CropLife Europe Scientific input to the consultation on the Restriction proposal on the manufacture, placing on the market and use of PFASs.

Executive Summary:

- A derogation for fluorinated packaging essential for safe handling of chemicals in regulated sectors should be introduced.
- Additional information is provided on biodegradation of PFAS substances which are not persistent and specified as out of scope of the restriction proposal.
- Derogations for intermediates should be introduced to avoid unintended loss of derogated substances.
- The wording for the active substance in Plant Protection Products derogations should be amended to avoid unintended loss of safeners and synergists, which are also subject to Regulation (EU) 1107/2009
- Information on the agronomic importance of fluorinated active substances is provided in support of the time-unlimited derogation.
- A time-unlimited derogation for PPORD and not-yet-approved active substances should be introduced to avoid unintended loss of innovation.
- The universal PFAS restriction should remove manufacture from the scope of the restriction.
- Emission estimates and reporting requirements for Paragraph 4 active substances (and safeners) should be adjusted for molecular weight to avoid distorted interpretation.

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1. Universal PFAS Restriction Scope

- The universal PFAS restriction should remove manufacture from the scope of the restriction.
- Derogations for intermediates should be introduced to avoid unintended loss of derogated substances.
- The wording for the active substance in Plant Protection Products derogations should be amended to avoid unintended loss of safeners and synergists, which are also subject to Regulation (EU) 1107/2009
- Information on the agronomic importance of fluorinated active substances is provided in support of the time-unlimited derogation.
- A time-unlimited derogation for PPORD and not-yet-approved active substances should be introduced to avoid unintended loss of innovation.

Manufacture

As a general comment CLE strongly recommends removal of manufacture from the scope of the universal PFAS restriction. Historically REACH restrictions have focused on placing on the market, only. There are currently only three REACH restrictions which apply to manufacture: Entries 6, 62, and 68, with the first (asbestos) being the only pre-REACH example. With this background, and the unprecedented scope of this PFAS restriction, there appears to be a large scope for unintended consequences. In our opinion **"placing on the market" is adequate to achieve the intended objectives**.

As a concrete example, Article 68(1) appears to exempt onsite isolated intermediates from the scope of REACH restriction: "*The first subparagraph shall not apply to the use of a substance as an on-site isolated intermediate.*" However, closer inspection of the Article 3(24) definition shows that "*use*" does not in fact cover manufacture: "*means any processing, formulation, consumption, storage, keeping, treatment, filling into containers, transfer from one container to another, mixing, production of an article or any other utilisation*;". **As a result, any restriction applied to manufacturing appears as it may apply directly to onsite isolated intermediates.**

As a further example, the Annex XV report proposes after 18 months all manufacture cease. Derogations apply for various downstream uses. This presumably places a significant compliance burden on the PFAS manufacturer at the start of the value chain, whose compliant manufacture is then directly coupled to all the downstream user's compliant interpretation of the derogations. The transfer of potentially confidential business information to back up the supply chain is also of concern. **A focus on placing on the market would presumably remove many of these issues while achieving the intended objectives.**

Intermediates

REACH Articles 17 and 18 enact specific provisions for substances used as on-site isolated intermediates that are used under strictly controlled conditions (SCC). SCC provisions apply if it is rigorously contained by technical means during its whole lifecycle, and control and procedural technologies are used to minimise emission and any resulting exposure. These provisions are further enumerated for transported isolated intermediates, which must be rigorously contained by technical means during the whole lifecycle including manufacture, purification, cleaning and maintenance of equipment, sampling, analysis, loading and unloading of equipment or vessels, waste disposal or purification and storage. Manufacture, use and placing on the market of intermediates under these

conditions effectively means there is **no exposure, and hence no unacceptable risk**, which is a key requirement to be demonstrated in Article 68(1) for a REACH restriction.

Intermediates lie upstream in the supply chain from products regulated by more specific vertical legislation, and which are proposed in the restriction Column 2, Paragraph 4, to benefit from a time unlimited derogation. To avoid **inadvertently removing these downstream products from the market, intermediates should be exempted from the proposed restriction**.

Precedent

The Annex XV Restriction Report for Undecafluorohexanoic acid (PFHxA), its salts and related substances (20.12.2019), clearly foresees an exemption for intermediates which was supported in the final RAC and SEAC opinion (8.12.2021):

> *9. Paragraphs 1 and 2 shall not apply to any of the following: (a) a substance that is to be used, or is used as a transported isolated intermediate, provided that the conditions in points (a) to (f) of Article 18(4) of this Regulation are met;*

Product and process orientated research and development (PPORD)

Scientific research and development (defined in REACH Article 3(23)) is exempted in REACH Article 67(1) from Annex XVII Restrictions up to a quantity of 1 ton/year. PPORD (Article 3(22)) offers a time limited mechanism to access quantities larger than this for development purposes. However, REACH Article 67(1) states that "*(…) Annex XVII shall specify if the restriction shall not apply to product and process orientated research and development, as well as the maximum quantity exempted*." The Annex XV report does not currently provide a derogation to allow for PPORD, which is critical for the development of active substances derogated in Column 2, Paragraph 4 for use in biocidal products, plant protection products human and veterinary medicinal products. More details are provided below.

Scope of derogations for active substances

The current restriction proposal Column 2, paragraph 4 reads:

By way of derogation, paragraphs 1 and 2 shall not apply to:

> *a. active substances in biocidal products within the scope of Regulation (EU) 528/2012*
> *b. active substances in plant protection products within the scope of Regulation (EC) 1107/2009*
> *c. active substances in human and veterinary medicinal products within the scope of Regulation (EC) No 726/2004, Regulation (EU) 2019/6 and Directive 2001/83/EC*

CropLife Europe supports the proposal to exempt active substances covered by more specific vertical legislation. A recent review, over the period 1998–2020, reveals that 60-70 % of newly launched or registered agrochemicals are organofluorine compounds. These compounds form an important part of a farmer's current crop protection toolkit. Maintaining and rotating the limited pool of agrochemicals with different and new modes of action is key to ensure the sustainability of agricultural productivity. When considering removing specific compounds there is always a risk that no alternatives are available - depending on the pest control segment.

Annex 1 contains a detailed analysis of the **agronomic importance** relevant for the **socio-economic** impacts of these substances for European farming. These agronomic comments are relevant to the "**plant protection products and biocides**" sectors specified in Table A.1 of Annex A to the restriction proposal, and specifically **section A.3.17** Active substances in Plant Protection Products (PPP), Biocidal Products (BP) and Medicinal Products (MP) of that Annex.

Safeners

The substances within the scope of Regulation (EC) 1107/2009 with special status are not only active substances (Article 2(2)), but also safeners (Article 2(3)a) and synergists (Article 2(3)b). Therefore, the restriction proposal should be amended to accurately reflect the regulation legal text:

> *b. active substances, safeners or synergists in plant protection products within the scope of Regulation (EC) 1107/2009.*

There are **two** such safener substances which meet the structural definition of a PFAS, and within the scope of Regulation (EC) 1107/2009. Safeners are substances which are used to eliminate or reduce phytotoxic effects of the plant protection product on certain plants. Data requirements are being finalized by the European Commission DG SANTE and Member States in a dedicated working group. The objective is to have them voted this year to initiate regulatory reviews of these specific substances. As written, without the above amendment, these would not benefit from the foreseen derogation, and require to be removed from the market within 18 months. Furthermore, the impact would be magnified by also implicitly restricting from use the active substances that inherently rely on the safener action for their function. If safeners are not explicitly derogated, the intent of the derogation is thus undermined.

Not yet approved active substances

The restriction proposal as written provides for a derogation of active substances within the scope of Regulation (EC) 1107/2009. As such, this does not cover early-stage development prior to submission of a dossier for first review. While a Restriction does not apply to scientific research and development, Article 3(23) limits this to <1 ton. The quantity of active substance required for testing and development purposes for a new active substance typically exceeds 1 ton. Furthermore, the Annex XV restriction proposal does not provide for a PPORD derogation, which would allow these quantities for registration purposes to be manufactured.

The registration strategy for active substances does not necessarily start with the EU, and it can often be the case that approvals are granted in third countries, prior to the EU. Depending on the target, a European registration may never be applied for if the pest or disease is not relevant for the EU. As written the restriction proposal is likely to make the EU a less attractive location for research and development, due to the limitations on available chemistries that can be used to maximise the effectiveness of active substances (Pazenok S et al, 2020).

Active substances which are no longer approved

In cases an active substance does not get renewed under the Plant Protection Regulation there are transitions periods in place for applicants and Member States to put the measure in place. This includes a grace period not exceeding six months for the sale and distribution, and in addition a maximum of one year for the disposal, storage, and use of existing stocks of the plant protection products concerned (article 20 in Regulation 1107/2009). The restriction should take into account this legal possibility and align accordingly.

In principle similar considerations on not-yet-approved and no-longer-approved active substances apply to all active substances in biocidal, plant protection, human and veterinary medicine products. **To avoid uncontrolled impacts on 3rd countries food and health systems, the derogation should apply to active substances intended for such uses, not only registered in the EU.**

Laboratory use

It should be noted that REACH Article 67(1) states that Restrictions do not apply to the manufacture, placing on the market or use of a substance in scientific research and development. This exemption **may** be inadequate for laboratories conducting routine testing as a commercial service e.g., such as toxicology or analytical studies. The total tonnage (including for academic research including other general chemical synthesis work, toxicology, use as a mobile phase modifier, etc.) **may exceed the 1 t/year research and development limit**.

One such example is the In Vitro Mammalian Cell Gene Mutation Test (OECD 490), which relies on the use of a $–CF_3$ moiety:

> OECD Test No. 490: In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene. Mutant cells deficient in thymidine kinase enzyme activity because of a mutation TK+/- to TK-/- are resistant to the cytostatic effects of the pyrimidine analogue **trifluorothymidine** (TFT). The TK proficient cells are sensitive to TFT, which causes the inhibition of cellular metabolism and halts further cell division. Thus, mutant cells are able to proliferate in the presence of TFT and form visible colonies, whereas cells containing the TK enzyme do not.

Another example is the use of trifluoroacetic acid (TFA) in analytical chemistry as a high-performance liquid-chromatography (HPLC) mobile phase modifier (Lardeux H. et al, 2021). Acids such as TFA are added to shift the pH of the mobile phase, and as a result the degree of ionization and hydrophobicity of the substances being analysed. In turn the retention time and selectivity of the substances change, thus allowing the reliable detection of specific substances to be optimized. TFA has particularly desirable properties for use with liquid chromatography–mass spectrometry (LC–MS) detection systems, because it is more volatile than alternatives and does not foul the ion source. For regulated sectors listed in Column 2, Paragraph 4 (biocidal, plant protection and human and veterinary medicinal products), analytical methods must be specified as part of the product registrations. These analytical methods are legally required, and used for product compliance, including compliance of imported food with Maximum Residue Levels (MRL). A change to the method requires development in a laboratory to demonstrate that it works, followed by an update of the respective registrations before it can be used.

CropLife Europe does not currently have an overview of the number of methods impacted, i.e., which use TFA as part of their description. However, empirically it is clear that an **18-month transition period is insufficient to develop new methods, register these with the relevant competent authorities for approval, and finally role out to government and industry testing laboratories.**

Given the above examples, and many more can be anticipated, **Column 2, Paragraph 5 (t), should be modified to include all laboratory uses independent of research and development status.**

2. Hazard Characterization

- Additional information is provided on biodegradation of PFAS substances which are not persistent, and specified as out of scope of the restriction proposal.

Biodegradation of PFAS substances

The starting point for the scope of the “universal”-PFAS restriction proposal is the OECD PFAS definition, which is then narrowed slightly to place out of scope specific compounds which carry single $-CF_3$ or $-CF_2-$ groups which in themselves have not been associated with extreme persistence i.e. cannot be considered “forever chemicals”. Although meeting the OECD PFAS definition, these functional groups cannot be considered to be “arrowhead” substances, because of their fundamental instability under environmentally relevant conditions.

The basis for identifying these specific functional groups is provided in CropLife Europe Position Paper #35461 available in Annex 4.

It is essential to realize that these experiments are **only** intended to prove the fundamental basis for the above theoretical work is correct. As such, the **precise details of the experimental conditions used here do not matter** (e.g., 20°C vs 12°C). This is because the observed degradation rate will vary with each molecule which contains one of these functional groups (e.g. $-OCF_3$), depending on the broader chemical structure of the larger parent molecule. The essential and key point is that **the identified functional groups (such as $-OCF_3$) do not confer persistence on a larger molecule** which may be registered under REACH, and hence there is no basis for an a priori ban on such

molecules. Molecules registered under REACH must still demonstrate lack of persistence in their respective dossiers.

The parent molecule for the below experiments (benzoic acid) was chosen with the expectation that it would biodegrade rapidly, thus allowing observation of the fate of the -OCF_3 moiety. Similarly, the standard OECD guideline experimental conditions (20°C vs 12°C) chosen were to ensure that sufficient degradation occurs to identify metabolites and half-lives with minimal uncertainty. Recalculation to 12°C is considered sufficiently accurate for these purposes, and because the context is not a REACH registration dossier for a specific substance, but rather the proof of concept.

Preliminary data on biodegradation in soil of ^{14}C-Trifluoromethoxy benzoic acid has been previously supplied to ECHA (RAC) in CropLife Europe Briefing Note #35973 in Annex 3. An update is provided in Chapter 3 of this document (Specific Information Requests, Question 9), and a study summary is attached to this document in Annex 2.

Placing the specifically identified functional groups out of scope of the restriction proposal, as proposed by the Dossier Submitters, 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, including any metabolites, in the respective REACH registrations.

Tonnage and emissions – molecular weight correction

Page 72 of the Annex XV makes reference to a list of active substances in PPP in Appendix A.3.17 (page 272) and includes a rough estimate that 2% of total EU sales of substances meet the PFAS definition. We wish to note that the vast majority of active substances contain only single fluorinated moieties (i.e. -CF2- or -CF3), and this "perfluorinated alkyl moiety" is thus only a small fraction of the overall mass of the substance in question. The remainder of the molecule can in no way be considered to be PFAS – the result is a clear overestimation of PFAS emissions by mass unless this is corrected for.

The restriction proposal Appendix A, Appendix A.3.17 provides a list of active substances. From the 41 plant protection active substances and safeners believed to meet the OECD PFAS definition and currently approved to be placed on the EU market, CLE has derived the following average information:

Table 1.

EU approved active substance & safeners *n=41*	**Minimum**	**Maximum**	**Average**
Molecular weight range (g/mol)	229.2	682.4	403.4
% PFAS moiety mass - based on CF2 (50 g/mol) and CF3 (69 g/mol) moieties that meet the OECD PFAS definition.	12.8	34.8	**20.0**

As a result, using the Annex XV estimate of 2% contribution, and assuming the worst case that a PFAS "arrowhead" substance were to be formed with no degradation, then the **actual mass-based emissions would be 0.4%** (i.e., 20% of the current estimate).

To avoid overestimation and distortion of reported tonnages, CLE strongly recommends use of "PFAS equivalent tonnages" for active substances in PPP and safeners where the moiety of interest forms only a minor part of the molecule. As such the **restriction proposal Column 2, Paragraph 4, ii) should be modified to require the reporting of "PFAS equivalent" quantities.**

Specific comments on Annex XV report

Annex 5 contains specific comments on the interpretation of toxicology studies reported in the restriction proposal in Annex B.

3. Specific Information Requests

For ease of cross referencing, the numbering in this section follows the questions in the public consultation Specific Information Requests.

1: Sectors and (sub-)uses:

Please specify the sectors and (sub-)uses to which your comment applies according to the sectors and (sub-)uses identified in the Annex XV restriction report (Table 9). If your comment applies to several sectors and (sub-)uses, please make sure to specify all of them.

The following four uses have not been covered in the Annex XV restriction proposal.

Fluorinated packaging in regulated sectors

Fluorinated packaging is required to inert plastic packaging, particularly where the contents involve aggressive organic solvents, and migration of the solvent through the plastic walls would pose a safety hazard. There is no clear allocation for this use to a sector specified in Annex XV report, Table 9. These comments are relevant as a minimum to the following sectors specified in Table A.1 of Annex A: **plant protection products** and biocides, and **chemical industry**. Further information for this use is provided under Question 6.

Intermediates

Intermediates in chemical synthesis have not been explicitly derogated. There is no clear allocation for this use to a sector specified in Annex XV report, Table 9. These comments are relevant as a minimum to the following sectors specified in Table A.1 of Annex A: **plant protection products** and biocides, and **chemical industry**. Further information for this use is provided under Question 6.

Laboratory use

The general exemption for research and development from REACH restrictions may be inadequate for laboratories conducting routine testing as a commercial service (see in vitro diagnostics discussion in microplastic restriction). There is no clear allocation for this use to a sector specified in Annex XV report, Table 9. As a minimum, these comments are relevant to the following sectors specified in Table A.1 of Annex A: **plant protection products** and biocides, and **chemical industry**. Further information for this use is provided under Question 6.

