUS Work Group on Degradation Kinetics, EC Document Reference Sanco/10058/2005 version 1.1 (December 2014), 440pp.

CropLife EUROPE

BRIEFING NOTE
10/10/2022 BRI/22/LO/35973

Experimental work on degradation of CF_3-containing molecules

Key messages

- **First results of an ongoing degradation study of trifluoromethoxy benzoic acid in soil, using a compound radio-labelled (^{14}C) directly at the CF_3-group to follow the fate of this special moiety, clearly show that the molecule is degraded very fast in soil and shows no persistence, despite carrying a CF_3-group.**
- **The results also show that the C-F bond of this single CF_3-group is not as stable as it is often postulated in documents describing the concerns around the behaviour of polyfluorinated alkyl substances (PFAS) in the environment.**
- **Further results will be presented as soon as they are available.**

Scope of the study

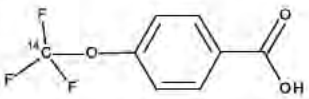
Within the upcoming "fire-fighting foam" and "universal" REACH restriction processes for PFAS, a chemical grouping concept is to be used in order to restrict all polyfluorinated alkyl substances (PFAS) falling under the respective PFAS definition. According to the call for evidence and currently available drafts, the OECD PFAS definition will be used, under which compounds which carry just one CF_3-group are defined as PFAS and consequently will fall within the restriction scope.

The major and consistent concern of PFAS as a group is their claimed non-degradability in the environment ("forever chemicals"), as proven in scientific publications for long and medium chain PFAS molecules (e.g. C4 and higher).

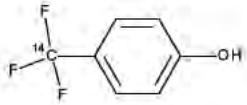
Single CF_3-groups are often used to improve the efficiency of active ingredients (e.g. in plant protection products or human or veterinary pharmaceuticals). Environmental as well as animal and plant metabolism studies performed within the regulatory EU approval processes clearly indicate that these single CF_3-groups are not the chemical moieties which decide on the overall persistency of a molecule. There are CF_3-carrying plant protection active ingredients which have very short half-lives in soil.

Despite of the wide-spread doctrine of the very stable and unbreakable C-F bond, scientific literature describes chemical and biological defluorination reactions, some of which can take place under environmentally relevant conditions. One such substance identified from the scientific literature is trifluoromethanol ($HO-CF_3$), which is both thermally and hydrolytically unstable. As part of a larger molecule such a moiety is expected to be unable to act as a terminal metabolite, or "arrowhead substance".

Single CF_3-groups are very useful chemical moieties which help to ensure that the active ingredient reaches the target thus allowing the reduction of the dose rates for active substances. The experimental study presented here intends to investigate if single CF_3-groups could potentially be degraded by defluorination, finally forming CO_2 and fluoride i.e. fully mineralize. Two model compounds with different bonding of the CF_3-group to the rest molecule ($O-CF_3$ and $C-CF_3$ bonds) were chosen.



4-^{14}C-trifluoromethoxy benzoic acid



4-^{14}C-trifluoromethylphenol

CropLife Europe aisbl | 9 Rue Guimard | 1040 Brussels | Belgium | BE 0447 618 871 Register of Legal Persons Francophone Section of the Business Court of Brussels | croplifeeurope@croplifeeurope.eu | www.croplifeeurope.eu Tel: +32 2 663 15 50 | Fax: +32 2 663 15 60

The first model compound, 4-^{14}C-trifluoromethoxy benzoic acid (p-TFMBA) was selected to test the hypothesis that biodegradation of a larger molecule would lead to trifluoromethanol formation, which because it is thermally and hydrolytically unstable, would immediately undergo abiotic decomposition to form CO_2 and HF. A benzoic acid derivative was used as the parent molecule, since these are known to undergo rapid biodegradation, and thus maximise the time available within the study for following the metabolites formed.

The second model compound, 4-^{14}C-trifluoromethylphenol, was selected to test the hypothesis that biodegradation of benzene substituted trifluoromethyl moieties do not always lead to persistent metabolites, depending on secondary substituents and their molecular position.

In order to get information about the possibility of metabolic defluorination reactions with O-CF_3 or C-CF_3 compounds, the necessary ^{14}C-label to be used in the respective metabolism studies needs to be introduced directly at the fluorinated carbon. The synthesis of this special radiolabel could only be achieved for the O-$^{14}CF_3$-labelled compound at this stage.

Further investigations are planned on the C-CF_3 compound. Unfortunately, the introduction of the $^{14}CF_3$- label next to a ring-C-atom is not easy to achieve experimentally. Currently, attempts are ongoing to find feasible and safe synthesis routes for the 2, 3 and 4 isomers. In case the molecule can be synthesized, the same soil metabolism investigations will follow as performed for the O-$^{14}CF_3$ compound.

Timelines

The final results from the present soil degradation study with the O-$^{14}CF_3$-compound are expected by end of November 2022. First interim results are presented in this briefing note.

In case the synthesis of the C-$^{14}CF_3$ model substance can be achieved, first results can be expected in Q1 2023.

Experimental outline

In order to investigate the potential degradation of the O-CF_3-moiety in soil, p-trifluoromethoxy benzoic acid (p-TFMBA) was chosen as a model compound, with the ^{14}C-label placed in the O-CF_3 group (Appendix 1). With this test compound an aerobic soil degradation study was conducted according to OECD guideline 307 *Aerobic and anaerobic transformation in soil* (April 2002).

The experiment was performed at the test facility of BASF Agricultural Center, Limburgerhof, Germany, which is equipped to routinely perform simulation studies (eg. OECD 307, OECD 308, OECD 309) within the frame of the requirements of EU directive 1107/2009 for placing plant protection chemicals on the market.

According to OECD guideline 307, soil samples were treated with the radio-labelled test item and incubated under controlled conditions at a soil moisture of ~40% of the maximum water holding capacity at a temperature of 20°C (to maximize metabolite formation), under dark conditions. The test concentration was chosen at 0.67 mg/kg (dry weight equivalent) to allow for a reliable analysis with radio-detection methods with a limit of quantification of at least 0.1% of the total applied radioactivity. A closed incubation system with continuous aeration was used with an attached trapping system for the determination of volatile compounds. The air was first going through an ethylene glycole trap followed by two NaOH-solution traps (Appendix 2).

The incubations were performed in three different German soils (Li 10, LUFA 2.2 and LUFA 2.4) with 8 samplings over a planned period of 28 days. The soil properties are shown in Appendix 3.

At each sampling date, evolved and trapped volatiles (e.g. $^{14}CO_2$ in NaOH trapping solution) were quantified by LSC (liquid scintillation counting). For each soil and sampling time, two replicates were taken and extracted with acetonitrile/water mixtures and acetone, and the extracts were analyzed by LSC and radio-HPLC in order to determine the amount of test substance remaining in soil and the number and amount of potential metabolites. To complete the radioactivity balance, the non-extractable residues were quantified by combustion in an Oxidizer and subsequent LSC measurement (Appendix 4).

In case the chromatographic analysis of the soil extracts revealed degradation products, it is planned to identify the chemistry by structure elucidation methods like HPLC-MS/MS or similar.

First Results

First results from the study with the O-^{14}CF3 model compound are meanwhile available from the soils Li 10 and LUFA 2.2 up to 14 days after treatment (DAT).

The distribution of radioactivity in the two soils and the material balance is displayed in Tables 1 and 2, respectively. All values are expressed as % of the total applied radioactivity (% TAR) if not stated otherwise.

After an incubation period of 14 days, the parent compound was almost completely degraded in the two soils (<2% TAR of parent recovered in extracts). For both soils, the major degradation product was CO_2 accounting for 57 - 58% TAR.