Uses in Production Equipment

Uses in production equipment have not been explicitly derogated. There is no clear allocation for this use to a sector specified in Annex XV report, Table 9. As a minimum, these comments are relevant to the following sectors specified in Table A.1 of Annex A: **plant protection products** and biocides, and **chemical industry**. Stringent safety, integrity and quality standards and requirements have been imposed in the EU's modern production systems. These standards and requirements can often only be reached by relying on PFAS materials technology. It should therefore be no surprise that the majority of valves, gaskets, pipes, column internals, linings, filters, membranes, diaphragms, electronics, etc, used in industrial settings contain PFAS based materials. The complexity of developing and testing alternatives that meet the same stringent safety and integrity standards as well as replacing PFAS in production equipment will not just be technologically complex and extremely expensive, it will also take decades with only limited probability for success (availability of true alternatives). A detailed socio-economic assessment will be provided by CEFIC representing the chemical

industry, and additional information is not provided here as a consequence. As CLE we support a request for a time-unlimited derogation for PFAS in production equipment; a provision that which is lacking in the current proposal.

2: Emissions in the end-of-life phase:

The environmental impact assessment does not cover emissions resulting from the end-of-life phase. To get a better understanding of the extent of the resulting underestimation, (sub-)use-specific information is requested on emissions across the different stages of the lifecycle of products, i.e., the manufacture phase, the use phase and the end-of-life phase. Please provide justifications for the representativeness of the provided information. In particular:

a) *Please provide, at the (sub-)use level, an indication of the share of emissions (as percentages) attributable to these three different stages. An indication of annual emission volumes in the end-of-life phase at sector or sub-sector level would also be appreciated.*
b) *If possible, please provide for each (sub-)use what share of the waste (as percentages) is treated through incineration, landfilling and recycling. Please provide information to justify the estimates as well as information on the form of recycling referred to.*

No information is currently available to CLE for this question.

3: Emissions in the end-of-life phase:

With respect to waste management options, additional information is requested on the effectiveness of incineration under normal operational conditions (for different waste types, e.g. hazardous, municipal) with respect to the destruction of PFAS and the prevention of PFAS emissions.

No information is currently available to CLE for this question.

4: Impacts on the recycling industry:

To get an understanding of the impacts of the proposed restriction on the recycling industry, information is requested on:

a) *The impacts that the concentration limits proposed in paragraph 2 of the proposed restriction entry text (see table starting on page 4 of the summary of the Annex XV restriction report) have on the technical and economic feasibility of recycling processes (together with a clear indication on the waste streams to which the described impacts relate).*
b) *The measures that recyclers would need to take to achieve the proposed concentration limits.*
c) *The costs associated with these measures.*

No information is currently available to CLE for this question.

5: Proposed derogations – Tonnage and emissions:

Paragraphs 5 and 6 of the proposed restriction entry text (see table starting on page 4 of the summary of the Annex XV restriction report) include several proposed derogations. For these proposed derogations, information is requested on the tonnage of PFAS used per year and the resulting emissions to the environment for the relevant use. Please provide justifications for the representativeness of the provided information.

No information is currently available to CLE for this question.

6: Missing uses – Analysis of alternatives and socio-economic analysis:

Several PFAS uses have not been covered in detail in the Annex XV restriction report (see uses highlighted in blue and orange in Table A.1 of Annex A of the Annex XV restriction report). In addition,

some relevant uses may not have been identified yet. For such uses, specific information is requested on alternatives and socio-economic impacts, covering the following elements:

a. *The annual tonnage and emissions (at sub-sector level) and type of PFAS associated with the relevant use.*
b. *The key functionalities provided by PFAS for the relevant use.*
c. *The number of companies in the sector estimated to be affected by the restriction.*
d. *The availability, technical and economic feasibility, hazards and risks of alternatives for the relevant use, including information on the extent (in terms of market shares) to which alternative-based products are already offered on the EU market and whether any shortages in the supply of relevant alternatives are expected.*
e. *For cases in which alternatives are not yet available, information on the status of R&D processes for finding suitable alternatives, including the extent of R&D initiatives in terms of time and/or financial investments, the likelihood of successful completion, the time expected to be required for substitution (including any relevant certification or regulatory approvals) and the major challenges encountered with alternatives which were considered but subsequently disregarded.*
f. *For cases in which substitution is technically and economically feasible but more time is required to substitute:*
    f.1. *the type and magnitude of costs (at company level and, if available, at sector level) associated with substitution (e.g. costs for new equipment or changes in operating costs);*
    f.2. *the time required for completing the substitution process (including any relevant certification or regulatory approvals);*
    f.3. *information on possible differences in functionality and the consequences for downstream users and consumers (e.g., estimations of expected early replacement needs or expected additional energy consumption).*
    f.4. *information on the benefits for alternative providers.*
g. *For cases in which substitution is not technically or economically feasible, information on what the socio-economic impacts would be for companies, consumers, and other affected actors. If available, please provide the annual value of EU sales and profits of the relevant sector, and employment numbers for the sector.*

6.1: Fluorinated packaging in regulated sectors

Fluorination in a chemical packaging context is a surface treatment technology required to inert otherwise “fluorine free” plastic packaging (such has high-density polyethylene (HDPE), particularly where the intended chemical contents involve aggressive organic solvents, and migration of the solvent through the plastic walls would pose a safety hazard.

Use of such packaging is required to meet the requirements for Transport of Dangerous Goods (TDG). Furthermore, such packaging forms part of the formal registration requirements of the Restriction proposal Column 2, Paragraph 4 derogated sectors i.e. biocidal products, plant protection products, human and veterinary medicinal products. These vertical legislations place significant cost and time constraints on the speed at which alternatives can be substituted, if available, or after they have been developed. **There is no clear allocation for this use to a sector specified in Annex XV report, Table 9.**

As a minimum, these comments are relevant to the following sectors specified in **Table A.1 of Annex A: plant protection products and biocides, chemical industry,** and other “**Uses unknown**” such as “**chemical laboratories**”.

Detailed impact information has **only** been provided for the plant protection product sector. The impact clearly applies to many other sectors packaging hazardous chemicals, and in particular organic solvents, in plastic bottles. **A derogation is requested to allow sufficient time for transition to alternative packaging materials.**

6.1.a: Annual tonnage and emissions

Industry lead Container Management Systems (CMS) have been introduced to collect used pesticide packaging within EU27 countries. The target collection rate for mature systems is 66% for EU27 (2021, aiming for 75% by 2025), and 20 of 27 countries are managed by industry driven CMS (aim is to include all 27 member states by 2025).

Overall, the collection rate is approximately 66 % in EU27-countries (2021, latest available data). The average quantity of pesticide packaging placed on the market (EU27) for the period 2018-2020 is approximately 33100t plastic (with an uncertainty ±17%). Of this 7% is estimated to be fluorinated rigid plastic packaging. This represents 2320t of fluorinated plastic packaging (but this is **not** the quantity potentially considered PFAS).

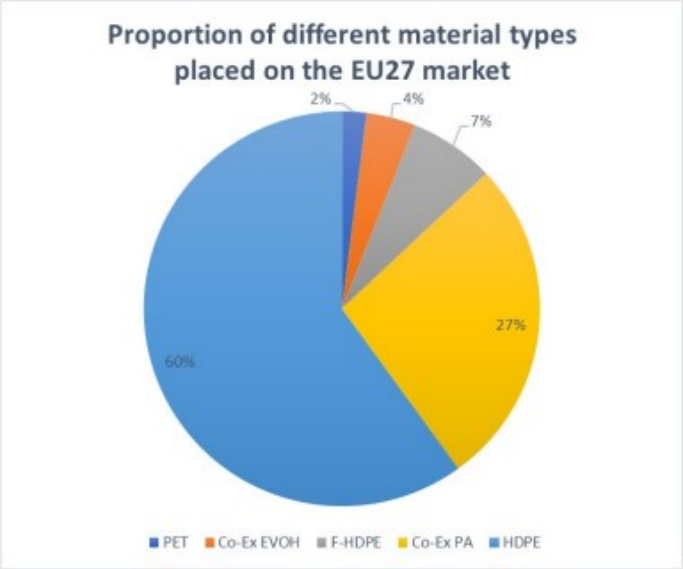

Figure 1. Proportion by percent weight of total shipped plastic packaging placed on the EU27 market. Source for this data are annual CMS reports generated by CropLife Europe. The estimated proportion of fluorinated packaging is the result of a survey of 8 member companies, with 5 respondents indicating use of fluorinated packaging. Average for the period 2018 – 2020 used.

The amount of potentially PFAS actually contained in a plastic container is very small, and is limited to a very thin barrier layer. The potentially PFAS substances formed depends on the plastic being treated. For plant protection products where the bottle plastic is HDPE, fluorination could be expected to produce polytetrafluoroethylene (PTFE) that, with a sufficient degree of fluorination of the surface carbon chains, would then meet the PFAS definition (Kharitonov A. P. et al, 2005).

There are three main methods of creating a fluorinated barrier on a plastic bottle: in-mold fluorination, plasma fluorination, and post-fluorination. The latter treats all surfaces of the bottle (inside and out), while the first two methods use fluorinated gas to treat only the inside of the bottle.

Commonly used in Europe is in-mold fluorination. In-mold fluorination applies the fluorine containing gas during the extrusion blow molding process to form the bottle into the mold. The treatment is therefore only on the inside of the bottle. Plasma-fluorination is a process step in the bottle production that also creates a barrier only on the inside of the container with similar barrier properties to in-mold fluorination. Post-fluorination of packaging is a separate process step where the surface of the fully molded / formed bottle (inside & outside) will be treated after the extrusion blow molding. The quantity of PFAS depends to some extent on the technology used to generate the thin fluorinated barrier layer on the bottle surface, but are expected to be roughly similar.

Although limited information is currently available, an effort has been made here to estimate the quantity of substances potentially triggering the PFAS definition in average fluorinated packaging.

Estimated possible PFAS tonnage calculation

The thickness of a fluorinated layer is estimated to vary between 0.1 and 10 µm. For modern fluorination technologies for small packaging we assume a thickness layer of 0.1µm, and that this layer consists of PTFE.

Mass of potential PFAS in packaging = thickness of barrier layer * total surface area of packaging * density of PTFE

Table 2.

Pack size	**Weight (in g)**	**Dimension (in mm)**	**Surface (m^2)**	**Number of bottles placed on the market**	**total surface (m^2)**	**Volume of 0.1 µm fluorinated layer**	**Mass assuming PTFE (kg)**
1L	78	90 x 235 (DxH)	0.141	640000	90240	0.009024	18.05
5L	200	195 x 135 x 320 (LxWxH)	0.317	6300000	1997100	0.19971	399.42
10L	350	245 x 180 x 380 (LxWxH)	0.494	1250000	617500	0.06175	123.5
20L	1000	250 x 300 x 400 (LxWxH)	0.71	435000	308850	0.030885	61.77
						Sum (in kg)	**602.74**

The above calculations make several ‘conservative’ assumptions. The packaging considered are bottles or canisters with a volume of 1L, 5L, 10L and 20L which represent 89% of the rigid plastic primary packaging for end users. The dimensions of the packaging used for the surface area calculation is an estimated average for the specified bottle volume. For simplification, the surface area calculation is based on a cube or cylinder with the given dimensions, and an increase of 20% to reflect any special shapes of round bottles and rectangular canisters. The number of bottles for each size is calculated from the total tonnage placed on the market (2320t), the proportion contributed by the market share of the respective bottle size and average mass (see CLE CMS-data). The barrier layer is assumed to be PTFE with a density of 2000 kg/m^3 (2 g/cm^3).

Not considered in this calculation are bulk packaging, such as drums or IBC’s, because the majority of packaging used is covered by the four small sizes. Assuming this represents approximately an additional 10% of the calculated quantity, the **fluorinated layer of rigid plastic primary packaging** placed on the market for crop protection products is **approximately 663 kg/year**.

Emissions to the Environment

CropLife Europe can only provide data for packaging that is collected by industry-run recovery programs (currently in 20 of the 27 EU MS). The average percentage of packaging not recovered via a CMS is currently 34% in EU27, with a 66% average collection rate across EU27 (average 71% in the 20 Members States with a CMS, and up to 84% in some Member States). 7 countries do not currently have an implemented CMS. This does not mean that where there is no CMS there is no recovery, because there are other unmonitored local systems in place that operate collections schemes. We aim at ensuring collection programs are available in all EU MS by 2025 with an average collection rate of at least 75% (i.e. reduce the unmonitored fraction below 25%).

Within the CMS, primary plastic packaging containers are considered for recycling by washing, shredding, and extruding to pellets. Any packaging not suitable for recycling is sent for incineration.

Assuming the relative proportion of fluorinated packaging sent to incineration is the same as placed on the market i.e. 7%, then approximately 394 t/year of fluorinated rigid packaging would be incinerated. Incineration of the collected packaging occurs via municipal waste incineration plants, or as refuse derived fuel (RDF) for high-temperature cement kilns. CropLife Europe does not have any information on possible PFAS emissions resulting from incineration of packaging waste streams. In principle, the packaging collected via established CMS for pesticide packaging, does not end up in landfill.

6.1.b: Key functionalities provided by PFAS

Fluorination is used as a barrier technology to protect the environment and users (customers, and those handling products along the supply chain, etc.) by maintaining the performance of dangerous goods certified packaging. It creates a fluorinated polymer layer on the surface of the plastic bottle which the contents are in contact with. This technique avoids issues such as stress cracking which can impact the performance of the packaging required for compliance with transport of dangerous goods regulations.

The barrier is very often but not exclusively used for solvent-based formulations. The required function is usually to create a barrier against permeation or migration of the product components (e.g., solvent, active substance, etc.) through the plastic bottle wall. Furthermore, the barrier can also be used as an oxygen barrier to keep formulation properties within the registered purity limits over the regulatory requirement for two-year shelf-life.

Surface fluorinated HDPE containers are considered as recyclable, and this does not impact or limit the use during the recycling process, unlike other barrier materials (HDPE/EVOH or HDPE/PA co-extruded), **thus reducing waste streams**.

See Tressaud et al (2007) in particular section “3.2.2.1. Barrier properties” for a more detailed scientific explanation of the technical properties introduced by surface fluorination of plastic packaging. Kharitonov A. P. et al (2005) provide example chemistry details of the surface treatment process.

6.1.c: Number of companies in the sector

In general, all companies producing pesticides, and chemical companies in general, use fluorinated packaging for specific product types due to regulatory requirements to comply with transport of dangerous goods. In addition, registration requirements imposed on plant protection products e.g., storage stability, can lead to the need to use fluorinated packaging, depending on the types of product manufactured by a given company.

6.1.d: Availability of alternatives

To our knowledge and as of today there are no alternatives available for a **surface treatment** creating a barrier without the use of fluorine gases in the market. However, there are other technologies based around co-extrusion of two plastic types to form the bottle, with one lining the inside and the second providing structural support. Examples available and currently on the market are HDPE/PA or HDPE/EVOH co-extruded packaging, however, there are significant hurdles to a rapid transition.

The current container shape used by the majority of the pesticide producers – a de-centered neck and asymmetric container shape - is designed for handling purposes. This design avoids exposure to the pesticide and contamination during emptying the packaging into the spray tank or induction hopper.

With co-extruded materials such as HDPE/PA or HDPE/EVOH, the distribution of the barrier layer (PA or EVOH) is not consistently even for an asymmetric bottle design and can infringe on requirements for a minimum wall thickness to have an efficient and effective barrier layer. When using coextruded materials, a new bottle design would need to be introduced by the majority of the pesticide producers. Furthermore, adaptations to producing packaging (new tools and design adaptations), testing for UN transport of dangerous goods certification, and production line modifications would be required.

The packaging for pesticides is specified in a plant protection product registration. For the registration, studies on the suitability of packaging are required (2 years storage stability). A change to an alternative barrier technology replacing surface fluorination would require new studies to be performed and provided as an update to the product registration. A change to the packaging can only occur **after** approval by the respective competent authorities.

Other packaging materials such as glass or metal have been historically used by the crop protection industry. The safety of end users has been increased since the shift to rigid plastic primary packaging – both with and without fluorination. The risk of glass bottle breakage, particularly in the large sizes required was higher, required more cushioning material, and impacted the transport and supply chain through increased weight. Metal packaging was less resistant to corrosion, required additional inner coatings, or was more easily damaged (by puncturing) during logistics handling.

These previously used materials are not considered as potentially allowable alternative packaging in current product registrations, or are easily available in the packaging industry, and cannot be considered viable alternatives due to the significant reduction in safety, carbon dioxide emissions (transport weight), etc.

It should be noted that potential alternative packaging technologies use other barrier materials (such as co-extruded HDPE/EVOH or HDPE/PA) have limitation on recyclability and **thus potentially increase waste streams**.

Shortages on raw materials for packaging are not currently known, but with an economy wide shift across other industry sectors (food, oil, chemistry, etc.), are considered a likely risk. Shortages on materials or industry capacities that are available to change, upgrade or build new production tools for bottles and canisters are considered to be very likely. Lead-times for new molds for plastic bottles have already been observed to increase due to the recent COVID-19 pandemic, and have not yet returned to pre-pandemic durations. Similar increases in lead-times required for changes to production equipment in filling and packing production lines have also been observed, and not yet returned to historical norms.

A bottle neck could be the authorities for re-registration or updates of existing product registrations as an immediate ban with a derogation period of 18 month only will lead to a huge amount of requests in a short timeframe.

6.1.e: Future development of alternatives

To the best of our knowledge there are no alternatives available for a **surface treatment** creating a barrier without the use of fluorine gases in the market.

There may be certain products for which current alternative barrier materials do not perform adequately to meet transport of dangerous goods, or plant protection product storage stability requirements.

6.1.f: Information on substitution requiring additional time

6.1.f.1: Costs

No estimate of costs to fully implement a change to alternative barrier material bottles is currently available but are obviously very substantial.

An appropriate derogation period would allow for a managed transition by both industry and Member State plant protection product regulators, and reduce investment needed for peak resource needs ("flattening the curve").

6.1.f.2: Time

It is estimated that **at least 6 years** would be required for transition **assuming no delays** e.g. capacity constraints in storage stability testing laboratories, or resource constraints by approving regulatory authorities considering the anticipated large number of application for changes to plant protection product registrations.

Figure 2. Timeline for substitution of fluorinated packaging specific to the plant protection product sector under Regulation (EU) 1107/2009.

When using coextruded materials, a new bottle design would need to be introduced by the majority of the pesticide producers. Furthermore, adaptations to producing packaging (new tools and design adaptations), and production line modifications would require additional time (up to 24 months).

After an alternative packaging has been found (including compatibility testing by an applicant, and UN transport of dangerous goods testing), there is a legal need to provide evaluating Member State authorities with the results of storage stability tests. Either 2-year storage stability at ambient temperature, or by extrapolation with accelerated storage studies (2 weeks at 54°C and/or 2 months at 40°C). CropLife Europe members experience shows that acceptance of extrapolation by authorities is variable and depends on the formulation type and material used. Data requirements are all listed in Regulation (EC) 284/2013 (see sections 2.7 for stability and 4.1, 4.4 for transport).

Finally, time is required for the actual evaluation by the Member State competent authority. Here the timeline is also variable depending on Member States' capacities to process plant protection products dossiers regulatory action (currently 6 to 12 months with no additional PFAS or other Chemical Strategy for Sustainability induced demands). See the DG SANTE report of Member States timelines for products actions (EC, 2020).

Considering the above, the default Restriction proposal of an 18-month transition period is completely insufficient and would result in loss of at least some plant protection products which are required by regulation to be packaged in specified fluorinated packaging. Agronomic losses and economic impacts on farmers and the food supply chain could be anticipated. Consequently, a **derogation for fluorinated packaging used in the regulated plant protection product sector** is requested, and more generally in the broader chemical sector handling hazardous substances under transport of dangerous goods. An appropriate derogation period would allow for a managed transition by both industry and Member State plant protection product regulators, minimising peak resource needs ("flattening the curve").

6.1.f.3: Differences in functionality

There is a risk that alternative barriers to PFAS do not perform as expected, including for larger packaging sizes – with an impact on transport of dangerous goods transport and product registrability.

For some chemicals it is likely that alternative barrier materials will require a greater packaging wall thickness to achieve the same barrier properties, thus using more plastic and increased weight per bottle. This could have impacts on sustainability goals of the European Union, in particular through use of more plastic, higher carbon footprint (plastic manufacture and transport of increased weight), and higher energy consumption during manufacturing. Similarly, alternative packaging technologies (such as co-extruded HDPE/EVOH or HDPE/PA) have limitation on recyclability and thus potentially increase waste streams, carbon footprint, raw material and energy usage.

6.1.f.4: Benefits

Suppliers of packaging to the crop protection sector will likely remain the same, as they currently provide both barrier technologies – both fluorinated and coextruded packaging.

6.1.g: Information on substitution not considered feasible

In the case that for specific products a co-extruded barrier material was not able to be found that adequately performed to meet the transport of dangerous goods, or plant protection product requirements on storage stability, this would result in loss of the product regulatory approval for sale.

6.2: Intermediates

- As a minimum, these comments are relevant to the following sectors specified in **Table A.1 of Annex A: plant protection products and biocides, and chemical industry**.

Detailed impact information has only been provided for the plant protection product sector.

6.2.a: Annual tonnage and emissions

The total tonnage is all approximately that of all substances within scope of the restriction proposal with a derogation longer than 18 months. The ultimate tonnage after expiry of the derogation transition periods would be the intermediates used to synthesize active substances in Column 2, Paragraph 4 regulated sectors, substances used in Research and Development (individually <1t/year per substance), and Column 2, Paragraph 5(t) “calibration of measurement instruments and as analytical reference materials".

By definition intermediates registered under REACH are required to be used under strictly controlled conditions, which includes inter alia rigorous containment. As such there should be no end-of-life or other emissions to the environment to consider.

6.2.b: Key functionalities provided by PFAS

The key functionalities for intermediates are determined by the end-use molecule, and the need for the fluorinated moiety for the function of that final molecule. In the vast majority of cases, the intermediate will only contain a fluorinated moiety if it is required to transfer this functional group. It is unlikely to have any function in the intermediate beyond this.

6.2.c: Number of companies in the sector

All companies using intermediates.

6.2.d: Availability of alternatives

In the vast majority of cases intermediates are defined by the molecule they are ultimately being used to synthesize. As such, the intermediate can usually not be changed without modifying the resultant chemical. In the specific case of fluorine chemistry, given the expense, it can be robustly assumed that fluorine is present in an intermediate only if the relevant moiety is intended to be transferred to the next step, and ultimately the final product. Therefore, it is reasonable to say that for intermediates in general, no alternatives are available.

An alternatives and socio-economic analysis can be performed on the final synthetic products – the outcome of which would inherently determine the ongoing need for any specific intermediate. For this reason, intermediates should receive time unlimited derogation, and any alternatives/socio-economic analysis conducted further downstream.

6.2.e: Future development of alternatives

No information is currently available to CLE for this question.

6.2.f: Information on substitution requiring additional time

Generally no alternatives are believed to be possible for intermediates.

6.2.g: Information on substitution not considered feasible

Intermediates lie upstream in the supply chain from products intended to receive a derogation. If intermediates do not receive at least similar derogation, immediate loss of all downstream products would follow after the default 18 month transition period expired. Instead a of attempting to manage multiple timelines with associated compliance issues, a generic time unlimited derogation should be put in place for intermediates.

6.3: Laboratory uses

- These comments are relevant as a minimum to the following sectors specified in **Table A.1 of Annex A: plant protection products and biocides, and chemical industry**.

Only limited information is provided here due to the very large number of potential uses which substances could call under this restriction proposal. These limited examples are only intended to provide a non-exhaustive outline of the kind of uses PFAS as substances and chemical reagents in commercial laboratory settings might have. The uses are distinct from use of PFAS materials and articles in laboratory settings which are not detailed here. These may or may not fall under research and development exemptions, and total tonnages across sectors may exceed 1 t/year.

6.3.a: Annual tonnage and emissions

Use in laboratories is under controlled conditions and the only emissions should be via established handling of hazardous waste streams.

6.3.b: Key functionalities provided by PFAS

The key functionalities provided by PFAS substances depend on the use. Some examples follow.

In Vitro Mammalian Cell Gene Mutation Tests (OECD Test No. 490) use trifluorothymidine (TFT). Mutant cells deficient in thymidine kinase enzyme activity because of a mutation TK+/- to TK-/- are resistant to the cytostatic effects of the pyrimidine analogue TFT. The TK proficient cells are sensitive to TFT, which causes the inhibition of cellular metabolism and halts further cell division. Thus, mutant cells are able to proliferate in the presence of TFT and form visible colonies, whereas cells containing

the TK enzyme are not. This is highly specific effect, and an alternative fluorine-free substance with the same effect is unlikely.

Trifluoroacetic acid (TFA) can be used in analytical chemistry as a high-performance liquid-chromatography (HPLC) mobile phase modifier (Lardeux H. et al, 2021). Acids such as TFA are added to shift the pH of the mobile phase, and as a result the degree of ionization and hydrophobicity of the substances being analysed. In turn the retention time and selectivity of the substances change, thus allowing the reliable detection of specific substances to be optimized. TFA has particularly desirable properties for use with liquid chromatography–mass spectrometry (LC–MS) detection systems, because it is more volatile than alternatives and does not foul the ion source.

6.3.c: Number of companies in the sector

All companies with laboratories involved in commercial activities.

6.3.d: Availability of alternatives

For substances used in specific toxicology studies such as OECD Test No. 490 for mutagenicity (i.e., trifluorothymidine), no alternatives are considered likely to be available, because the test relies on blocking a highly specific metabolic pathway using thymidine.

For substances used in analytical chemistry as mobile phase modifiers, alternatives are likely to be available, with case-by-case suitability for substitution.

For substances used in academic research, commercial research and development, calibration of equipment, and analytical reference materials, it is highly unlikely alternatives will be available, given the highly specialized uses.

6.3.e: Future development of alternatives

No information is currently available to CLE for this question.

6.3.f: Information on substitution requiring additional time

No information is currently available to CLE for this question.

6.3.g: Information on substitution not considered feasible

It is not realistic to perform a detailed analysis of all the uses to which PFAS substances are put in chemical laboratories.

7: Potential derogations marked for reconsideration – Analysis of alternatives and socio-economic analysis:

Paragraphs 5 and 6 of the proposed restriction entry text (see table starting on page 4 of the summary of the Annex XV restriction report) include several potential derogations for reconsideration after the consultation (in [square brackets]). These are uses of PFAS where the evidence underlying the assessment of the substitution potential was weak. The substitution potential is determined on the basis of i) whether technically and economically feasible alternatives have already been identified or alternative-based products are available on the market at the assumed entry into force of the proposed restriction, ii) whether known alternatives can be implemented before the transition period ends (taking into account time requirements for substitution and certification or regulatory approval), and iii) whether known alternatives are available in sufficient quantities on the market at the assumed entry into force to allow affected companies to substitute.

A summary of the available evidence as well as the key aspects based on which a derogation is potentially warranted are presented in Table 8 in the Annex XV restriction report, with further details being provided in the respective sections in Annex E.

To strengthen the justifications for a derogation for these uses, additional specific information is requested on alternatives and socio-economic impacts covering the elements described in points a) to g) in question 6 above.

No information is currently available to CLE for this question.

8: Other identified uses – Analysis of alternatives and socio-economic analysis:

Table 8 in the Annex XV restriction report provides a summary of the identified sectors and (sub-)uses of PFAS, their alternatives and the costs expected from a ban of PFAS. More details on the available evidence are provided in the respective sections in Annex E.

For many of the (sub-)uses, the information on alternatives and socio-economic impacts was generic and mainly qualitative. In particular, evidence on alternatives was inconclusive for some applications falling under the following (sub-)uses: technical textiles, electronics, the energy sector, PTFE thread sealing tape, non-polymeric PFAS processing aids for production of acrylic foam tape, window film manufacturing, and lubricants not used under harsh conditions.

More information is needed on alternatives and socio-economic impacts to conclude on substitution potential, proportionality, and the need for specific time-limited derogations. Therefore, specific information (if not already included in the Annex XV restriction report or covered in the questions above) is requested on alternatives and socio-economic impacts covering the elements listed in points a) to g) in question 6 above.

No information is currently available to CLE for this question.

9: Degradation potential of specific PFAS sub-groups:

A few specific PFAS sub-groups are excluded from the scope of the restriction proposal because of a combination of key structural elements for which it can be expected that they will ultimately mineralize in the environment. RAC would appreciate to receive any further information that may be available regarding the potential degradation pathways, kinetics or produced metabolites in relevant environmental conditions and compartments for trifluoromethoxy, trifluoromethylamino- and difluoromethanedioxy-derivatives.

See Chapter 2, Hazard Characterization, Biodegradation of PFAS Substances (above) for the context of this experimental work conducted by CropLife Europe. In particular:

> *It is essential to realize that these experiments are **only** intended to prove the fundamental basis for the above theoretical work is correct. As such, the **precise details of the experimental conditions used here do not matter** (e.g. 20°C vs 12°C). This is because the observed degradation rate will vary with each molecule which contains one of these functional groups (e.g. -OCF_3), depending on the broader chemical structure of the larger parent molecule. The essential and key point is that **the identified functional groups (such as -OCF_3) do not confer persistence on a larger molecule** which may be registered under REACH.*

The same considerations apply for other heteroatom bonded -CF_3 and -CF_2- groups e.g. oxygen, nitrogen, etc, where the formation of stable species on degradation cannot be assumed, and standard environmental fate studies required by REACH must be conducted for proof or absence of concerns.

Defluorination of ^{14}C-Trifluoromethoxy Benzoic Acid in Soil

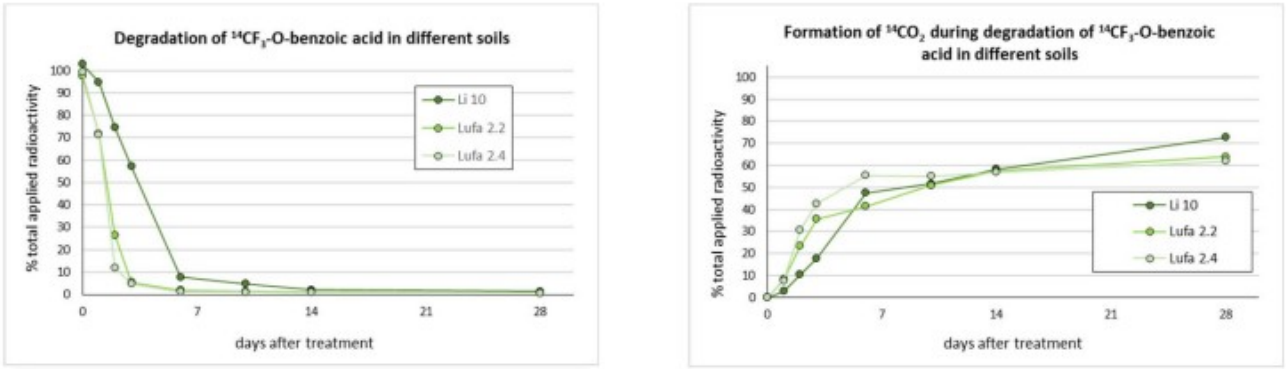

Figure 3. The above plots show preliminary degradation results for trifluoromethoxybenzoic acid presented at SETAC Europe 33rd Annual Meeting 30 April – 4 May 2023 (3.16.P-Tu216 Defluorination of 14C-Trifluoromethoxy Benzoic Acid in Soil). The study summary for the final report is now available in Annex 2.

CropLife Europe Briefing Note #35973 (Annex 3) first reported preliminary results on the defluorination of ^{14}C-trifluoromethoxybenzoic acid in soil. Figure 3 are plots of preliminary degradation data presented at SETAC Europe 33rd Annual Meeting 30 April – 4 May 2023.

Annex 2 contains the OECD study summary for the now completed and reported experimental work on defluorination of ^{14}C-trifluoromethoxybenzoic acid. The executive summary is reproduced below.

The objective of the present aerobic soil metabolism study was to investigate if molecules carrying an O-CF_3-group can be degraded in soil in a way that the CF_3-group is partially or fully defluorinated so that the respective carbon atom can finally be degraded to CO_2.

As a model test compound, 4-(trifluoromethoxy)benzoic acid radio-labeled directly at the CF_3- group was chosen for performing an aerobic soil degradation study according to OECD guideline 307 with special analytical focus on the formation of $^{14}CO_2$.

For this, three soils from the Southwestern region of Germany (Li 10, LUFA 2.2, and LUFA 2.4) were treated with ^{14}C-trifluoromethoxy-labeled test item at a target application rate of 0.67 mg a.s./kg dry soil, which corresponds to a field application rate of 250 g a.s./ha, calculated on the basis of an equal distribution in the top 2.5 cm soil layer and a soil density of 1.5 g/cm³.

The soil moisture was adjusted to 40% of the maximum water holding capacity (MWHC). The soils were filled in 50 g portions in individual glass test vessels, treated and then incubated in the dark at a temperature of 20 ±2°C in a closed incubation system with continuous aeration for up to 56/57 days.

Soil samples were taken at day 0 and at seven additional sampling times throughout the entire incubation period. The sampling dates were 0, 1, 2, 3, 6/7, 10, 14, and 28 days after treatment (DAT). Volatiles were collected for each test container individually through dedicated trapping systems and sampled together with the respective test container (except at day 0). For each sampling time two replicate soil samples were worked up. One additional sampling was performed at 56/57 days in order to check if the decrease of the non-extractable residues is proceeding after 4 weeks of incubation.

The radioactivity in the volatile trapping solutions was analyzed by liquid scintillation counting (LSC). In order to check also for remaining transformation products in soil, the soil samples were consecutively extracted with 3 × 50 mL acetonitrile/water (9/1, v/v), 1 × 100 mL acetonitrile/water (1/1, v/v) and washed twice with 50 mL acetone. The individual extracts were analyzed by LSC and combined fractions were concentrated and analyzed by radio-HPLC.

The soil residue after extraction was dried under N_2 while being attached to another CO_2 trapping system. Aliquots of the dried soil were combusted to determine the amount of non-extractable residues (NER), so that a ^{14}C-mass balance could be provided for each sampling interval.

The radioactive test item peak in the soil extracts was confirmed by means of mass spectrometry and in addition by comparison of the retention time of the radiopeak in the soil extracts with the retention time of the ^{14}C-labeled test item in the application solution.

The results show that after 28 days the mineralization to CO_2 reached values between 61.8 and 72.7% of the total applied radioactivity (TAR). The mass balances were > 90% TAR during the 28 days and ranged from 91.8 to 103.6% TAR. Only one sampling point with LUFA 2.2 showed a slightly lower mass balance of > 87.6%.