In order to confirm that the radioactivity in the NaOH-trapping solutions consisted indeed of CO_2 and not of any other potential (still fluorinated) volatile transformation product, two different methods were used. (1) An aliquot of the NaOH trapping solution was treated with $BaCl_2$. Any CO_2 in the NaOH will be transformed to $BaCO_3$ which then can be precipitated by centrifugation, leaving no or insignificant traces of radioactivity in the solution. (2) A second aliquot of the NaOH trapping solution is treated with conc. HCl, leading to the effect that trapped CO_2 is released and can be expelled from the solution, leaving again no or only insignificant traces of radioactivity in the solution.

With both methods, the radioactivity measurements of the NaOH trapping solutions clearly showed that $^{14}CO_2$ was formed during soil incubation, indicating that the radiolabelled carbon atom in the parent molecule was completely defluorinated.

No other volatile degradate could be detected. The radioactivity in the ethylene glycole trapping solution was always < 0.05%.

Besides mineralization to CO_2, formation of non-extractable residues (NER) was observed which reached maximum levels of 45.5% TAR (Li 10 / 6 DAT) and 50.6% TAR (LUFA 2.2 / 3 DAT) before they decreased again to levels of 32% TAR and 35.6% TAR at 14 DAT, respectively.

This indicates that part of the parent test item was bound to the humic matrix in soil, which is a known reaction of aromatic carboxylic acids as benzoic acid. The proceeding defluorination and mineralization (increasing CO_2-levels) also show that this does not stop the further degradation of trifluoromethoxy-group, but just slows it down to a certain extent.

HPLC analysis of the soil extracts revealed that the extracted radioactivity consisted only of the parent compound ^{14}C-p-TFMBA (see Figure 1), i.e. extractable metabolites were not formed in appreciable amounts (no single peak >0.2 % TAR in any sample).

Conclusion

The first results of the soil degradation study with trifluoromethoxy-benzoic acid clearly shows that despite carrying a CF_3-group, the entire molecule is very quickly degraded in soils and not at all stable as postulated for all PFAS molecules. Furthermore, it can also be shown that the C-F bond can be broken rapidly, leading to a complete defluorination of the C-atom with final formation of CO_2. No other critical (highly persistent) reaction products were detected.

Outlook

Further results with the O-CF_3 model compound will be summarized as soon as they are available. If synthesis can be achieved, similar experiments will be performed with a C-CF_3 model compound.

Table 1: Distribution of radioactivity and material balance in Li 10 soil treated with ^{14}C-pTFMBA

DAT	Soil extraction							NER	Volatiles		Material balance
	ACN/H_2O (9:1) 1	ACN/H_2O (9:1) 2	ACN/H_2O (9:1) 3	ACN/H_2O (1:1) 4	Acetone 5	Acetone 6	Sum extracts 1 - 6		CO_2 [a]	CO_2 [b]	
0	75.6	20.9	4.6	1.4	0.2	0.0	102.8	0.1	0.0		102.8
	76.1	20.2	4.6	1.5	0.2	0.1	102.7	0.1	0.0		102.8
mean	**75.9**	**20.6**	**4.6**	**1.4**	**0.2**	**0.0**	**102.7**	**0.1**	**0.0**		**102.8**
1	67.0	20.0	5.6	1.4	0.5	0.2	94.7	6.1	0.3	2.9	104.0
	67.0	20.6	5.8	1.2	0.8	0.2	95.6	4.9	0.1	2.6	103.2
mean	**67.0**	**20.3**	**5.7**	**1.3**	**0.6**	**0.2**	**95.2**	**5.5**	**0.2**	**2.8**	**103.6**
2	50.7	16.4	4.6	2.1	0.7	0.2	74.8	16.6	0.3	10.4	102.1
	50.8	16.3	4.5	2.0	0.8	0.2	74.6	16.2	0.3	9.8	100.8
mean	**50.8**	**16.4**	**4.6**	**2.1**	**0.7**	**0.2**	**74.7**	**16.4**	**0.3**	**10.1**	**101.5**
3	40.5	13.3	3.9	2.1	0.4	0.3	60.5	24.1	0.4	16.1	101.2
	36.2	11.5	3.4	2.1	0.4	0.2	53.9	28.8	0.4	19.0	102.1
mean	**38.3**	**12.4**	**3.6**	**2.1**	**0.4**	**0.2**	**57.2**	**26.4**	**0.4**	**17.5**	**101.6**
6	4.9	1.9	0.7	1.2	0.2	0.1	9.0	44.7	0.8	46.3	100.8
	3.2	1.3	0.5	1.1	0.2	0.1	6.5	46.3	0.8	47.1	100.7
mean	**4.1**	**1.6**	**0.6**	**1.2**	**0.2**	**0.1**	**7.8**	**45.5**	**0.8**	**46.7**	**100.7**
10	4.5	1.6	0.6	0.9	0.2	0.1	8.0	42.6	0.2	49.5	100.4
	1.1	0.5	0.3	0.7	0.2	0.1	2.8	39.5	0.4	53.0	95.9
mean	**2.8**	**1.1**	**0.4**	**0.8**	**0.2**	**0.1**	**5.4**	**41.1**	**0.3**	**51.3**	**98.1**
14	0.7	0.3	0.2	0.6	0.1	0.0	2.0	28.9	0.1	57.4	88.4
	0.7	0.4	0.2	0.6	0.1	0.0	1.2	35.1	0.1	58.8	95.2
mean	**0.7**	**0.3**	**0.2**	**0.6**	**0.1**	**0.0**	**1.6**	**32.0**	**0.1**	**58.1**	**91.8**

ACN = acetonitrile
DAT = days after treatment
NER = non-extractable residues
CO_2[a] = CO_2 which evolved during the drying time of the extracted soil residue before combustion
CO_2[b] = CO_2 measured in the volatile trapping solutions

Table 2: Distribution of radioactivity and material balance in LUFA 2.2 soil treated with ^{14}C-pTFMBA

DAT	Soil extraction							NER	Volatiles		Material balance
	ACN/H_2O (9:1) 1	ACN/H_2O (9:1) 2	ACN/H_2O (9:1) 3	ACN/H_2O (1:1) 4	Acetone 5	Acetone 6	Sum extracts 1 - 6		CO_2 [a]	CO_2 [b]	
0	61.4	24.4	7.6	3.1	0.6	0.1	97.3	0.5	0.0		97.8
	61.0	24.6	7.8	3.3	0.6	0.2	97.6	0.5	0.0		98.1
mean	**61.2**	**24.5**	**7.7**	**3.2**	**0.6**	**0.2**	**97.4**	**0.5**	**0.0**		**97.9**
1	43.1	17.1	6.7	4.9	0.8	0.2	72.8	13.3	0.1	7.3	93.6
	42.1	16.8	6.4	4.8	0.7	0.2	71.0	15.4	0.1	8.8	95.3
mean	**42.6**	**16.9**	**6.5**	**4.8**	**0.8**	**0.2**	**71.9**	**14.3**	**0.1**	**8.1**	**94.4**
2	13.7	5.7	2.3	1.1	0.2	0.0	23.0	45.4	0.6	23.9	92.9
	17.7	7.6	2.9	1.4	0.2	0.0	29.7	42.9	0.4	22.0	95.0
mean	**15.7**	**6.7**	**2.6**	**1.2**	**0.2**	**0.0**	**26.4**	**44.1**	**0.5**	**22.9**	**94.0**
3	2.5	0.7	0.5	2.2	0.2	0.1	6.2	48.5	1.1	34.4	90.2
	1.5	1.2	0.3	1.7	0.2	0.1	4.9	52.7	0.5	35.4	93.5
mean	**2.0**	**0.9**	**0.4**	**2.0**	**0.2**	**0.1**	**5.6**	**50.6**	**0.8**	**34.9**	**91.8**
6	0.9	0.5	0.2	0.5	0.1	0.0	2.2	46.7	0.0	41.2	90.1
	0.8	0.4	0.2	0.5	0.1	0.0	2.1	41.6	0.3	41.0	85.0
mean	**0.9**	**0.5**	**0.2**	**0.5**	**0.1**	**0.0**	**2.1**	**44.2**	**0.2**	**41.1**	**87.6**
10	0.5	0.3	0.1	0.3	0.1	0.0	1.3	40.8	0.4	50.2	92.8
	0.6	0.4	0.1	0.3	0.1	0.0	1.4	39.0	0.7	50.5	91.6
mean	**0.5**	**0.3**	**0.1**	**0.3**	**0.1**	**0.0**	**1.4**	**39.9**	**0.6**	**50.3**	**92.2**
14	0.4	0.2	0.1	0.2	0.0	0.0	1.0	35.7	0.1	58.3	95.1
	0.5	0.2	0.1	0.2	0.0	0.0	1.1	35.6	0.1	56.1	92.9
mean	**0.4**	**0.2**	**0.1**	**0.2**	**0.0**	**0.0**	**1.1**	**35.6**	**0.1**	**57.2**	**94.0**