The amount of extractable radioactive residues decreased from ≥ 97.4% TAR at day 0 to values between 0.6 and 1.3% TAR after 28 days of incubation. The non-extractable residues increased from ≤ 2.6% TAR at day 0 to maxima of 45.5 to 54.5% TAR at 2-6 days, and then decreased to values between 26.0 and 37.8% TAR at 28 days and further to 22.9 and 31.1% TAR after 56/57 days.

The release of $^{14}CO_2$ from the soils continued even after the extractable radioactivity and thus the test item had reached negligible levels. The decline of NERs after 2-6 days suggests that the degradation of the $^{14}CF_3$-group proceeded despite the fact that the benzoic acid reacted with the organic matrix in soil and was partly incorporated into the humic substances.

Precipitation with $Ba(OH)_2$ as well as acidification with HCl of selected samples confirmed that the radioactivity trapped in the NaOH solutions is attributed to $^{14}CO_2$. Other volatile compounds were observed at levels ≤ 0.04% TAR.

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 after 6 - 14 days. Besides the parent compound, a few unidentified transformation products were detected, but all at levels ≤ 0.2% TAR.

Kinetic evaluation and calculation of $DegT_{50}$ and $DegT_{90}$ values (trigger endpoints) for the parent 4-(trifluoromethoxy)benzoic acid was performed following the recommendations of the FOCUS Kinetics workgroup. The obtained $DegT_{50}$ and $DegT_{90}$ values are given below.

Table 3. Trigger endpoints of 4-(trifluoromethoxy)benzoic acid at 20 °C

Soil	**Kinetic model**	**X^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

Trigger endpoints at 12°C were estimated using the Q_{10} approach, following the recommendations of the FOCUS Kinetics workgroup. The obtained $DegT_{50}$ and $DegT_{90}$ values are given below.

Table 4. Estimation of trigger endpoints for 4-(trifluoromethoxy)benzoic acid at 12°C Soil Kinetic model

Soil	Kinetic model	X^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

The results show that 4-(trifluoromethoxy)benzoic acid is rapidly degraded in soil. The only transformation reactions 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.

Overall, the experimental data show (1) that the presence of an OCF_3-group does not automatically leave a molecule persistent in the environment or lead to persistent degradation products and (2) that the C-F bond is not that stable as commonly postulated.

Further experimental work being carried out

Further experimental work by CropLife Europe on biodegradation is scheduled in the near future. While this work is expected to be useful in expanding scientific knowledge on the environmental fate of certain fluorinated moieties, the fact that such rapid degradation and mineralization is observed in soil, we believe it has been sufficiently demonstrated that **extreme persistence** for at least the moieties for which information has been submitted **cannot be assumed**. As a result, molecules containing e.g. $-OCF_3$ are no different to others in assumptions around persistence, and the case-by-case assessment in a REACH registration is appropriate and proportionate policy option.

10: Analytical methods:

Annex E of the Annex XV restriction report contains an assessment of the availability of analytical methods for PFAS. Analytical methods are rapidly evolving. Please provide any new or additional information on new developments in analytics not yet considered in the Annex XV restriction report.

No information is currently available to CLE for this question.

4. References

EC (2020) Report on the compliance with the legal deadlines set out in the Regulation (EC) No 1107/2009 concerning the authorisation of plant protection products reported by Member States and Norway for the years 2017, 2018, 2019 and 2020. Directorate E – Food and feed safety, innovation. European Commission. https://food.ec.europa.eu/system/files/2022-09/pesticides_ppp_report_ms-survey_regulatory-procedures-timing_2017-20_0.pdf

Kharitonov A. P. (2005) The kinetics and mechanism of the direct fluorination of polyethylenes. Surface Coatings International Part B: Coatings Transactions, **88**, pages 201–212. https://doi.org/10.1007/BF02699574

Lardeux H. et al (2021) Alternative mobile phase additives for the characterization of protein biopharmaceuticals in liquid chromatography – Mass spectrometry. Analytica Chimica Acta, Volume 1156, 29 April 2021, 338347. https://doi.org/10.1016/j.aca.2021.338347

Pazenok S., et al (2020) Chapter 16: Modern Fluorine-Containing Agrochemicals in Frontiers of Organofluorine Chemistry, pp. 695-732. https://doi.org/10.1142/9781786347336_0016

Tressaud A. et al (2007) Modification of surface properties of carbon-based and polymeric materials through fluorination routes: From fundamental research to industrial applications. Journal of Fluorine Chemistry, Volume 128, Issue 4, April 2007, Pages 378-391. https://doi.org/10.1016/j.jfluchem.2006.12.015

5. Annex 1 - Analysis of the potential agronomic impact from the loss of fluorinated agrochemicals in the EU

CropLife Europe Position #33669. Pages 1-6.

6. Annex 2 – OECD summary, Aerobic soil metabolism of ^{14}C-trifluoromethoxybenzoic acid

Previously unpublished OECD summary on the Aerobic soil metabolism of ^{14}C-trifluoromethoxybenzoic acid. Pages 1-23.

7. Annex 3 – Experimental work on degradation of CF_3-containing molecules

Document previously supplied to the Dossier Submitters (ECHA) and RAC in the context of the PFAS in firefighting foam restriction proposal. CropLife Europe Briefing Note #35973. Pages 1-8.

8. Annex 4 – CropLife Europe information on functional groups

Document previously supplied to the Dossier Submitters (ECHA) and RAC in the context of the PFAS in firefighting foam restriction proposal. CropLife Europe Position Paper #35461. Pages 1-17.

9. Annex 5 – Specific comments and additional references linked to the restriction report Annex B.

Detailed comments on toxicology studies reported in Annex B of the restriction proposal. Pages 1-2.

Annexes 1-5 follow, in the above order. Pagination is non-consecutive.

08/05/2023

Analysis of the potential agronomic impact from the loss of fluorinated agrochemicals in the EU

1. **A recent review, over the period 1998–2020, reveals that 60-70 % of newly launched or registered agrochemicals are organofluorine compounds. These compounds form an important part of a farmer's current crop protection toolkit.**

2. **Maintaining and rotating the limited pool of agrochemicals with different and new modes of action is key to ensure the sustainability of agricultural productivity. When considering removing specific compounds there is always a risk that no alternatives are available - depending on the pest control segment.**

3. **Loosing fluorinated agrochemicals could have severe impacts across all sectors of the Crop Protection Industry with the loss of key actives and Modes of Action (MoA) drastically reducing the resistance management options available for EU growers: Insecticides/Acaricides would see the loss of 9 active substances (AS) and complete loss of 4 MoA groups. Fungicides would see the loss of 11 AS with 5 MoA groups lost entirely. Whereas the herbicide sector would see the loss of 15 AS and the complete loss of 1 MoA.**

4. **We outline in more detail the potential impacts across Cereal Fungicides, Sugar Beet fungicides, Potato fungicides, Oil Seed Rape – Insecticides, Protected Vegetable Insecticides, Fruit crops Insecticides, Cereal Herbicides, Corn Herbicides, Vines and Orchards herbicides.**

The importance of fluorinated agrochemicals in crop protection

A survey of 45 new pesticide active ingredients used as modern agrochemicals over the last 10 years has shown that around 84% of the launched products are halogen-substituted (10 herbicides, 15 fungicides, 13 insecticides/acaricides, and 3 nematicides). From these, 31 active ingredients are fluorinated and around 45% of them contain a CF_3-group, approximately 19% a CHF_2- and around 3% a CF_3O-group as a substituent on the phenyl or heterocyclic moieties[1].

The importance of fluorine chemistry as a tool for enhancing the biological activities of active ingredients is well recognized. A clear indication of the key role that fluorine plays in the development of new agrochemicals is the dramatic increase in the number of fluorinated active ingredients in the past three decades, from 23 out of 543 listed in 1977 to 186 out of 862 listed in 2015. The most common fluorine containing groups is aromatic CF_3-group and aromatic fluorine atom.[2] A more recent review, over the period 1998–2020, indicates that 60-70 % of newly launched or registered agrochemicals are organofluorine compounds (Ogawa et al, 2020).

[1] P. Jeschke, Current trends in the design of fluorine-containing agrochemicals, in: *Organofluorine Chemistry – Synthesis, Modeling, and Applications*, K. J. Szabo, Nicklas Selander (eds.), Wiley-VCH GmbH, (2021), pp. 363-395.

[2] The pesticide manual 17th edn 2015.

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Polyfluoro-alkyl groups for example, as substituents on the phenyl or heterocyclic moieties play an important role in agrochemicals used in plant protection. This can be exemplified by a remarkable number of CF_3- and CHF_2-group containing herbicides (46%) and fungicides (56%) launched over the last decade. Furthermore, a couple new and innovative insecticides bearing heptafluoro-*iso*-propyl groups, were successfully launched for global control of important insect pest species like fall armyworm[5]. Almost all modern nematicides, already launched or under development, with considerably improved overall toxicological and environmental profiles contain CF_3-groups. A unique feature of fluorine on active ingredients, the so-called *"fluorine effect"*, such as the effects on steric and electronic properties, conformation and polarity has been discussed in detail in recent reviews[6-8]. In addition, improving the metabolic, oxidative, and thermal stability (C-F bond energy: 485 kJ/mol, metabolic stabilization), the pK_a value effects (H-bonding, protein binding affinity), and the influence of fluorine on physicochemical properties such as molecular lipophilicity (key parameter for absorption and transport, important for bioavailability) can be underlined (Jeschke, 2021).

Lipophilicity is an important physicochemical parameter quantified by the log P-value; it also determines ligand–target binding interactions, solubility, and ADME (absorption, distribution, metabolism, and elimination) properties. This is exemplified by the (F_3C-X) groups (X = S, O), which contribute to the pest's overall pharmacological activity by enhancing the insect central nervous system (CNS) penetration. Moreover, the influence of fluorine on modulation of biological properties of an active substance (AS) has been described in detail by shifts of biological activity arising from the introduction of fluorine atoms and/or fluorine-containing substituents into biological active ingredients such as the commercialized insecticides γ-aminobutyric acid (GABA)-gated chloride channel blockers (phenylpyrazoles), sodium channel modulators (pyrethroids), or inhibitors of chitin biosynthesis, type 0 (benzoyl ureas)[9].

The role of fluorinated agrochemicals in resistance management

Polyfluoro-alkyl- groups for example, as substituents on the phenyl or heterocyclic moieties cover different indications such as herbicides, insecticides/acaricides, fungicides and nematicides. These belong to different chemical groups (N-phenyl-imides, butenolides, diamides/carboxanilides, benzamides, carboxamides) and offer potent modes of action that are critical in effective and complementary pest management. Resistance to chemical pesticides in all indications is considered as an extremely serious global and increasing problem for food production. Therefore, an effective resistance management strategy is mandatory, and the Herbicide Resistance Action Committee (HRAC)[10], Insecticide Resistance Action Committee (IRAC)[11] and the Fungicide Resistance Action Committee (FRAC)[12] have been dedicated to making this a reality for the past three decades. Regardless of numerous research programs, only a few new modes of action have entered the market in the past 30 years.

Maintaining and rotating, let alone reducing the limited pool of agrochemicals with different and new modes of action is therefore key not to endanger significantly the sustainability of agricultural productivity as simply no alternatives might be available dependent on the pest control segment.

Indeed, without adequate plant protection products, yield can be reduced already today by – on average- 16% by diseases, 18% by insects and 34% by weeds[3]. In addition, globalization and climate change are redrawing the landscape of plant pest distribution. This trend poses a threat to natural and managed environments, agricultural and forestry production, ecosystems and biodiversity in the European Union territory[4]. For instance, 50 to 100 percent increase in pest-induced crop losses in European wheat should be anticipated even if countries meet their existing commitments to reduce greenhouse gas emissions[5].

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[3] C.E. Oerke, 2006. Crop Losses to pests. Journal of Agricultural Science (2006), 144, 31–43.

[4] https://www.efsa.europa.eu/en/news/priority-plant-pests-eu-5-things-you-need-know

[5] C. A. Deutsch, J. J. Tewksbury, M.Tigchelaar, D. S. Battisti, & S. C. Merrill, Increase in crop losses to insect pests in a warming climate. S*cience* 31 Aug 2018:Vol. 361, Issue 6405, pp. 916-919,DOI: 10.1126/science.aat3466
Y. Ogawa, Tokunaga, E., Kobayashi, O., Hirai, K., & Shibata, N.Current Contributions of Organofluorine Compounds to the Agrochemical Industry. iScience 23, 101467, September 25 (2020),202, 1-53

[5] M. L. Quacemi, S. Rendine, & P. Maienfisch, Recent applications of fluorine in crop protection – new discoveries originating from the unique heptafluoro-iso-propyl group, in: *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, (eds. G. Haufe and F. Leroux), London, Oxford: Academic Press (2018), pp. 607-629.

[6] P. Maienfisch & R. G. Hall, The importance of fluorine in the life sciences. *Chimia* (2004) 58, 93-99.

[7] G. Theodoridis, Fluorine-containing agrochemicals: an overview of recent developments, in: Advances in Fluorine Science, Vol. 2, (ed. A. Tressaud), Elsevier, Amsterdam, (2006), pp. 121-175.

[8] P. Jeschke, Latest generation of halogen-containing pesticides. Pest Manag. Sci. (2017), 73, 1053-1066.

Adequate and sufficient pesticide mode of action options need to remain available to face this dynamic and to sustain agricultural productivity.

The agronomic impact of a loss of fluorinated agrochemicals in the EU

Loosing fluorinated agrochemicals would have severe impact across all sectors of Crop Protection industry with the loss of key actives and Modes of Action (MoA) drastically reducing the resistance management option available for EU growers. Insecticides/Acaricides would see the loss of 9 AS, impact the availability of 6 MoA groups and result in the complete loss of 4 MoA groups. In the EU fungicides would see the loss of 11AS, impact the availability of substances in 8 MoA groups, with 5 MoA groups lost entirely. Whereas the herbicide sector would see the loss of 15 AS, impact the availability of substances in 7 MoA groups and see the complete loss of 1 MoA.

Expert judgement on the interaction between inherent resistance risk factors and resistance modifiers suggest that for PPP / target interactions considered medium risk at least 3 MoA are needed whilst for scenarios considered high risk then a minimum of 4 MoA would be needed for sustainable pest management[6]. In many of the crop sectors mentioned below the number of available and effective MoA are already limited and further losses of AS and MoA would exacerbate the resistance risk on other chemistries.

Cereal Fungicide

Cereals are grown in large quantities across the EU and are susceptible to a wide range of diseases which can significantly affect yield and quality. Key countries include Germany, France, Poland, Romania, Spain and Italy. The number of MoA groups available for the control of cereal diseases is already limited. Recent regulatory measures have seen the loss of a number of multisite solutions, which apply increased pressure on the remaining AS. SDHI (MoA group 7) are a relatively new and very effective MoA group against key cereal diseases. The loss of fluorinated agrochemicals would see the removal of 2 out of 10 AS currently available.

Active substances from the DMI chemistry group (MoA group 3) are the cornerstone of cereal fungicide programs. Many DMI's are already at risk from the regulatory scrutiny under regulation 11107/2009. Further loss of key DMI's in this market would severely limit the availability of effective solutions. With no fluorinated agrochemicals, 2 triazoles would be lost from this important group.

In addition, the QoI fungicides (Group 11) are a key part of the toolbox for fungal control in cereals with wide-spectrum activity. One of these active substances would also be removed from the options available.

In addition, France, Germany, Poland and Spain would have a loss of 1 unique mode of action from the currently registered fungicides for powdery mildew control in cereals (Group U06).

Based on the very low number of MoA within the cereal fungicide area the loss of a significant number of SDHIs threaten disease control across Europe, crop losses of between 40% (yellow rust) and 20-25 % (Septoria) can be expected if control fails. The loss of SDHI and key DMI's in wheat would seriously impact the ability to control Septoria and yellow and brown rust. Disease control in barley would be impacted to an even greater extent with the recent loss of a key multisite active substance and high levels of resistance to existing chemistry in key diseases such as Net blotch, Ramularia, Rhynchosporium already making disease management difficult. Growers can manage disease risk to some extent through

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[9] P. Jeschke, O. Gutbrod, & F. Leroux, The role of fluorine in the design of nicotinic acetylcholine receptor (nAChR) competitive modulators. in: *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, (eds. G. Haufe and F. Leroux), London, Oxford: Academic Press (2018), pp. 631-651.

[10] R. Beffa, H. Menne, & H. Köcher, Herbicid resistance action committee (HRAC): Herbicide classification, resistance evolution, survey, and resistance mitigation activities, in *Modern Crop Protection Compounds*, Vol. 1, Herbicides, 3rd edition (eds. P. Jeschke, M. Witschel, W. Krämer, U. Schirmer), VCH-Wiley, Weinheim, (2019), pp. 5-32.

[11] R. Nauen, R. Slater, T. C. Sparks, A. Elbert, & A. McCaffery, IRAC: Insecticide resistance and mode-of-action classification of insecticides, in *Modern Crop Protection Compounds*, Vol. 3, Insecticides, 3rd edition (eds. P. Jeschke, M. Witschel, W. Krämer, U. Schirmer), VCH-Wiley, Weinheim, (2019), pp. 995-1012.

[12] D. Herrmann & K. Stenzel, FRAC Mode-of-action classification and resistance risk of fungicides, in *Modern Crop Protection Compounds*, Vol. 2, Fungicides, 3rd edition (eds. P. Jeschke, M. Witschel, W. Krämer, U. Schirmer), VCH-Wiley, Weinheim, (2019), pp. 589-608.

[6] T. Rotteveel, L. N. Jorgensen and U. Heimbach 2011- EPPO Bulletin 41, 432-438. Resistance management in Europe: a preliminary proposal for the determination of a minimum number of active substances necessary to manage resistance.

selection of specific cereal varieties however it is important to also remember that crop protection products also help to protect varietal disease resistance in the medium to long term.

Sugar Beet fungicides

The number of actives and MoA is very limited for sugar beet currently relying primarily on QoI, and DMI chemistries exacerbated by the recent loss of key DMI's used in the sugar beet crop. A key disease Cercospora has widespread resistance to QoI chemistry and there are concerns about potential DMI shift in sensitivity in Europe. The yield loss on this strategic crop for many Member States caused by Cercospsora in absence of good disease control can be up to 20% sugar yield. New MoA are urgently needed to manage diseases in this important crop.

France, Germany and Poland are the largest producers of sugar beet (Eurostat, data from 2022). In Germany there are currently only 7 modes of action registered for sugar beet, the additional loss of SDHI (MoA gp 7) chemistry would result in a further loss of a mode of action group. In Poland registered sugar beet fungicides would be reduced to only 4 active substances and 4 modes of action. In France, Germany, Poland, Spain and Italy only a single DMI fungicide, from the current options of 2-3 from this mode of action would remain from the currently registered substances in sugar beet

Some of the identified actives (e.g. SDHIs and DMI) are relatively new to the market and are still in development or registration phase in crops such as sugar beet. Loss of these new actives will not just impact existing registrations but also future product development on key European crops and significantly increase the selection pressure on the remaining MoAs.

Potato –fungicides

Potato late blight, caused by *Phytophthora infestans* is a major disease of potatoes causing losses by destroying foliage and by infecting tubers. It is one of the few plant diseases that can absolutely destroy a crop, producing a 100% crop loss[7]. Fungicides are an important component of late blight control with up to 15 applications being used per season. An effective disease control programme would use between 4-8 AS formulated as solo or mixture products applied in blocks and sequence over the growing season. The most important EU countries for potato production according to production in 2022 (Eurostat) are Germany, France, Poland, The Netherlands and Belgium.

Currently there are 12 MoA represented in European crop protection for late blight control in potatoes. The recent loss of key multisite solutions has placed additional pressure on the available single site actives. Further losses would see the removal of 3 AS, each of them being the sole representatives of their MoA-group resulting in loss the complete loss of 3 MoA against this very challenging pathogen.

Grape fungicides

Across Europe, grape yield and quality can be significantly impacted by a range of diseases. Viticulture is a sector with one of the highest use of fungicides with 10 to 20 applications required to control these diseases[8]. Powdery mildew is a major disease of grapevine, with most varieties having no genetic resistance to the pathogen, therefore many different modes of action are required to ensure long term management of this disease. In addition, botrytis is a high-risk pathogen in terms of resistance development which requires a diversity of different modes of action. Downy mildew and a range of other diseases can also severely reduce yield.

Grape production in Europe covers 3,132 thousand ha (Eurostat, 2022), with the largest producers being Spain, France, Italy, Portugal and Germany.

The loss of fluorinated agrochemicals would lead to the loss of 3 unique modes of action in Spain, Italy, France and Germany and loss of 4 of the currently registered modes of action in Portugal.

[7] Mercure, P. (1998). University of Connecticut, Integrated Pest Management.2p. Early Blight and Late Blight of Potato.

[8] Kunova, A.; Pizzatti, C.; Saracchi, M.; Pasquali, M.; Cortesi, P. Grapevine Powdery Mildew: Fungicides for Its Management and Advances in Molecular Detection of Markers Associated with Resistance. Microorganisms 2021, 9, 1541.

OSR – Insecticides

The peach–potato aphid and mealy cabbage aphid are the main aphid pests of OSR. The Peach-potato aphid is responsible for transmitting viruses in autumn and can reduce the yield by 20%. There are currently only 2 MoA available against aphid in OSR, these being pyrethroids (MoA group 3a) and chordotonal organ modulators (MoA group 29) with peach–potato aphids already showing high levels of resistance to pyrethroids across EU. MoA group 29 in OSR would disappear and its loss would have severe impact on the ability to grow OSR in Europe.

The loss of key pyrethroids (MoA group 3a) against cabbage stem flea beetle in autumn period will lead to high damages of OSR during the crop establishment phase. The recent loss of key neonicotinoid chemistry from OSR crops already places extreme pressure of the remaining Actives with regards to CSF Beetle control. The loss of key pyrethroids against weevils (*Ceutorhynchus* spp.) would be severe since there are no other solutions after the wintertime to control this type of pests at low temperatures.

Pollen beetle is a very important pest in OSR in northern and central Europe. Key countries include Northern France, Germany, Poland, Czech Republic, Hungary, Romania.. The beetle can cause serious yield losses in both winter and spring oilseed rape crops, and for spring oilseed rape, more than 80% yield reduction can occur[9]. There are currently only three MoA approved for use against pollen beetle: pyrethroids, oxadiazines, and neonicotinoids. Resistance to pyrethroid insecticides has been recorded in samples of beetles collected in Europe since at least 1999, and problems with the control of the beetle in the field have been widely reported[10]. Where pyrethroid resistance is present, the most effective insecticide control is already limited to 2 MoA. The losses of further AS within these MoA-groups would be catastrophic with significant yield losses anticipated.

Protected Vegetable Insecticides

The loss of AS in MoA group 29 and key pyrethroids in MoA group 3a against aphids in Solanaceae and Cucurbitacea would be catastrophic. Key countries include for protected vegetable production include The Netherlands, France, Italy and Spain. Direct yield losses as a result of viruses transmitted by the pests will have a big impact on vegetable production. Biological solutions are not effective alone and they need an IPM approach including chemical PPP's.

Whitefly are a serious problem in protected crop production, acting as vectors for economically damaging viruses. Under the current proposal we would see the loss of five AS against Whitefly across 3 MoA Groups: pyrethroids MoA group 3a; nAChR (MoA group 4) and Chordotonal organ modulators (MoA group 29). MoA group 29 would disappear. Very few effective solutions remain, and these would be under extreme pressure if growers were reliant on such a limited selection of products.

Lepidoptera pest in protected cropping conditions control targets such as *Helicoverpa armigera* and T*uta absoluta*. The loss of key pyrethroids and voltage-dependent sodium channel blockers against lepidoptera species would have a big impact and would see the effective loss an entire MoA group (22) in European protected vegetable production.

It is notable that if a number of insecticide Active Substances are lost on major crops, then there will be serious knock-on effect on minor crops within the vegetable sector since the availability of crop protection products are already limited.

Fruit crops Insecticides

Many insecticides used in fruit crops are already under severe regulatory pressure and are being lost under the 1107/2009 regulation in Europe. Further loss of key Active Substances would have serious effects on the ability to produce high quality fruit in Europe. Key producers of pome fruit include Poland, France, Germany, Italy and Spain. Stone fruit are grown in key countries such as Poland, France, Italy, Spain and Greece whilst citrus crops are grown primarily in Spain, Italy and Greece.

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[9] Lars Monrad Hansen. Crop Protection, Volume 23, Issue 1, January 2004, Pages 43-46 Economic damage threshold model for pollen beetles (Meligethes aeneus F.) in spring oilseed rape (Brassica napus L.) crops

[10] Russell Slater et al. Pest Management Science, Vol 67, issue 6,2011. Pyrethroid resistance monitoring in European populations of pollen beetle (Meligethes spp.): a coordinated approach through the Insecticide Resistance Action Committee (IRAC)

Some substances are an important tool for aphid control in IPM programmes. The potential loss of use against aphids *(e.g. Dysaphis plantaginea* and *Aphis pomi)* in speciality crops will lead to high levels of damages because beneficials in orchards are not good enough to control mentioned pests specially in the beginning of season.

Lepidoptera such as codling moths, leafrollers, and leaf miners are serious pests of pome, stone and citrus fruit crops, damaging leaves and fruit, reducing the quality of the fruit and consequently significantly impacting marketable yields. The Voltage-dependent sodium channel blockers MoA would be removed entirely and severely impact the ability to control lepidopteran pests in these crops.

Cereal Herbicides

The complete loss of the Inhibition of Phytoene Desaturase (MoA group 12) mode of action in autumn cereals would have impact on overall dicot weed control strategy as this mode of action is important for control of species which should not be left until spring (i.e V*iola* spp.*, Veronica* spp.). The loss of the Inhibition of Phytoene Desaturase (MoA group 12) mode of action and the ALS compound (MoA group 2), in autumn will dramatically impact the control of V*iola* spp.*, Veronica* spp., and leave no autumn herbicides in the market controlling those dicots weeds. Important countries include France, Spain, Romania, Poland, and Germany.

The loss of the ALS compounds (MoA group 2) approved in Europe for autumn application, would impact significantly the control of grasses like (*Bromus* spp.) in key countries such as France, Spain, Romania**,** and (*Apera spica venti)* in Romania, Poland, Czech Republic, Slovakia, and Germany.

The increased reliance on ALS and ACCase products for control of grasses in spring would further add to the resistance pressure.

Corn Herbicides

The loss of key AS in MoA group 27 would increase the pressure on the remaining ALS products to give broad spectrum post-emergence grass and dicot control, with resistance an increasing problem, especially in Echinochloa. The post-em diversity of HPPD, ALS, auxin and PSII chemistries in corn, used following pre-em chloroacetamides, has largely kept resistance to a minimum in Europe, but regulatory impacts on existing pre-em and post-em AS and the PFAS proposals could leave growers very short of options. Important corn countries include France, Germany, Spain Italy, Romania, Hungary & Poland.

Vines and Orchards herbicides

Today there is a limited number of AS on vines and orchards for the control of grass and broadleaf weeds. Further losses would impact AS across 3 MoA groups (2,14, and 1). Problem weeds like *Conyza* spp and *Lolium* spp. have limited effective control options and sustainable weed management of those crops will be severely challenged. These species have developed resistance to multiple mode of actions, the loss of multiple herbicides **(**flazasulfuron, penoxsulam, fluazifop, oxyfluorfen) for its management would exacerbate the already high weed pressures and increase development of resistance in countries such as Spain, Italy (*Conyza* spp and *Lolium* spp) and France (Lolium spp).

OECD Summary

Study Title

Aerobic soil metabolism of ^{14}C-trifluoromethoxybenzoic acid

Test Guidelines

OECD guideline 307
US EPA OPPTS 835.4100

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BASF Study Identification Number (Study ID)

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Report authors	Reinhard, K; Heck, C., P40 , D.
Report year	2023
Report title	**Aerobic soil metabolism of ^{14}C-trifluoromethoxybenzoic acid**
Report No.	NG 935316
Guidelines followed in study	EPA OPPTS 835.4100 (2008) OECD 307 (2002)
Test Facility	BASF SE, Agricultural Solutions Ecology and Environmental Analytics Speyerer Strasse 2 67117 Limburgerhof, Germany
Deviations from current test guideline	No
GLP	No

Executive Summary

In general, molecules carrying a CF_3-group are assumed to be non-degradable in the environment because of the very stable C-F-bond. And in cases where they are degradable, it is expected that they will form persistent transformation products.

The objective of the present aerobic soil metabolism study was to investigate if molecules carrying an O-CF_3-group can be degraded in soil in a way that the CF_3-group is partially or fully defluorinated so that the respective carbon atom can finally be degraded to CO_2.

As a model test compound, 4-(trifluoromethoxy)benzoic acid radio-labeled directly at the CF_3-group was chosen for performing an aerobic soil degradation study according to OECD guideline 307 with special analytical focus on the formation of $^{14}CO_2$.

For this, three soils from the Southwestern region of Germany (Li 10, LUFA 2.2, and LUFA 2.4) were treated with ^{14}C-trifluoromethoxy-labeled test item at a target application rate of 0.67 mg a.s./kg dry soil, which corresponds to a field application rate of 250 g a.s./ha, calculated on the basis of an equal distribution in the top 2.5 cm soil layer and a soil density of 1.5 g/cm³.

The soil moisture was adjusted to 40% of the maximum water holding capacity (MWHC). The soils were filled in 50 g portions in individual glass test vessels, treated and then incubated in the dark at a temperature of 20 ± 2 °C in a closed incubation system with continuous aeration for up to 56/57 days.

Soil samples were taken at day 0 and at seven additional sampling times throughout the entire incubation period. The sampling dates were 0, 1, 2, 3, 6/7, 10, 14, and 28 days after treatment (DAT). Volatiles were collected for each test container individually through dedicated trapping systems and sampled together with the respective test container (except at day 0). For each sampling time two replicate soil samples were worked up. One additional sampling was performed at 56/57 days in order to check if the decrease of the non-extractable residues is proceeding after 4 weeks of incubation.

The radioactivity in the volatile trapping solutions was analyzed by liquid scintillation counting (LSC). In order to check also for remaining transformation products in soil, the soil samples were consecutively extracted with 3 × 50 mL acetonitrile/water (9/1, v/v), 1 × 100 mL acetonitrile/water (1/1, v/v) and washed twice with 50 mL acetone. The individual extracts were

analyzed by LSC and combined fractions were concentrated and analyzed by radio-HPLC. The soil residue after extraction was dried under N_2 while being attached to another CO_2 trapping system. Aliquots of the dried soil were combusted to determine the amount of non-extractable residues (NER), so that a ^{14}C-mass balance could be provided for each sampling interval.

The radioactive test item peak in the soil extracts was confirmed by means of mass spectrometry and in addition by comparison of the retention time of the radiopeak in the soil extracts with the retention time of the ^{14}C-labeled test item in the application solution.

The results show that after 28 days the mineralization to CO_2 reached values between 61.8 and 72.7% of the total applied radioactivity (TAR).

The mass balances were > 90% TAR during the 28 days and ranged from 91.8 to 103.6% TAR. Only one sampling point with LUFA 2.2 showed a slightly lower mass balance of > 87.6%.

The amount of extractable radioactive residues decreased from ≥ 97.4% TAR at day 0 to values between 0.6 and 1.3% TAR after 28 days of incubation. The non-extractable residues increased from ≤ 2.6% TAR at day 0 to maxima of 45.5 to 54.5% TAR at 2-6 days, and then decreased to values between 26.0 and 37.8% TAR at 28 days and further to 22.9 and 31.1% TAR after 56/57 days.

The release of $^{14}CO_2$ from the soils continued even after the extractable radioactivity and thus the test item had reached negligible levels. The decline of NERs after 2-6 days suggests that the degradation of the $^{14}CF_3$-group proceeded despite the fact that the benzoic acid reacted with the organic matrix in soil and was partly incorporated into the humic substances.

Precipitation with $Ba(OH)_2$ as well as acidification with HCl of selected samples confirmed that the radioactivity trapped in the NaOH solutions is attributed to $^{14}CO_2$. Other volatile compounds were observed at levels ≤ 0.04% TAR.

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 after 6 - 14 days. Besides the parent compound, a few unidentified transformation products were detected, but all at levels ≤ 0.2% TAR.

Kinetic evaluation and calculation of $DegT_{50}$ and $DegT_{90}$ values (trigger endpoints) for the parent 4-(trifluoromethoxy)benzoic acid was performed following the recommendations of the FOCUS Kinetics workgroup. The obtained $DegT_{50}$ and $DegT_{90}$ values are given below.

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

Trigger endpoints at 12 °C were estimated using the Q_{10} approach, following the recommendations of the FOCUS Kinetics workgroup. The obtained $DegT_{50}$ and $DegT_{90}$ values are given 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

The results show that 4-(trifluoromethoxy)benzoic acid is rapidly degraded in soil. The only transformation reactions 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.

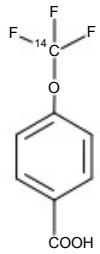
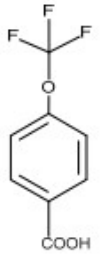
Overall, the experimental data show (1) that the presence of an OCF_3-group does not automatically leave a molecule persistent in the environment or lead to persistent degradation products and (2) that the C-F bond is not that stable as commonly postulated.

I. MATERIAL AND METHODS

A. MATERIALS

1. Test Material

A mixture of ^{14}C-radiolabeled and unlabeled 4-(trifluoromethoxy)benzoic acid was used for soil treatment. Detailed information on the test item is presented below.

Reg. No.:	4271078	
Chemical name (IUPAC):	4-(trifluoromethoxy)benzoic acid	
Molecular formula:	$C_8H_5F_3O_3$	
Molecular weight:	206.12 g/mol (unlabeled)	
Radiolabel:	trifluoromethoxy-^{14}C	unlabeled
Batch No.:	1353-1001	0001442922 (obtained from Sigma Aldrich)
Specific radioactivity (a.i.):	10.15 MBq/mg (609,000 dpm/µg)	n.a.
Chemical purity:	n.a.	99.9%
Radiochemical purity:	99.9%	n.a.
Solvent:	acetonitrile	none
Structural formula:		

2. Soil

Three different soils from Germany were used in this study, Li10, LUFA 2.2 and LUFA 2.4. Within five years prior to field soil collection, no plant protection products were applied to any of the soils.

All soils were passed through a 2 mm sieve and subsequently shipped to BASF. After arrival at BASF, all soils were stored in the dark at about 4 °C until further processing. The storage time between soil sampling and application of the test item was less than three months. One day before each application, the soil moisture was determined and 50 g dry soil equivalents each were filled into 18 test containers. The soil moisture was adjusted to 35% of the maximum water holding capacity (MWHC) by adding water to each test container. The test containers were closed and stored at room temperature over night.