ACN = acetonitrile
DAT = days after treatment
NER = non-extractable residues
CO_2[a] = CO_2 which evolved during the drying time of the extracted soil residue before combustion
CO_2[b] = CO_2 measured in the volatile trapping solutions

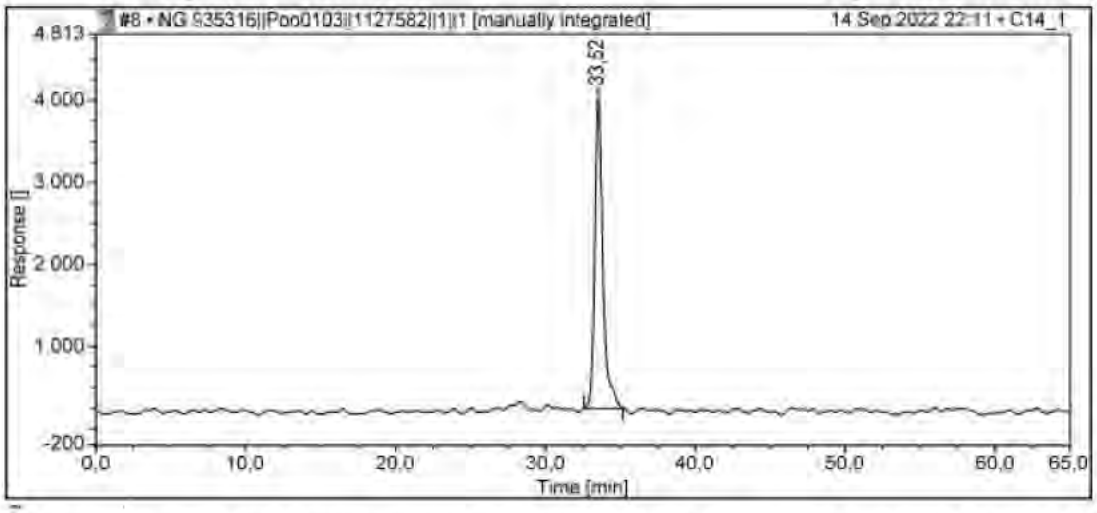
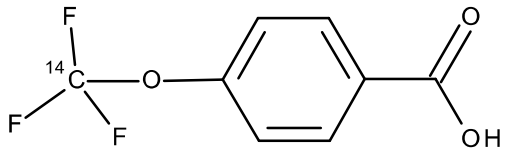


Figure 1: Radio-HPLC chromatogram of ACN/H2O (9:1) extract 1-3 of soil Li10, 6 days after treatment

Appendices

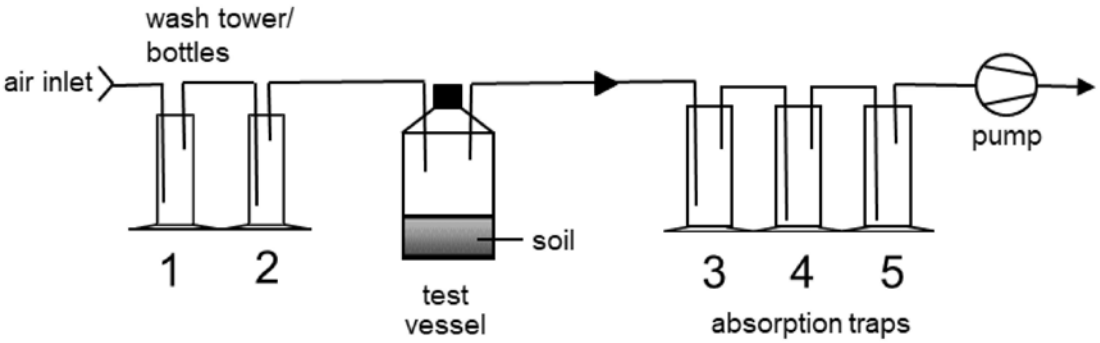
Appendix 1: Test item information

Structure



IUPAC Name:	4-(Trifluoromethoxy)benzoic acid,
Abbreviated Name:	p-TFMBA
Label:	[trifluoromethoxy-C14]
Specific radioacitivty:	308945 dpm/µg
Radiochemical purity:	99.9%
Applied amount:	0.67 mg/kg (250 g/ha) dry soil

Appendix 2: Test setup



Sequence of volatile trapping solutions:

flask 3: ethylene glycole
flask 4: 0.5 N NaOH
flask 5: 2.0 N NaOH

Appendix 3: Soil properties

Soil	Li 10	LUFA 2.2	LUFA 2.4
Soil texture [USDA]	Sandy loam	Sandy loam	Loam
Clay [%]	6.5	9.3	16.8
Silt [%]	23.4	16.7	42.0
Sand [%]	70.1	74.0	41.2
Soil texture [DIN]	Slightly loamy sand	Medium loamy sand	Slightly sandy loam
Clay [%]	7.1	8.5	18.9
Silt [%]	24.5	17.6	45.2
Sand [%]	68.4	73.9	35.9
Organic carbon [%]	1.07	2.14	2.14
pH [$CaCl_2$]	5.04	5.45	7.46
Max. water-holding cap. [g/100 g dry soil]	34.3	44.9	56.7
Microbial biomass (SIR) [mg C/100 g dry soil]	30.8	71.4	153.0

Appendix 4: Analytical methods

Liquid scintillation counting:

Instrumentation:

For LSC:	Tri-Carb 2910 TR (Perkin Elmer Life Sciences, Germany)	
	Tri-Carb 4910 TR (Perkin Elmer Life Sciences, Germany)	
For combustion:	Biological Oxidizer OX-501 (R.J. Harvey Instrument Corporation)	
Scintillators used:	Liquid samples:	Insta-Gel Plus, Perkin Elmer
		Ultima Gold XR, Perkin Elmer
	Combusted samples:	Oxysolve C-400, Zinsser Analytic

LSC (all samples):
The external standardization method with a built-in β-radiation source was used for the determination of counting efficiencies.

Combustion (solid samples):
The radioactivity of soil samples was determined by combustion of four aliquots (about 0.4 to1.0 g each). Combustion products were absorbed in Oxysolve C-400 scintillation cocktail. The recovery for the oxidizer was determined by combusting a carbon ^{14}C-standard. Measurements of radioactivity were corrected for oxidizer efficiency.

Radio-HPLC:

Pre-column:	Phenomenex SecurityGuard C12 4 mm x 3 mm i.d.
Column:	Phenomenex Luna PFP (2) 5 µm, 250 mm x 4.6 mm i.d.
Temperature:	25°C
Flow rate:	1.0 mL/min
Wavelength:	254 nm
Radiocell:	YG400-S5D
Mobile phase:	A: H_2O + HCOOH 1000 + 2.5 (v/v)
	B: Acetonitrile + HCOOH 1000 + 2.5 (v/v)

Gradient:

Time [min]	%B
0	0
7.5	0
40	75
41	100
51	100
52	0
65	0

CropLife EUROPE

POSITION PAPER
POSI/22/LO/3546 I

Additional information on the Scope of the proposed restriction of Per- and polyfluoroalkyl substances (PFASs) in firefighting foams.

Key Messages:

- **Additional information is provided to RAC on the lack of Persistence (hazard) for certain PFAS substances, thus impacting the definition scope of the proposed restriction of Per- and polyfluoroalkyl substances (PFAS) in firefighting foams.**
- **The OECD definition is a literal conversion of "per- and polyfluoroalkyl substances" into structural chemistry terms. The OECD authors clearly state that for regulatory action the scope should be further narrowed to a subset matching the critical properties under consideration e.g. Persistence. It is thus a misuse of the OECD definition in its unabridged form if this principle is not applied.**
- **The review of the scientific literature presented in the Annex XV dossier is inadequate and misses a significant body of known chemistry. Chemical property data available from the scientific literature and regulatory submissions show that certain single -CF_3 functional groups cannot be persistent due to chemical reactivity with water e.g. -OCF_3, -NCF_3. In our view this justifies a modification of the definition scope (grouping) for the restriction proposal.**
- **The restriction proposal should be amended to: *Per- and polyfluoroalkyl substances (PFASs) defined as: any substance that contains at least one fully fluorinated methyl (CF_3) or methylene (CF_2) carbon atom (without any H/Cl/Br/I attached to it, and excluding -OCF_3, -NCF_3)***
- **Certain additional single -CF_2- or -CF_3 functional groups cannot also be assumed to be inherently persistent due to chemical reactivity with water or to other degradation mechanisms, which in our view justifies a further "safety net" derogation, for case-by-case use where evidence is available.**
- **Placing the above substances out of scope, or potentially subject to a derogation, does not in any way lower protection of human health or the environment, because it remains incumbent on any REACH registrants to demonstrate the lack of persistence in the respective REACH registrations.**

1. Introduction

CropLife Europe wishes to provide additional information to the Dossier Submitter on the lack of Persistence (hazard) for certain PFAS substances, thus impacting the scope and definition used in the Annex XV Restriction Report for a Proposal for a Restriction on Per- and polyfluoroalkyl substances (PFASs) in firefighting foams (Version 2.0, dated 23rd March 2022). While the definitions discussed here do not appear to be highly applicable to the chemistries used in firefighting foams, never-the-less the general claims being presented by the Dossier Submitter about PFAS substances are of more widespread applicability, including several specific references in the Restriction Report Annex to active substances, necessitating detailed comments from CropLife Europe.

CropLife Europe aisbl | 9 Rue Guimard | 1040 Brussels | Belgium | BE 0447 618 871 Register of Legal Persons
Francophone Section of the Business Court of Brussels | croplifeeurope@croplifeeurope.eu | www.croplifeeurope.eu
Tel: +32 2 663 15 50 | Fax: +32 2 663 15 60

As has been noted on page 13 of the Restriction Report, the OECD definition is a literal conversion of "per- and polyfluoroalkyl substances" into structural chemistry terms, **not taking into account hazardous properties or risks**. The authors of the OECD definition clearly state that for regulatory use the definition should be further narrowed to match the properties under consideration, and it is thus a misuse in its unabridged form if this is not justified.

If the unabridged OECD structural definition is used to define PFAS, the result is that the Restriction Report (page 1) incorrectly states "*All PFASs are very persistent in the environment. This is the key hazardous property common to all PFASs*". For this statement to remain correct, the OECD structural definition would need to be further refined for use in this restriction, including such that the requirements of Article 68(1) "unacceptable risk to human health or the environment" are met. **We request such simplistic and incorrect statements are removed from the Restriction Report.**

The Dossier Submitter confirms this on page 54 of the Annexes to the Restriction Report:

> *If there are specific PFASs for which sufficient evidence is provided that the perfluorinated bond is broken at a rate which indicates them to be not persistent, resulting a substance/substances which is/are not a PFAS, then those substances/groups should be excluded from the scope. Currently, no such PFASs are known to the dossier submitter.*

Chemical property data and degradation information from the scientific literature are presented here to demonstrate that, as a minimum, certain OECD structural PFAS substances are not chemically stable, and furthermore cannot be "arrowhead" substances for these moieties found in larger molecules. Examples are presented for CF_2/CF_3 containing substances which clearly demonstrate that carbon fluorine bonds in certain substances can be, and in practice are, broken under environmentally relevant conditions.

2. Definitions and Scope

The recently published OECD structural 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 Annex XV restriction proposal (page 6, and Section 1.1.1.1) aligns with the full OECD structural definition without further refinement to align with the grouping justification (page 16, Section 1.1.2), thus constituting a misuse of the OECD structural definition:

> *"To summarise, the grouping is based on structural similarity (common perfluorinated moieties) that triggers equivalent hazards and risks among the substances covered, primarily related to the very persistent property of the substances."*

In light of these considerations, **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 proposed restriction. The following amendment to the restriction definition in Column 1 (page 6) is proposed on the basis of extensive chemical property and degradation information presented is subsequent sections:

> *Per- and polyfluoroalkyl substances (PFASs) defined as: 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,* **and excluding -OCF_3, -NCF_3***)*

3. Single CF_3 moieties which are unstable towards hydrolysis

The -CF_3 moiety is the shortest alkyl group within scope of the proposed PFAS restriction definition. Data from the scientific literature are presented here for 5 trifluoromethoxy (CF_3O-) containing molecules, and thus shows that should the corresponding alcohol be formed as an "arrowhead" substance, it will be rapidly hydrolysed.

Similarly, data is presented 13 molecules which show simple trifluoromethylamino (CF_3N<) groups will directly hydrolyse.

These molecules meet the proposed PFAS definition, and yet they are demonstrably not persistent (Table 1). Any persistence which precursor (parent) molecules may demonstrate cannot be linked to the presence of these moieties in those molecules. **As a result, these functional groups should be placed out of scope of the PFAS restriction.**

Further details on these compounds substantiating the lack of persistent properties despite meeting the PFAS definition are provided in the subsequent sections. It must be emphasized this is a cursory inspection of the literature, and there are very likely many CF_2/CF_3 compounds with similar properties which are not identified here.

Table 1. List of 18 substances which meet the OECD structural definition which do NOT demonstrate persistent properties attributable to the presence of -OCF3 or >NCF3.

Substance	Structure	Moiety
trifluoromethanol	CF_3OH	-OCF_3
potassium trifluoromethoxide	CF_3OK	-OCF_3
rubidium trifluoromethoxide	CF_3ORb	-OCF_3
cesium trifluoromethoxide	CF_3OCs	-OCF_3
10-trifluoromethoxy-decane-1-sulfonate	$CF_3OC_{10}H_{20}SO_3H$	-OCF_3
trifluoromethylamine	CF_3NH_2	>NCF_3
1-phenyl-4-(trifluoromethyl)piperazine	See Figure 3	>NCF_3
4-methoxy-N-methyl-N-(trifluoromethyl)aniline	See Figure 3	>NCF_3
N-methyl-N-(trifluoromethyl)aniline	See Figure 3	>NCF_3
N,4-dimethyl-N-(trifluoromethyl)aniline	See Figure 3	>NCF_3
N-ethyl-N-(trifluoromethyl)aniline	See Figure 3	>NCF_3

1-(trifluoromethyl)-2,3-dihydro-1H-indole	See Figure 3	>NCF_3
1-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline	See Figure 3	>NCF_3
4-[methyl(trifluoromethyl)amino]benzonitrile	See Figure 3	>NCF_3
4-fluoro-N-methyl-N-(trifluoromethyl)aniline	See Figure 3	>NCF_3
3-fluoro-N-methyl-N-(trifluoromethyl)aniline	See Figure 3	>NCF_3
N-methyl-N,4-bis(trifluoromethyl)aniline	See Figure 3	>NCF_3
ethyl N-benzyl-N-(trifluoromethyl)glycinate	See Figure 3	>NCF_3

3.1. Trifluoromethoxy groups

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 precursor molecules featuring this group on the basis of inherent persistence of metabolites is justified depends on the ultimate stability of the arrowhead substance trifluoromethanol.