An overview on the soil parameters is given below.

Soil designation Origin	**Li 10 (22/1680/03)** Limburgerhof, Germany	**LUFA 2.2 (22/736/03)** Hahnhofen, Germany	**LUFA 2.4 (22/1807/03)** Leimersheim, Germany
Textural class (USDA)	sandy loam	sandy loam	loam
Soil texture (USDA) [%] sand 0.050 – 2 mm silt 0.002 – 0.050 mm clay <0.002 mm	 70.1 23.4 6.5	 74.0 16.7 9.3	 41.2 42.0 16.8
Textural class (DIN 19682)	slightly loamy sand (Sl2)	medium loamy sand (Sl3)	slightly sandy loam (Ls2)
Soil texture (ISO 11277) [%] sand 0.063 – 2 mm silt 0.002 – 0.063 mm clay <0.002 mm	 68.4 24.5 7.1	 73.9 17.6 8.5	 35.9 45.2 18.9
Organic carbon [%]	1.07	2.14	2.14
Organic matter [%] [a]	1.84	3.69	3.69
pH ($CaCl_2$) [-]	5.04	5.45	7.46
pH (H_2O) [-]	6.06	6.25	8.16
Cation exchange capacity [$cmol^+/kg$]	2.8	6.8	18.8
Max. water holding capacity [g/100 g dry soil]	34.3	44.9	56.7
Microbial biomass [mg C/100 g dry soil]	30.8	71.4	153.0

[a] Calculated as organic matter = organic carbon × 1.724

B. STUDY DESIGN

1. Experimental conditions

Prior to application of the test item, soil moisture was checked and re-adjusted if necessary.

The target application rate was 0.67 mg a.s./kg dry soil, which corresponds to a field application rate of 250 g a.s./ha, calculated on the basis of an equal distribution in the top 2.5 cm soil layer and a soil density of 1.5 g/cm³.

An application solution was prepared by combining stock solutions of the labeled and unlabeled test item (in acetonitrile). The application solution was diluted in water and appropriate aliquots pipetted to the soil portions in the individual test containers. By addition of the water/application solution mixture, the moisture of all soils was finally brought to 40% MWHC. The soil portions were stirred with a spatula for homogenization. The number of vessels was sufficient to allow for duplicate sampling at each sampling time plus several reserve vessels. The total amount of organic solvent (from the application solution) added to soil was always ≤0.1%. The target application rate of 0.67 mg/kg was defined as 100% TAR (total applied radioactivity).

The 0 day samples were not incubated but worked up immediately. All other test vessels to be used for subsequent samplings were closed with caps equipped with air inlet and outlet tubes allowing a continuous air flow-through. The vessels were placed into a temperature-controlled incubation chamber and incubated in the dark at a temperature of 20 °C ± 2 °C. Throughout the incubation, the samples were continuously aerated with a slight stream of moistened air.

The exiting air went through a trapping system for volatiles consisting of a sequence of three gas washing flasks filled with:

(1) 45 mL ethylene glycol
(2) 45 mL 0.5 M NaOH
(3) 45 mL 2 M NaOH

Volatiles were led through a dedicated set of wash bottles for each test container.

The weight of the individual test vessels was monitored upon sampling to check the water content. Where necessary, evaporated water was replaced by deionized water.

2. Sampling

Eight sampling times were scheduled within 28 days after treatment (DAT). One additional sampling was performed after 56/57 days in order to check if the decrease of non-extractable residues is proceeding after 4 weeks of incubation. The individual sampling dates are summarized below:

Soil Li 10:	0, 1, 2, 3, 6, 10, 14, 28, (*57)* DAT
Soil LUFA 2.2:	0, 1, 2, 3, 6, 10, 14, 28, (*56)* DAT
Soil LUFA 2.4:	0, 1, 2, 3, 7, 10, 14, 28, (*56)* DAT

At each sampling time, two replicate test vessels were sampled together with their attached volatiles traps (except for day 0, where no traps were attached).

Prior to sampling, the flow rate of air through the sampled test containers was increased for 15 min and the test containers slightly tilted in order to release $^{14}CO_2$ present in the air space in the soil bulk so that it could be trapped and not escape during further sample workup.

Furthermore, the first extraction solution (see below) was added with the trapping systems still attached to the test containers. The resulting slurry was ultra-sonicated for 5 min and then put to rest for another 5 min with the air stream still running through the volatile traps. Only after that the trapping system was detached and soil extraction proceeded as described below. These steps proved necessary to catch the still remaining $^{14}CO_2$ in the soil bulk to obtain the required full material balance.

3. Description of analytical procedures

For each sampled test container, the complete amount of soil was removed and filled into a centrifuge tube. The soil was consecutively extracted three times for 30 min with 50 mL acetonitrile (ACN)/water (9/1, v/v) and once with 100 mL ACN/water (1/1, v/v), followed by two additional extractions for two to three minutes with 50 mL acetone, all on a laboratory shaker at 150 rpm. After each extraction step, the sample was centrifuged for 5 min at 4,200 rpm and the supernatant decanted. The extracts were adjusted to 50 mL or 100 mL (ACN/water 1/1 extract) with the respective extraction solvent mixture and aliquots of each extract were analyzed by LSC.

After extraction, the remnant soil was transferred back into the test container, attached to a new wash bottle with 45 mL 0.5 M NaOH and subjected to a constant stream of nitrogen for drying at room temperature. Two aliquots of the trapping solution were measured by LSC.

The ACN/water (9/1, v/v) extracts were combined, and the ACN/water (1/1, v/v) extract was combined with the acetone extracts, respectively. Aliquots of each pool solution were analyzed

by LSC. Aliquots of each pool solution were centrifuged, aliquots of the resulting supernatants measured by LSC, followed by concentration in a rotary evaporator at 40 °C. The concentrated solution was transferred to a 2 mL volumetric flask and made up to volume with ACN/water (1/9, v/v). Aliquots were measured by LSC. The remaining solution was centrifuged and aliquots of the supernatant measured by LSC and HPLC. HPLC measurements were conducted for all samples until 6/7 DAT, further samples were only measured if the total extracted radioactivity was at least 2.0% TAR.

Determination and characterization of non-extractable residues
For analysis of non-extractable residues (NER), the dried soil was ground in an analytical mill. Four aliquots were combusted, the released $^{14}CO_2$ was trapped in Oxysolve C-400 scintillator and analyzed by LSC.

Investigation of volatiles
The traps for volatiles were sampled together with the respective attached test container at each sampling time except for day 0. Three aliquots of each solution were analyzed by LSC.

To verify that the radioactivity in the NaOH traps originated from evolved $^{14}CO_2$, six samples of each application group were selected and 3 mL aliquots from the respective NaOH traps subjected to precipitation with $Ba(OH)_2$. The samples were treated with excess $Ba(OH)_2$*8 H_2O and centrifuged for 2 min at 13,000 rpm to precipitate the formed $BaCO_3$. Then the supernatants were analyzed by LSC. No significant amount of radioactivity was found in the supernatants (≤1.89% TAR), confirming that the trapped radioactivity corresponded to $^{14}CO_2$.

As a second verification step, 4 mL of the representative samples were transferred to a 5 mL volumetric flask and acidified with 0.6 mL concentrated HCl. The samples were made up to volume with water, subjected to ultrasonication and purged with nitrogen for 10 min in order to expel the released CO_2. Afterwards, no radioactivity (≤0.02% TAR) was detected in the solutions, thus confirming that the radioactivity previously found in the NaOH traps indeed originated from $^{14}CO_2$.

Mass spectrometry (MS)
MS was used to confirm the identity of the test item in application solutions and soil extracts. Identification was based on the determination of the specific isotope pattern caused by the labeled test item and on the calculation of the molecular formulae from the accurate masses of the detected ions achieved with ESI MS and ESI MS/MS. Structures in pool samples were assigned by comparison of the retention time and the MS/MS data with the test item.

4. Calculation of the degradation rate

Kinetic analysis and calculation of $DegT_{50}$ and $DegT_{90}$ values at 20 °C for the parent compound 4-(trifluoromethoxy)benzoic acid were performed following the recommendations of the FOCUS Kinetics workgroup [Ref. 1]. The analysis was done by non-linear regression methods using the software package CAKE (version 3.6). Replicate samples were taken into account for each sampling time. The $DegT_{50}$ and $DegT_{90}$ values at 12 °C were estimated using the Q_{10} approach according to FOCUS [Ref. 1].

II. RESULTS AND DISCUSSION

A. DISTRIBUTION OF RADIOACTIVITY AND MATERIAL BALANCE

The distribution of radioactive residues is presented in Table 1 - Table 3.

Within the 28 day incubation, the mass balances were complete (> 90% TAR) for all soils and sampling times, except for the 6 day sampling of Lufa 2.2 where one replicate reached only 85% (resulting in a mean value of 87.6%).

For the extended sampling after 56/57 days, lower mass balances were observed together with unusually high radioactivity values in the second NaOH trapping solutions (21.7 to 34.3% TAR). For each application group, the amount of CO_2 at 56/57 DAT was lower than the one at 28 DAT. This indicates that the low mass balances at 56/57 DAT are caused by losses of CO_2 due to the insufficient capacity of the NaOH trapping solutions to capture the still evolving $^{14}CO_2$.

Soil Li 10
The amount of radioactivity extracted with ACN/water 9/1 and 1/1 (v/v) and acetone from soil samples decreased from 102.7% TAR at day 0 to 1.3% TAR after 28 days.

The mineralization to CO_2 reached 72.7% TAR after 28 days. Non-extractable residues increased from 0.1% TAR on day 0 to a maximum of 45.5% TAR at 6 days, while falling again to 26.0 %TAR at 28 days and then further to 22.9% TAR after 57 days.

As described above, a slightly lower mineralization value of 66.6% TAR was observed after 57 days caused by volatile (CO_2) losses. Other volatiles were negligible and never exceeded 0.04% TAR.

Soil LUFA 2.2
The amount of radioactivity extracted with ACN/water 9/1 and 1/1 (v/v) and acetone from soil samples decreased from 97.4% TAR at day 0 to 0.7% TAR after 28 days.

The mineralization to CO_2 reached 63.9% TAR after 28 days. Non-extractable residues increased from 0.5% TAR on day 0 to a maximum of 50.6% TAR at 3 days, while falling again to 29.5% TAR at 28 days and then further to 25.9% TAR after 56 days.

As described above, a slightly lower mineralization value of 56.4% TAR was observed after 56 days caused by volatile (CO_2) losses. Other volatiles were negligible and never exceeded 0.01% TAR.

Soil LUFA 2.4
The amount of radioactivity extracted with ACN/water 9/1 and 1/1 (v/v) and acetone from soil samples decreased from 99.4% TAR at day 0 to 0.6% TAR after 28 days.

The mineralization to CO_2 reached 61.8% TAR after 28 days. Non-extractable residues increased from 2.6% TAR on day 0 to a maximum of 54.5% TAR at 2 days, while falling again to 37.8% TAR at 28 days and then further to 31.1% TAR after 56 days.

As described above, a slightly lower mineralization value of 54.1% TAR was observed after 56 days caused by volatile (CO_2) losses. Other volatiles were negligible and never exceeded 0.01% TAR.

Table 1 Distribution of radioactivity after application of ^{14}C-4-(trifluoromethoxy) benzoic acid on soil Li 10 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	101.1	1.6	102.8	0.0	n.a.	0.1	102.8
0	101.0	1.7	102.7	0.0	n.a.	0.1	102.8
0 mean	**101.0**	**1.7**	**102.7**	**0.0**	**n.a.**	**0.1**	**102.8**
1	92.7	2.1	94.7	3.2	0.01	6.1	104.0
1	93.4	2.2	95.6	2.7	0.01	4.9	103.2
1 mean	**93.0**	**2.1**	**95.2**	**2.9**	**0.01**	**5.5**	**103.6**
2	71.8	3.0	74.8	10.7	0.01	16.6	102.1
2	71.6	2.9	74.6	10.1	0.02	16.2	100.8
2 mean	**71.7**	**3.0**	**74.7**	**10.4**	**0.01**	**16.4**	**101.5**
3	57.7	2.8	60.5	16.5	0.05	24.1	101.2
3	51.1	2.7	53.9	19.4	0.03	28.8	102.1
3 mean	**54.4**	**2.8**	**57.2**	**17.9**	**0.04**	**26.4**	**101.6**
6	7.5	1.6	9.0	47.1	0.01	44.7	100.8
6	5.0	1.5	6.5	47.9	0.01	46.3	100.7
6 mean	**6.2**	**1.5**	**7.8**	**47.5**	**0.01**	**45.5**	**100.7**
10	6.8	1.3	8.0	49.8	0.01	42.6	100.4
10	1.9	0.9	2.8	53.5	0.02	39.5	95.9
10 mean	**4.3**	**1.1**	**5.4**	**51.6**	**0.01**	**41.1**	**98.1**
14	1.2	0.8	2.0	57.5	0.01	28.9	88.4
14	1.3	0.7	1.9	58.9	0.02	35.1	95.9
14 mean	**1.3**	**0.7**	**2.0**	**58.2**	**0.02**	**32.0**	**92.1**
28	0.9	0.4	1.3	72.5	0.02	25.1	98.9
28	0.9	0.4	1.3	72.8	0.01	27.0	101.1
28 mean	**0.9**	**0.4**	**1.3**	**72.7**	**0.02**	**26.0**	**100.0**
57	0.7	0.3	0.9	*69.3*[b]	0.01	22.7	92.9
57	0.6	0.3	0.9	*63.9*[b]	0.03	23.0	87.8
57 mean	**0.6**	**0.3**	**0.9**	***66.6***[b]	**0.02**	**22.9**	**90.4**

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

Table 2 Distribution of radioactivity after application of ^{14}C-4-(trifluoromethoxy) benzoic acid on soil LUFA 2.2 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	93.4	3.9	97.3	0.0	n.a.	0.5	97.8
0	93.5	4.1	97.6	0.0	n.a.	0.5	98.1
0 mean	**93.4**	**4.0**	**97.4**	**0.0**	**n.a.**	**0.5**	**97.9**
1	66.9	5.9	72.8	7.5	0.00	13.3	93.6
1	65.3	5.7	71.0	8.9	0.00	15.4	95.3
1 mean	**66.1**	**5.8**	**71.9**	**8.2**	**0.00**	**14.3**	**94.4**
2 [b]	21.7	1.4	23.0	24.4	0.01	45.4	92.9
2 [b]	28.2	1.6	29.7	22.4	0.01	42.9	95.0
2 mean	**24.9**	**1.5**	**26.4**	**23.4**	**0.01**	**44.1**	**94.0**
3	3.7	2.5	6.2	35.5	0.00	48.5	90.2
3	3.0	1.9	4.9	35.9	0.01	52.7	93.5
3 mean	**3.4**	**2.2**	**5.6**	**35.7**	**0.01**	**50.6**	**91.8**
6	1.6	0.6	2.2	41.2	0.00	46.7	90.1
6	1.5	0.6	2.1	41.3	0.00	41.6	85.0
6 mean	**1.5**	**0.6**	**2.1**	**41.3**	**0.00**	**44.2**	**87.6**
10	1.0	0.4	1.3	50.6	0.00	40.8	92.8
10	1.0	0.4	1.4	51.2	0.00	39.0	91.6
10 mean	**1.0**	**0.4**	**1.4**	**50.9**	**0.00**	**39.9**	**92.2**
14	0.7	0.3	1.0	58.4	0.00	35.7	95.1
14	0.8	0.3	1.1	56.2	0.00	35.6	92.9
14 mean	**0.8**	**0.3**	**1.1**	**57.3**	**0.00**	**35.6**	**94.0**
28	0.4	0.2	0.7	62.8	0.00	30.6	94.1
28	0.5	0.2	0.7	65.0	0.00	28.4	94.1
28 mean	**0.5**	**0.2**	**0.7**	**63.9**	**0.00**	**29.5**	**94.1**
56	0.3	0.2	0.5	*56.9* [c]	0.00	24.7	82.1
56	0.3	0.2	0.5	*55.9* [c]	0.01	27.0	83.4
56 mean	**0.3**	**0.2**	**0.5**	***56.4*** [c]	**0.01**	**25.9**	**82.8**

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] accidentally, the fourth extraction step (with ACN/H_2O 1/1, v/v) was carried out with 50 mL instead of 100 mL of extraction solvent at 2 days.
[c] values too low due to insufficient trapping of CO_2

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.

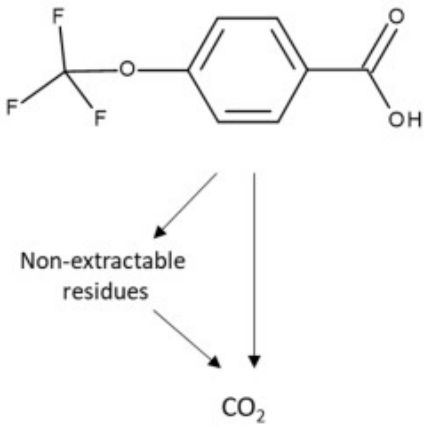


Figure 1 Proposed route of degradation for 4-(trifluoromethoxy)benzoic acid in soil

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.