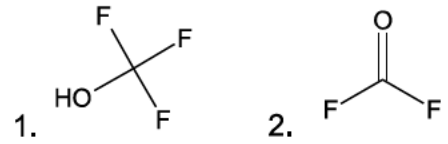


Figure 1. Model compounds: 1) trifluoromethanol (CF_3OH), and 2) carbonyl difluoride (CF_2O).

Trifluoromethanol (Figure 1) has been grouped with the "F-gases", implying atmospheric behavior is the most relevant context. However, since trifluoromethanol is not itself commercially manufactured and its thermal and hydrolytic stability precludes plausible future uses, its primary relevance in this discussion is as an example of a PFAS substance which is not persistent, and as an arrowhead, formed via hydrolysis and biodegradation reactions in soil (including soil pore water) and in aqueous media. **We suggest that the discussion of trifluoromethanol and precursor molecules is more appropriately placed in the general chemistry section, rather than with "F-gases".**

Trifluoromethanol (CAS No. 1493-11-4) is an unstable substance which is a gas at room temperature. It was initially speculated that it was too reactive to exist, and was only 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. Trifluoromethanol is not REACH registered, nor appears on any global chemical inventories: it is not a commercially relevant substance, and given the above thermal instability, it cannot plausibly be considered a "regrettable substitution" candidate.

Østerstrøm *et al* (2019) reported a similar substance, gaseous difluoromethanol, to decompose with a first-order rate coefficient of $k = (1.68 \times 10^{-3})\ s^{-1}$, corresponding to an atmospheric half-life of 6.9 minutes at room temperature.

CF_3OH is strongly acidic and some salt (K, Rb, Cs) 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).

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

Redwood et al (1965) noted “The trifluoromethoxides are reactive compounds and are immediately hydrolyzed on contact with water.”, confirming this analytically for the K, Rb, and Cs salts with the stoichiometric presence of fluoride ions in hydrolyzed aqueous solution. Inspection of the synthetic method reported by Klöter et al (1979) reveals other inorganic compounds featuring the CF_3O moiety with high likelihood of being unstable towards hydrolysis, and thus potentially invalidating the current PFAS definition proposed e.g. trifluoromethyl hypochlorite (CF_3OCl). **We request these above examples are taken account of, and a further search of the academic literature is likely to reveal more hydrolytically unstable examples.**

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 environment will not be under anhydrous conditions, decomposition into CF_2O and HF is considered inevitable and rapid.

The restriction report Annex (p107) incorrectly attributes a million-year half-life below 40km for trifluoromethanol to Buszek and Francisco (2009). In fact, this was a theoretical estimate calculated by Schneider et al (1995), and is purely considering photolysis, and not the overall atmospheric half-life. The 40km arises because UV light with sufficient energy to directly cause degradation was calculated to be insufficient in the lower atmosphere. Schneider et al (1995) although concluding photolysis was not an important mechanism, never-the-less stated in their conclusion ***“Once in the lower atmosphere, CF_3OH will be rapidly removed by incorporation into rainwater-seawater-cloudwater where hydrolysis will give CO_2 and HF.***”

The work of Buzek and Francisco in fact showed that the atmospheric behavior is more complex, and presented a new mechanism whereby the presence of water and OH molecules can catalyze decomposition in the atmosphere. It is important to recognize these are not experimental studies, and there can be additional unrecognized processes in play. **We request that this paragraph (bottom p107) in the Restriction Report Annex is corrected so as not to suggest that the true atmospheric half-life of trifluoromethanol is in the order of millions of years.** It is also claimed by several of the above authors that trifluoromethanol in the upper atmosphere is a potential sink for the oxidative degradation of longer chain perfluorochemicals. **It is important to recognize that the hypothesized source of these CF_3 radicals are the longer perfluorinated molecules otherwise within scope of this restriction, and applying the restriction to CF_3OH itself or potential -OCF_3 precursor molecules, would be misdirected and have no effect.**

Carbonyl difluoride (eqn 1) 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). Although not formally meeting the PFAS structural definition, once formed, carbonyl difluoridealso 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). Figure B.41 (page 107) implies carbonyl difluoride is a PFAS, and provides an unattributed half-life of 5 years. **We request this is corrected c.f. De Bruyn 1995, with the relevant hydrolysis half-life, and the atmospheric half-life attributed or removed.**

Examples of trifluoromethoxy degradation from larger precursor 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). This demonstrates that in in-vivo biological systems the carbon fluorine bonds can be broken.

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 proceeded in comparison very slowly (unrelated to the trifluoromethoxy group), but still ultimately led to trifluoromethanol, which once formed, underwent rapid mineralisation. As a result, virtually complete mineralization was claimed. **While Peschka (2008) appears in the Restriction Report reference list, the results of this study do not appear to have been taken into account in the discussion. We request the mineralization of 10-trifluoromethoxy-decane-1-sulfonate be acknowledged in the Restriction Report.**

3.2. Trifluoromethylamino groups

Chemical stability of trifluoromethylamine towards hydrolysis

The trifluoromethylamino moiety (Figure 2) features the shortest terminal alkyl group (-CF_3) within scope of the proposed PFAS restriction definition. Whether the inclusion of larger precursor molecules featuring this group on the basis of inherent persistence of metabolites is justified, depends on the stability of the arrowhead substance trifluoromethylamine. Klöter *et al* (1977) synthesised the trifluoromethylamine using similar approaches to trifluoromethanol, under strictly anhydrous conditions, with spontaneous thermal decomposition increasing above -21°C to form a mixture of compounds (Klöter, 1979).

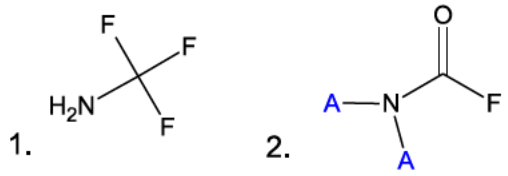


Figure 2. Model compounds: 1) trifluoromethylamine (CF_3NH_2), 2) carbamoyl fluoride (A,A'-NCOF).

Inspection of the synthetic method reported by Klöter et al (1979) reveals several other inorganic compounds featuring the CF_3N moiety with high likelihood of being unstable towards hydrolysis, and thus potentially invalidating the current PFAS definition proposed e.g. trifluoromethyliminosulfur difluoride ($CF_3N{=}SF_2$), trifluoromethylamine dichloride (CF_3NCl_2), trifluoromethylamine hydrochloride ($CF_3NH_2.HCl$). **We request these above examples are taken account of, and a further search of the academic literature is likely to reveal more hydrolytically unstable examples.**

Examples of trifluoromethylamine degradation from larger molecules

Schiesser *et al* (2020) synthesised 12 model trifluoromethylamine derivatives (Figure 3) 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 precursor trifluoromethylamines for the purpose of the proposed restriction. **We request that these examples demonstrating rapid hydrolysis of the trifluoromethylamine group are taken account of the Restriction Report.**

Unlike simpler amines, N-pyrazole and N-imidazole on the other hand, were more stable towards hydrolysis *on the timescale of the experiment* (72 hours). Never-the-less, further investigations in regulatory hydrolysis studies or studies on biodegradation in environmental media could also demonstrate consistent hydrolysis or degradation for these functional groups. See also H-pyrazole and H-imidazole in section 4.5 below.

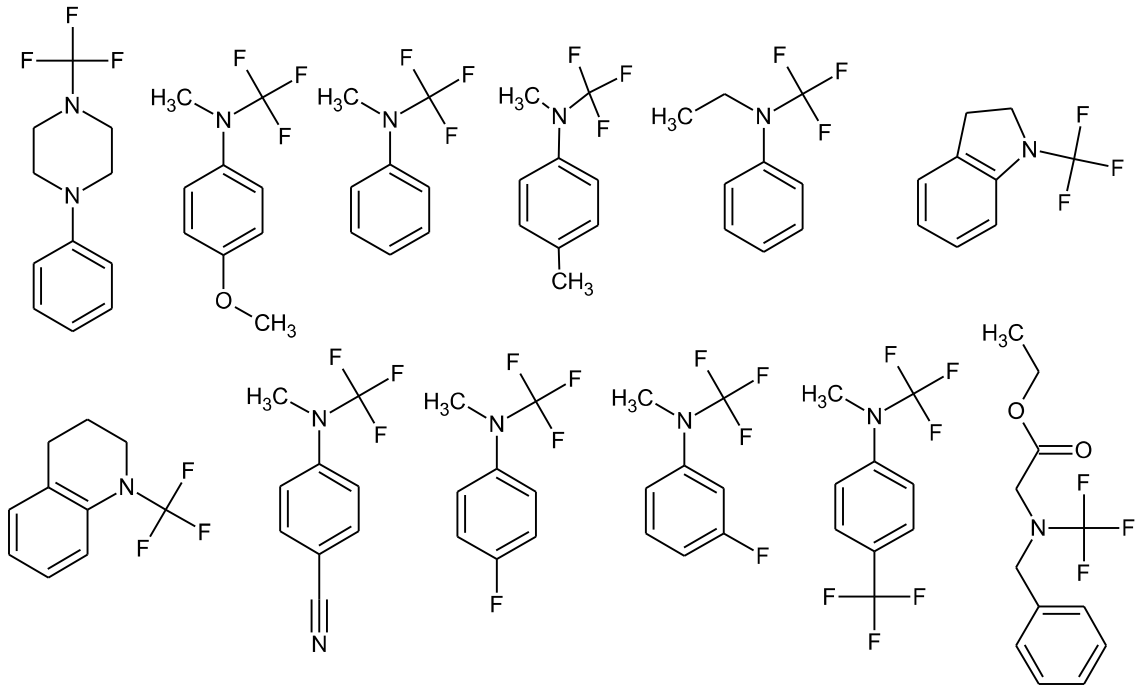


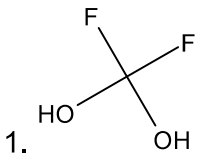
Figure 3. 12 model trifluoromethylamine compounds demonstrating hydrolysis within 72 hours (Schiesser et al (2020).

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

Data from the scientific literature are presented here which shows that at least 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, depending on the details of the chemistry, without forming persistent PFAS metabolites. This should not be seen as an exhaustive list, but rather support the need for a “safety net” derogation for those molecules which have been, or could potentially be, demonstrated to be not persistent, nor form persistent metabolites.

4.1. Difluoromethanediol

Difluoromethanediol meets the OECD structural definition of a PFAS and features the shortest alkyl group (O-CF_2-O) 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 (Figure 4, CAS No. 491379-14-5), and whether it forms an “arrowhead” substance.



1.

Figure 4. Model substance difluoromethanediol

There is very little scientific literature for this compound, with only 6 references reported by Chemical Abstracts, all of which are theoretical studies performing ab initio calculations. It appears to have never been synthesized nor isolated, nor 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).

Despite meeting the OECD structural PFAS definition as a CF_2 containing molecule, on the weight of evidence, it appears extremely unlikely that difluoromethanediol is persistent, let alone sufficiently stable to be isolated. We request that this be taken account of in the Restriction Report.

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.

Although difluoromethanediol is clearly unlikely to be stable, the available data indicates that generalizations about the O-CF_2-O moiety depend on the details of the chemical environment, and case-by-case assessments are required.

4.2. Trifluoromethylphenyl groups

Chemical stability of trifluoromethylphenyl groups

No data on the chemical stability of the model compound (trifluoromethyl)benzene has been identified in the literature (Figure 5).

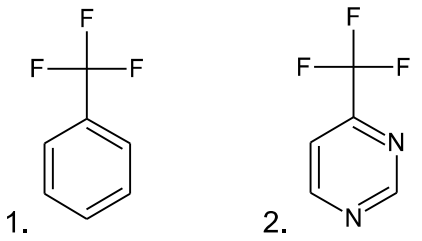


Figure 5. Model compound: 1) (trifluoromethyl)benzene, 2) (trifluoromethyl)pyrimidine

In related aromatic heterocyclic rings, it has been reported by Fischer (1993) that ortho substituted trifluoromethylpyrimidines undergo hydrolysis of the trifluoromethyl group under alkaline conditions. The hydrolyzability of the trifluoromethyl group was indicated to be influenced by additional substituents, and location on the aromatic ring.

Examples are presented below 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.

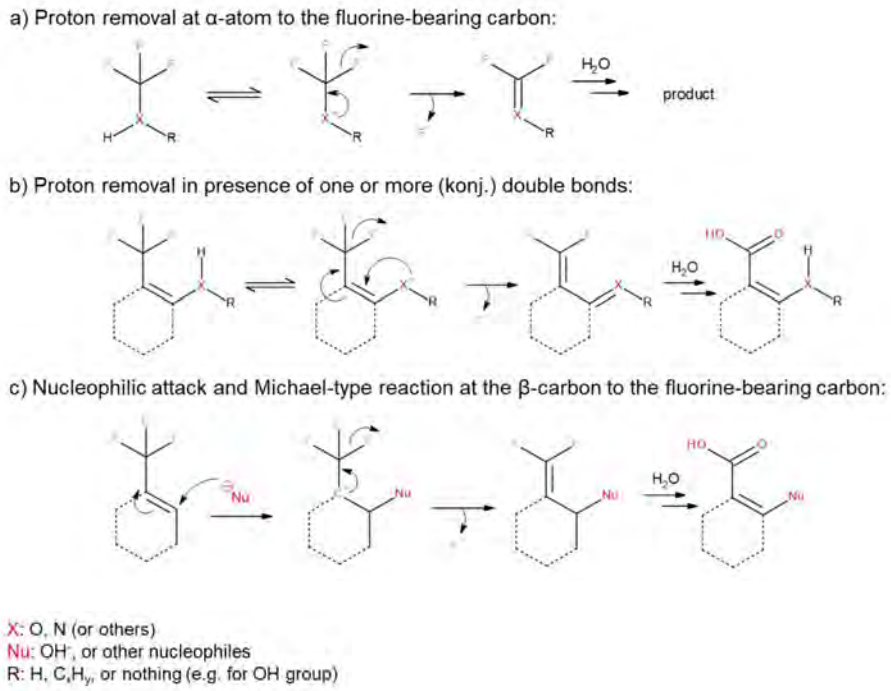
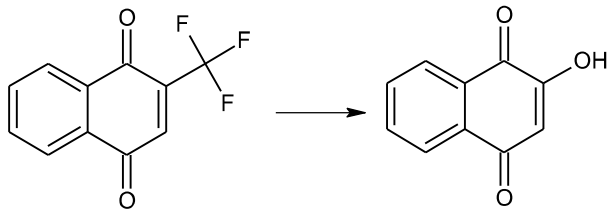


Figure 6. Schematic reaction mechanism as described by Sakai & Santi (1973). Especially reaction c) is described for enzymatic degradation in trifluoromethyl uracil derivates.

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).



1. 2.

Figure 7. 1) trifluoromenadione, 2) lawsone.

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).

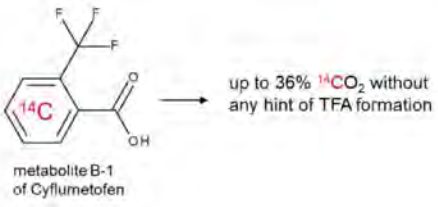


Figure 8. Soil degradation of 2-(trifluoromethyl)benzoic acid (metabolite B-1) of Cyflumetofen (data based on public version of *Cyflumetofen renewal dossier 2021*). Range of metabolite B-1 soil DT50s = 6.3 - 36.3 days (n=7).

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 $^{14}CO2$. 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).