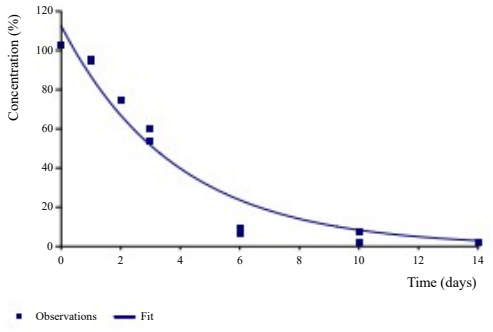
⇨ DFOP kinetic model provides a visually acceptable fit (very similar to SFO fit), but no improvement over SFO and FOMC; the χ^2 error is higher than for SFO and FOMC; the parameter g is estimated as 1 indicating that degradation is close to first-order kinetics.

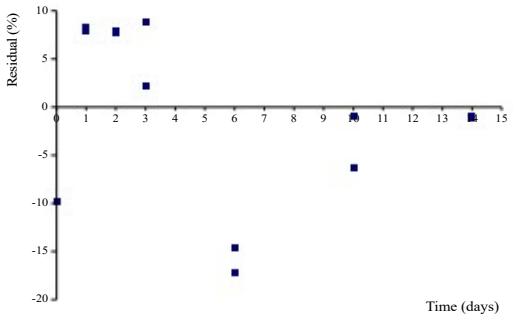
⇨ HS kinetic model improved the visual and statistical fit compared to SFO, FOMC and DFOP models. HS model provides a visually good fit; the fitted initial concentration matches well and the overall decline pattern is well represented, with no systematic deviations; χ^2 error is lower than for SFO kinetics;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

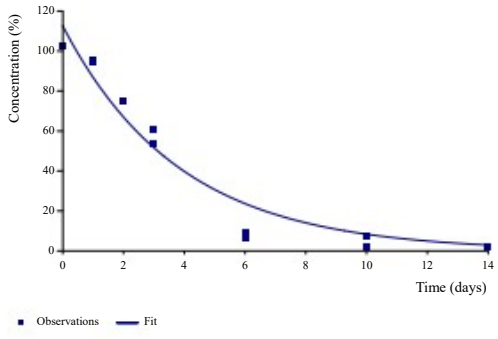
NA = Not applicable.
nd = Not determined. “Statistics may be missing because the covariance matrix could not be fully calculated. This may be because the higher-order model fitted is close to an SFO fit: g_Parent is approximately 1”
* Since α and β are no rate constants, t-test results were not reported.

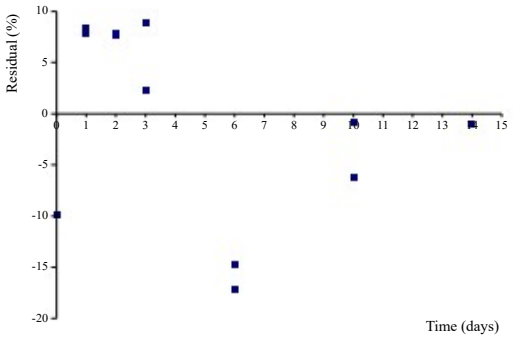
SFO



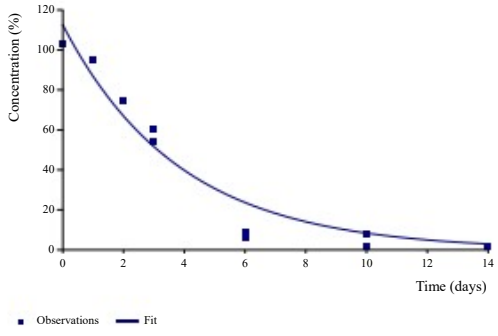


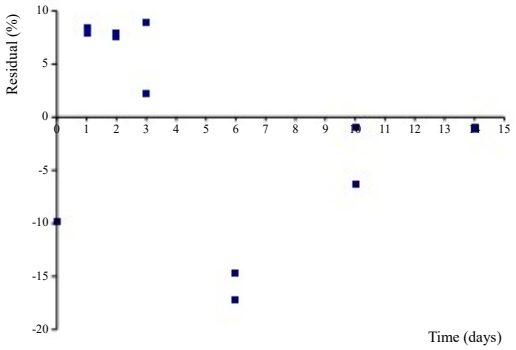
FOMC


Concentration (%)
Time (days)
Observations
Fit

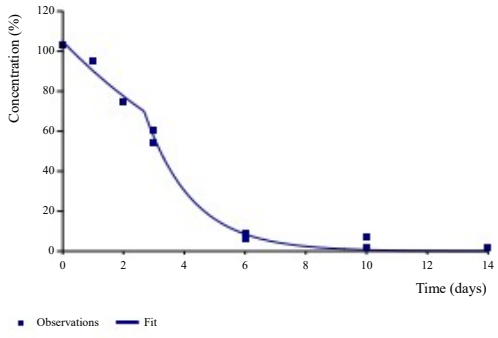

Residual (%)
Time (days)

DFOP


Concentration (%)
Time (days)
Observations
Fit


Residual (%)
Time (days)

HS


Concentration (%)
Time (days)
Observations
Fit

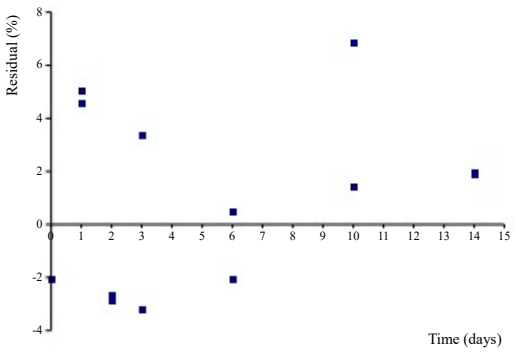

Residual (%)
Time (days)

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.

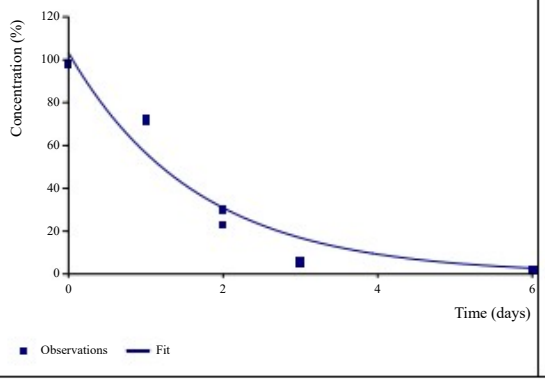
⇨ DFOP kinetic model provides a visually acceptable fit (very similar to SFO fit), but no improvement over SFO and FOMC; the χ^2 error is higher than for SFO and FOMC; the parameter g is estimated as 1 indicating that degradation is close to first-order kinetics.

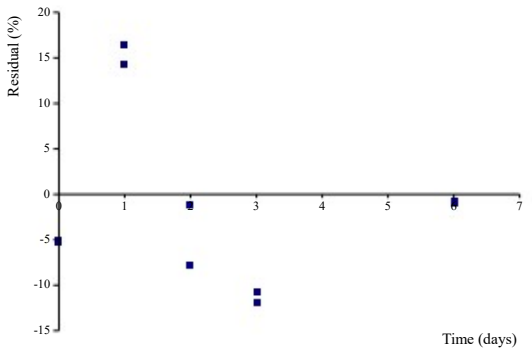
⇨ HS kinetic model provides a visually acceptable fit (very similar to SFO fit), but no improvement over SFO and FOMC; The parameter t_b is not adequately inside the observation range.

⇨ **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.

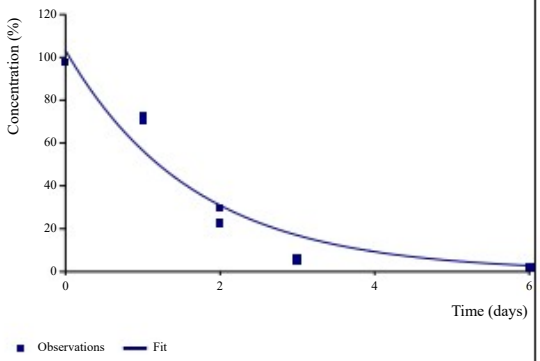
NA = Not applicable.
nd = Not determined “Statistics may be missing because the covariance matrix could not be fully calculated. This may be because the higher-order model fitted is close to an SFO fit: g_Parent is approximately 1”
* Since α and β are no rate constants, t-test results were not reported.

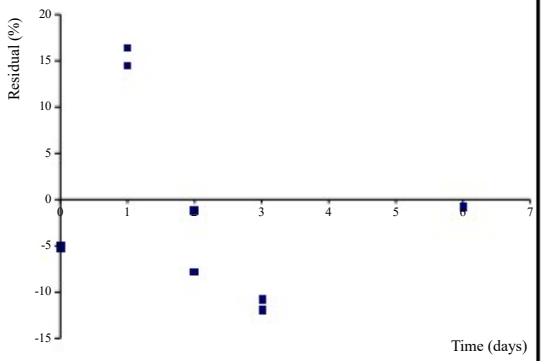
SFO



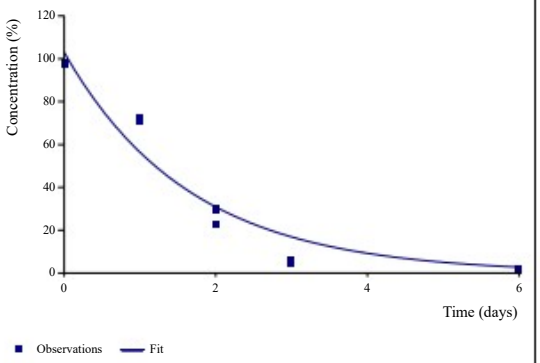


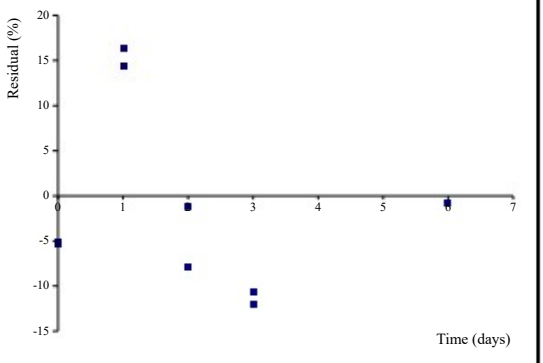
FOMC


Concentration (%)
Time (days)
Observations
Fit

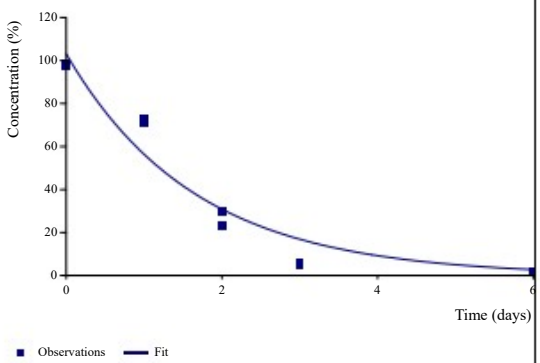

Residual (%)
Time (days)

DFOP


Concentration (%)
Time (days)
Observations
Fit


Residual (%)
Time (days)

HS


Concentration (%)
Time (days)
Observations
Fit

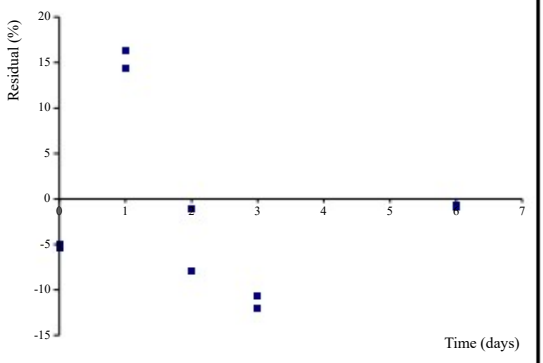

Residual (%)
Time (days)

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.

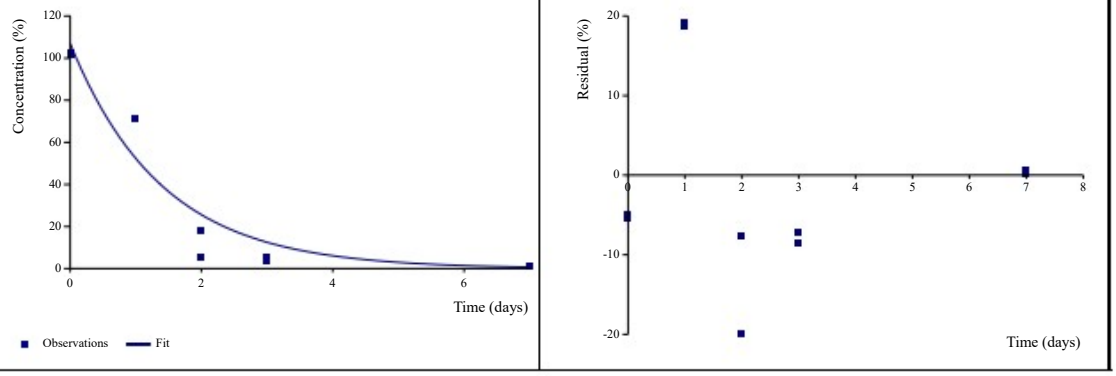
⇨ DFOP kinetic model provides a visually acceptable fit (very similar to SFO fit); but no improvement over SFO and FOMC; the χ^2 error is higher than for SFO and FOMC; the parameter g is estimated as 1 indicating that degradation is close to first-order kinetics.

⇨ 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.

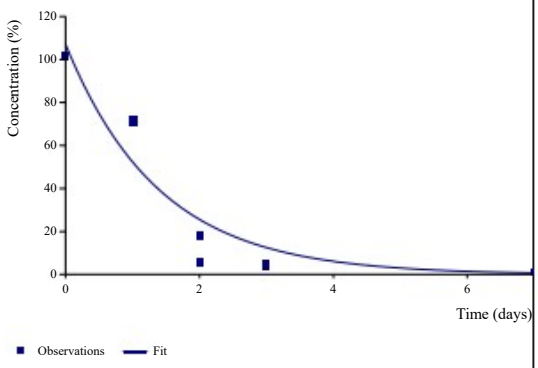
⇨ **Conclusion: HS** model is considered the best-fit model appropriate to derive trigger endpoints for ^{14}C-trifluoromethoxybenzoic acid: $DegT_{50}$ = 1.19 d, $DegT_{90}$ = 2.13 d.

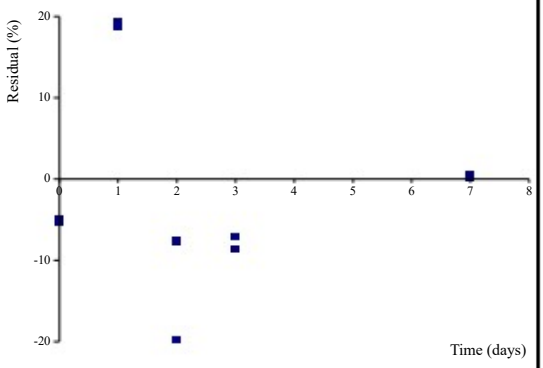
NA = Not applicable.
nd = Not determined “Statistics may be missing because the covariance matrix could not be fully calculated. This may be because the higher-order model fitted is close to an SFO fit: g_Parent is approximately 1”
* Since α and β are no rate constants, t-test results were not reported.

SFO

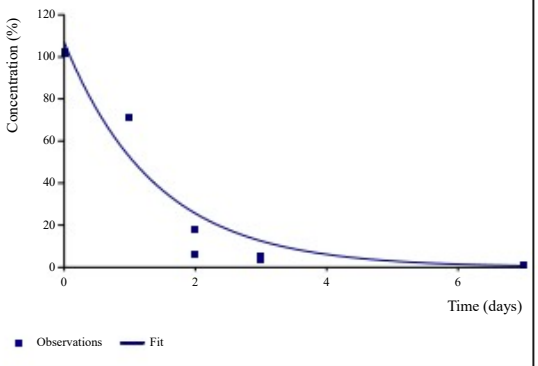


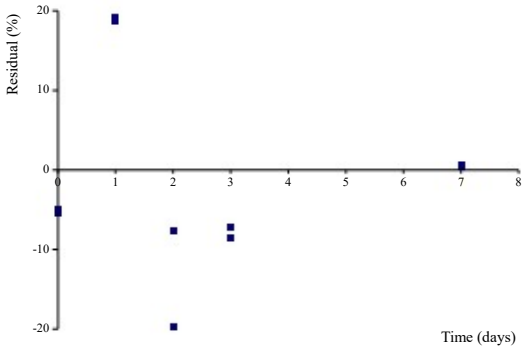
FOMC


Concentration (%)
Time (days)
Observations
Fit

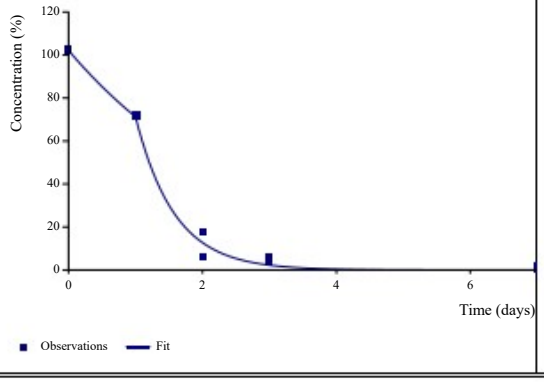

Residual (%)
Time (days)

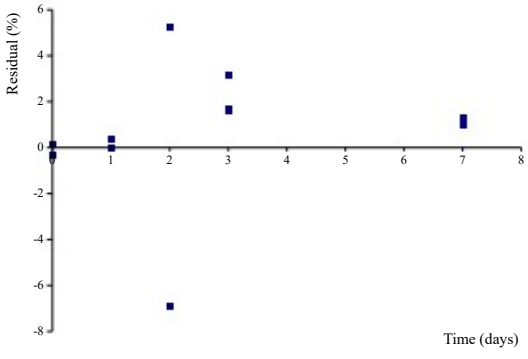
DFOP


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.