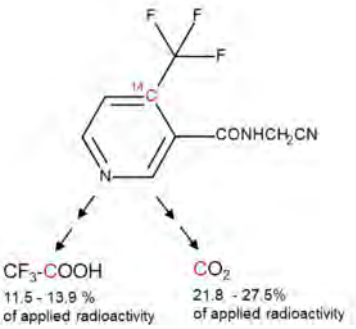


Figure 9. Soil degradation of insecticide Flonicamid (data based on public version of *Flonicamid renewal dossier 2020*). Range of Flonicamid soil DT50s = 0.3 – 1.9 days (n=4).

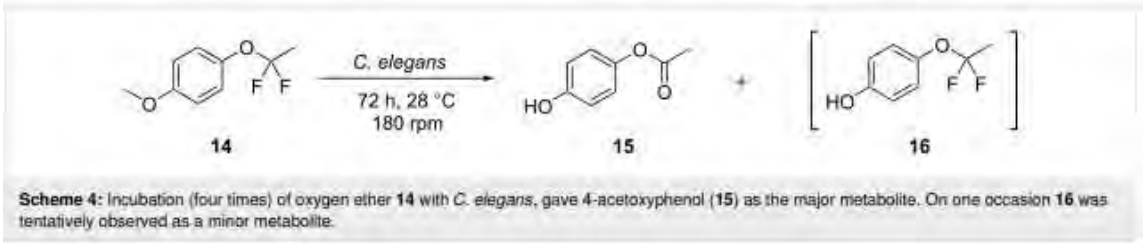
These findings show that (1) it is not the single CF_3-group which defines the potential persistence of a parent compound and (2) not every -CF_3 group results in formation of trifluoroacetic acid.

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 precursor 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. The conclusions in the Restriction Report Annex regarding the degradation of precursors (page 105) appear to rely heavily on justifications previously made and accepted for PFOA. **However, we wish to point out that the chemistry and environmental fate of single CF_2/CF_3 groups is quite different from perfluorinated alkyl C_8 chains, and requires more detailed discussion than reference to previous reports.**

4.3. Difluoroethoxy groups

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* (Figure 10).



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. Metabolism of a difluoromethoxy ether (Rodil et al (2019)).

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.

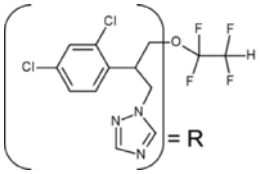


Figure 11. Structure of Tetraconazole

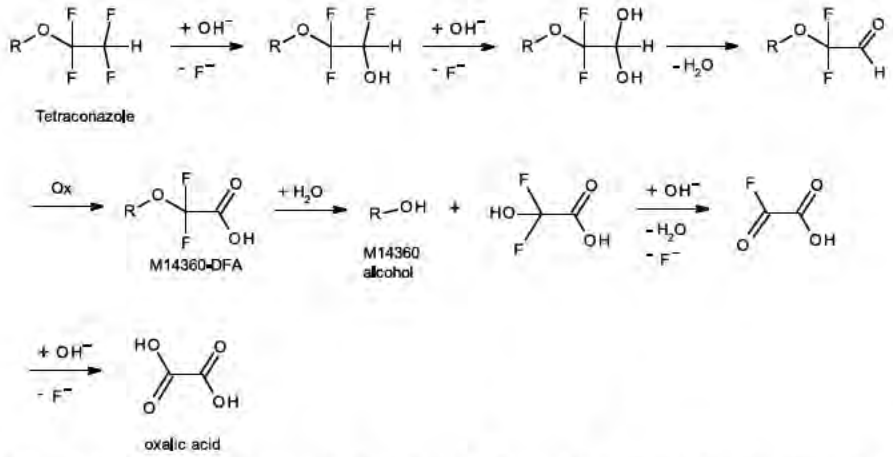


Figure 12. Reaction mechanisms at the tetrafluoroethoxy-group leading to the Tetraconazole metabolites M14360-DFA and M14360 alcohol in soil under photolytic conditions

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

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.

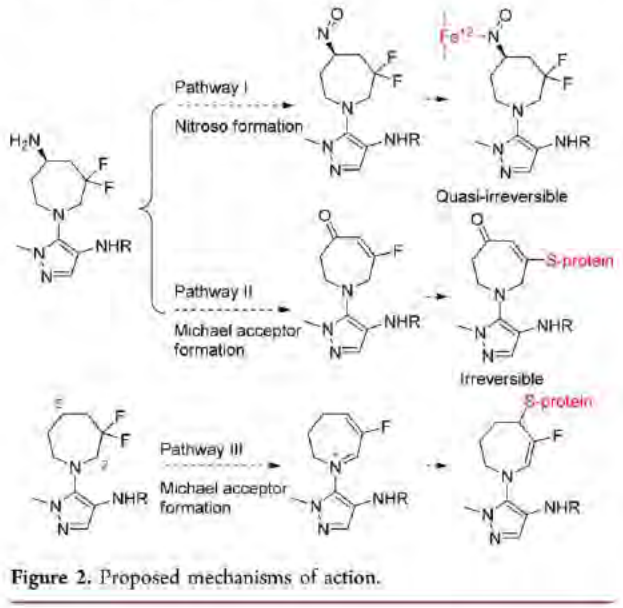


Figure 2. Proposed mechanisms of action.

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

4.5. (Trifluoromethyl)imidazole groups

Hayakawa et al (1998) describe the synthesis and subsequent hydrolysis of (trifluoromethyl)pyrazoles (Figure 14).

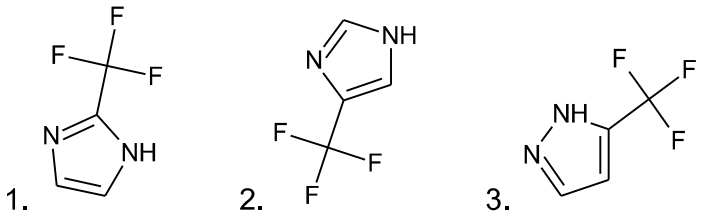


Figure 14. Model structures 1) 2-(trifluoromethyl)-1H-imidazole, 2) 4-(trifluoromethyl)-1H-imidazole, 3) 5-(trifluoromethyl)-1H-pyrazole

The 2- and 4- substituted imidazoles are reported to undergo rapid elimination of hydrogen fluoride under mild alkaline (pH = 8-9) laboratory conditions (Figure 15). Additional electronegative substituents can influence the rate of elimination of fluoride ion. **We request that this information is accounted for in the Restriction Report.**

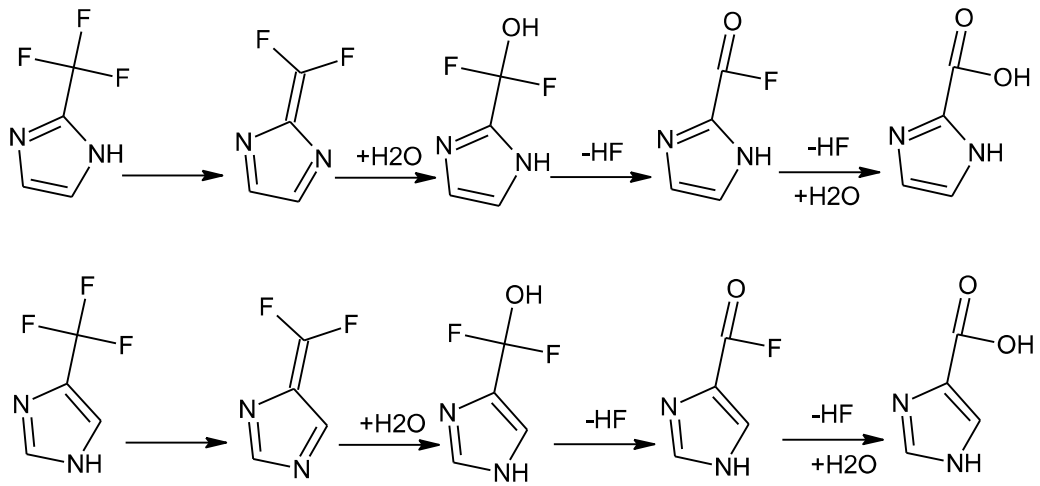


Figure 15. Hydrolysis of 2 and 4-trifluoromethylimidazole according Hayakawa et al (1998) under alkaline laboratory conditions. At pH=9 (30°C) 2-(trifluoromethyl)-1H-imidazole has a half-life of 80h, and 4-trifluoromethylimidazole a half-life of 200h.

Hydrolysis of (trifluoromethyl)-1H-pyrazoles with elimination of hydrogen fluoride was observed by Ermolenko et al (2012), and was subsequently optimized for yield by using much more aggressive laboratory conditions.

No data on the chemical stability of the Figure 14 imidazole or pyrazole model compounds under environmental conditions or susceptibility towards biodegradation has yet been identified in the literature.

5. Conclusion

The Dossier Submitter states on page 54 of the Annexes to the Restriction Report:

> *If there are specific PFASs for which sufficient evidence is provided that the perfluorinated bond is broken at a rate which indicates them to be not persistent, resulting a substance/substances which is/are not a PFAS, then those substances/groups should be excluded from the scope. Currently, no such PFASs are known to the dossier submitter.*

We believe we have provided adequate evidence for specific functional groups that are not persistent, and cannot be "arrowhead" substances, despite meeting the OECD structural definition of PFAS. We request that these substances be removed from the scope of the restriction by amending the grouping definition.

We believe we have also adequately shown that there are also functional groups meeting the OECD structural definition of PFAS which, depending on the specific chemical details of the molecule, may or may not form persistent "arrowhead" (metabolite) substances. Being unable to predict the full chemical behaviour of this chemical space, we suggest introduction of a conditional derogation for those substances as a "safety net".

Placing the above substances out of scope, or potentially subject to a derogation, does not in any way lower protection of human health or the environment, because it remains incumbent on any REACH registrants to adequately risk assess the substances in the respective REACH registration dossiers.

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Comments to the proposal for a restriction on PFASs (08.05.2023)

Publications can be obtained upon request.

General remark	The information in the PFAS restriction report does not include the results of the EOGRTS with TFA (Labcorp 2022[i])
Annex B, Page 158 B.5.2.1.4. Thyroid effects in experimental animals	It is indicated that for TFA there are almost no indications for thyroid effects, which may partially be explained by the limited available data. However the results of the recent EOGRTS (Labcorp 2022[i]) show that mean serum T4 levels in the mid and high dose were low compared with controls but no thyroid effects were observed
Annex B, Page 159 B.5.2.1.5. Immune effects in experimental animals	It is indicated that changes in lymphocyte counts or proliferation were observed for TFA (BayerCropScience, 2014[ii]). The reference refers to the summary of the toxicological and metabolism studies for an active substance where the results of an exploratory 14-day tox study (Bayer CropScience, 2001[iii]) with TFA are described on pages 32 – 37. This study was performed at dietary doses of 600, 1200 and 2400 ppm. A lower mean absolute lymphocyte count (-38% compared to the controls) was measured in females. However, neither in the 28 day study (at dietary doses of 600, 1800, 5400 and 16000 ppm; (Bayer CropScience 2005[iv])) nor in the 90-day study (at dietary doses of 160, 1600 and 16000 ppm; (Bayer CropScience 2007[v])) changes in lymphocyte counts were observed. In addition, the immunophenotyping analysis that was performed as part of a recent EOGRTS (Labcorp, 2022[i]) did not show an alert going in the direction of immunotoxicity. Therefore it is not justified to conclude that changes in lymphocyte counts or proliferation were observed for TFA.
Annex B, Page 161 B.5.2.2.1. Developmental effects in experimental animals	It is indicated that (total) litter loss was observed in experimental animal models after exposure to TFA (Covance Laboratories, 2020a[vi]). The cited study is a preliminary study for effects on embryo-fetal development in NZW Rabbit by oral gavage at 250, 500 and 1000/750 mg/kg/day. No litter losses were observed in this DRF study. In the PNDT study in NZW rabbits by oral gavage at 180, 360 and 750 mg/kg, one female at 750 mg/kg/day was killed on GD27 for animal welfare reasons following evidence of pregnancy loss (Covance Laboratories, 2020b[vii]). As this pregnancy loss was an isolated incidence, it was not attributed to administration of the test substance. Neither in the preliminary study of reproductive performance in Wistar rats (Labcorp, 2021[viii]) nor in the EOGRTS (Labcorp 2022[i]), litter losses were observed.
Annex B, Page 163 B.5.2.2.2. Fertility effects in experimental animals	It is indicated that reduced weight of reproductive organs might further affect fertility and is a consistent effect across various non-polymeric PFASs such as TFA. This conclusion is based on a PNDT study in NZW rabbits (Covance Laboratories, 2020b[viii]). It is however not clear which organs are being referred to since it is not part of a PNDT study to measure weights of reproductive organs. Neither in the preliminary study of reproductive performance in Wistar rats (Labcorp, 2021[viii]) nor in the EOGRTS (Labcorp 2022[i]), effects on reproductive organ weights were observed.
Annex B, Page 163 B.5.2.2.3. Effects on or via lactation in experimental animals	It is indicated that reduced pup weight during the lactation period was observed after exposures to TFA (Covance Laboratories, 2020a[vii]). The cited study is a preliminary study for effects on embryo-fetal development in NZW Rabbit by oral gavage and in this study no lactation period is included.

	In the EOGRTS (Labcorp, 2022[i]) body weight gain of F1 offspring during lactation was slightly lower at the high dose (3000 ppm) as compared to controls. As the differences were minor, it was not considered an adverse effect. Overall, there were no adverse effects on reproductive performance/offspring development and for general systemic toxicity.
Core text p. 22	"All PFASs are considered to be very persistent, either on the basis of their own very persistent properties or the very persistent properties of their terminal degradation product (arrowhead). …" There is a recent publication by Bayer researchers with the University of Strasbourg on "Modern Fluorine-containing agrochemicals": https://doi.org/10.1002/9780470682531.pat1013 In Section 5 it discusses known degradation mechanisms for -CF3 groups; see e.g. Scheme 40. This can be cited to put the statement in the Restriction Proposal into context.

[i] Labcorp, 2022; Sodium trifluoroacetate: Extended one generation reproductive toxicity study in the Han Wistar rat by dietary administration; Study ID 8439567; Bayer DocID: M-778992-01-1

[ii] Bayer CropScience, 2014, Summary of the toxicological and metabolism studies for flurtamone; Bayer Doc ID M-482296-01-1

[iii] Bayer CropScience, 2001, Trifluoroacetate - Exploratory 14-day toxicity study in the rat by dietary administration; Report No. C016316, Bayer Doc ID M-202165-01-1

[iv] Bayer CropScience, 2005, Sodium trifluoroacetate (TFA) - 28-day toxicity study in the rat by dietary administration; Report No. SA 05054, Bayer Doc ID M-259106-01-1

[v] Bayer CropScience, 2007, Sodium trifloroacetate (TFA) 90-day toxicity study in the rat by dietary administration; Report No: SA 06080; Bayer Doc ID M-283994-01-1

[vi] Covance Laboratories 2020a (actual report date is 2021), Sodium trifluoroacetate: Preliminary study for effects on embryo-fetal development in the New Zealand white rabbit by oral gavage administration; Report No. YQ44HR; Bayer Doc ID M-766460-01-1

[vii] Covance Laboratories 2020 a, Sodium trifluoroacetate: Study for effects on embryo-fetal development in the New Zealand white rabbit by oral gavage administration; Report No. 8437242; Bayer Doc ID M-772129-02-4

[viii] Labcorp 2021, Sodium trifluoroacetate: Preliminary study of reproductive performance in the female Han Wistar rat by dietary administration; Report No. 8437241, Bayer Doc ID M-782518-01-1