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

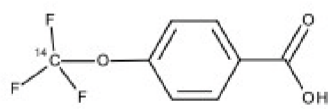
Within the upcoming “fire-fighting foam” and “universal” REACH restriction processes for PFAS, a chemical grouping concept is to be used in order to restrict all polyfluorinated alkyl substances (PFAS) falling under the respective PFAS definition. According to the call for evidence and currently available 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).

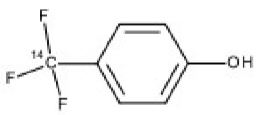
Single CF_3-groups are often used to improve the efficiency of active ingredients (e.g. in plant protection products or human or veterinary pharmaceuticals). Environmental as well as animal and plant metabolism studies performed within the regulatory EU approval processes clearly indicate that these 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 ($HO\text{-}CF_3$), 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 ($O\text{-}CF_3$ and $C\text{-}CF_3$ bonds) were chosen.



4-^{14}C-trifluoromethoxy benzoic acid



4-^{14}C-trifluoromethylphenol

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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

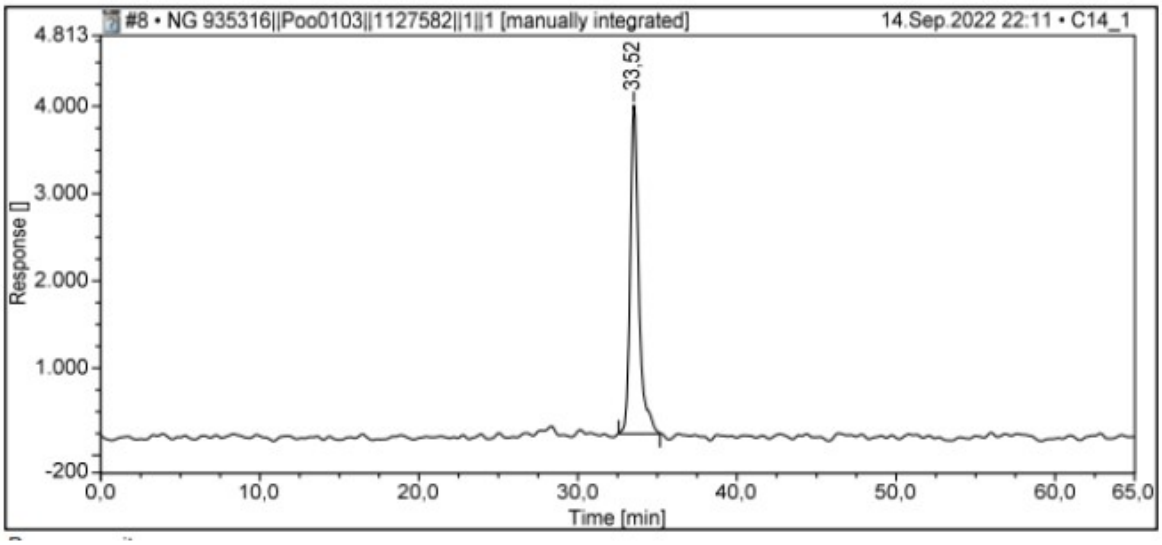
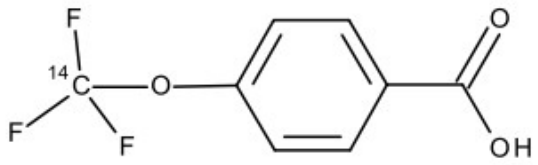


Figure 1: Radio-HPLC chromatogram of ACN/H2O (9:1) extract 1-3 of soil Li10, 6 days after treatment

Appendices

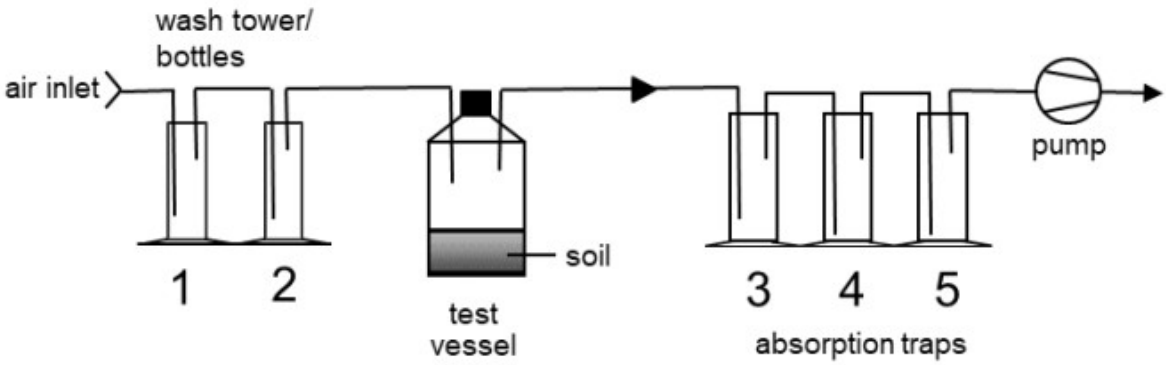
Appendix 1: Test item information

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

POSITION PAPER
POS/22/LO/35461

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.

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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.

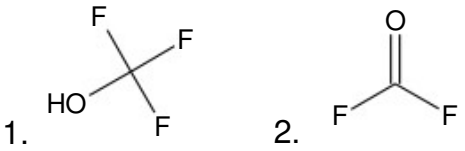


Figure 1. Model compounds: 1) trifluoromethanol (CF_3OH), and 2) carbonyl difluoride (CF_2O).

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.**

P17 *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 P17 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. P17 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).

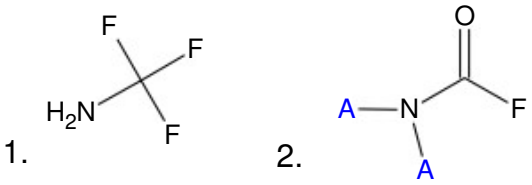


Figure 2. Model compounds: 1) trifluoromethylamine (CF_3NH_2), 2) carbamoyl fluoride (A,A'-NCOF).

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.

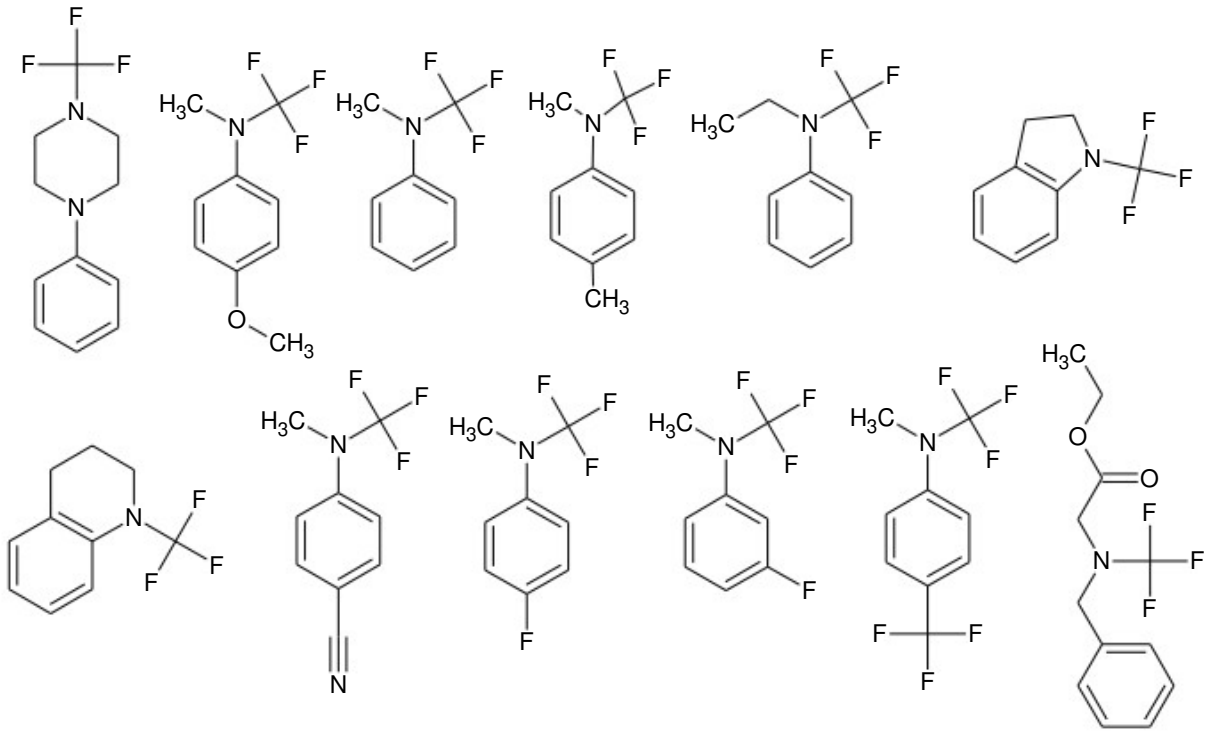


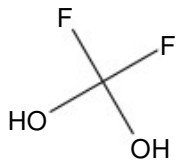
Figure 3. 12 model trifluoromethylamine compounds demonstrating hydrolysis within 72 hours (Schiesser et al (2020).

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.

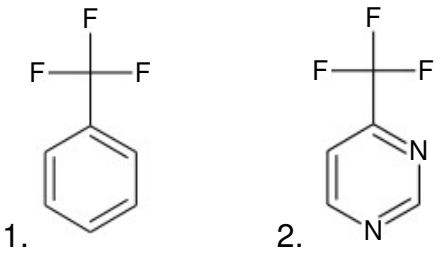
Minor biotransformation in humans of fluorinated benzodioxoles has been reported for the pharmaceutical Lumacaftor (FDA 2014). The biotransformation was not elaborated on in the regulatory document, but potential degradation pathways were recently proposed, both relying on arene oxidation followed by 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).



1. 2.

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.

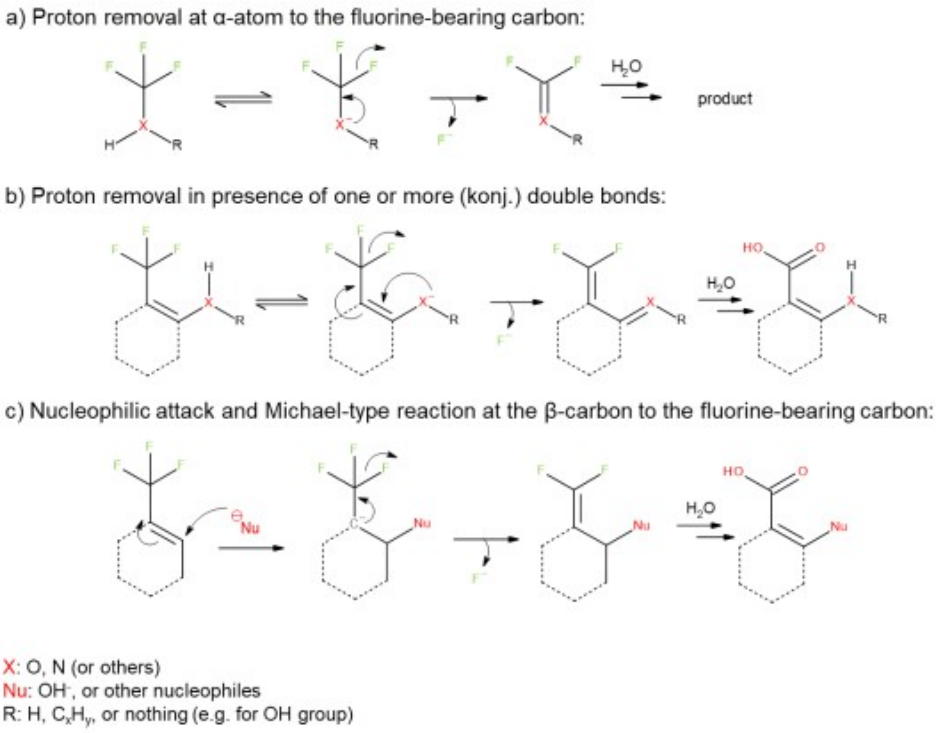
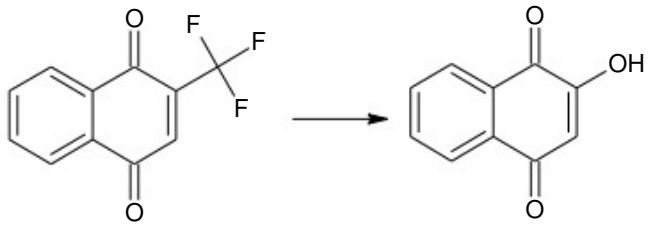


Figure 6. Schematic reaction mechanism as described by Sakai & Santi (1973). Especially reaction c) is described for enzymatic degradation in trifluoromethyl uracil derivates.

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).

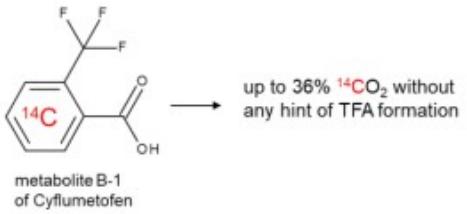


Figure 8. Soil degradation of 2-(trifluoromethyl)benzoic acid (metabolite B-1) of Cyflumetofen (data based on public version of *Cyflumetofen renewal dossier 2021*). Range of metabolite B-1 soil DT50s = 6.3 - 36.3 days (n=7).

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).

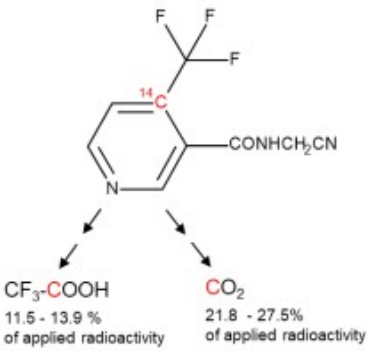


Figure 9. Soil degradation of insecticide Flonicamid (data based on public version of *Flonicamid renewal dossier 2020*). Range of Flonicamid soil DT50s = 0.3 – 1.9 days (n=4).

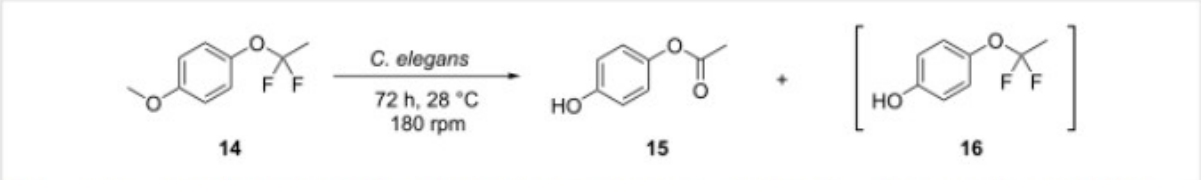
These findings show that (1) it is not the single CF_3-group which defines the potential persistence of a parent compound and (2) not every -CF_3 group results in formation of trifluoroacetic acid.

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.

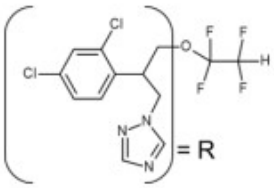


Figure 11. Structure of Tetraconazole

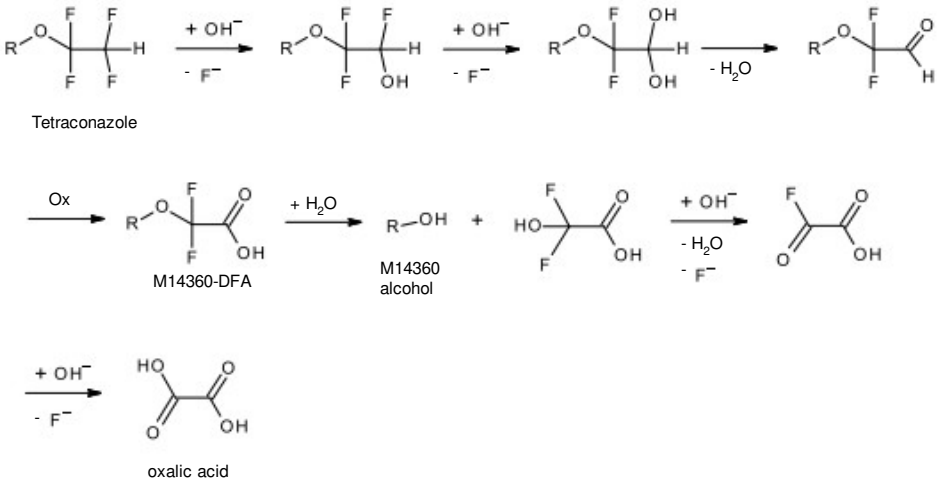


Figure 12. Reaction mechanisms at the tetrafluoroethoxy-group leading to the Tetraconazole metabolites M14360-DFA and M14360 alcohol in soil under photolytic conditions

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.

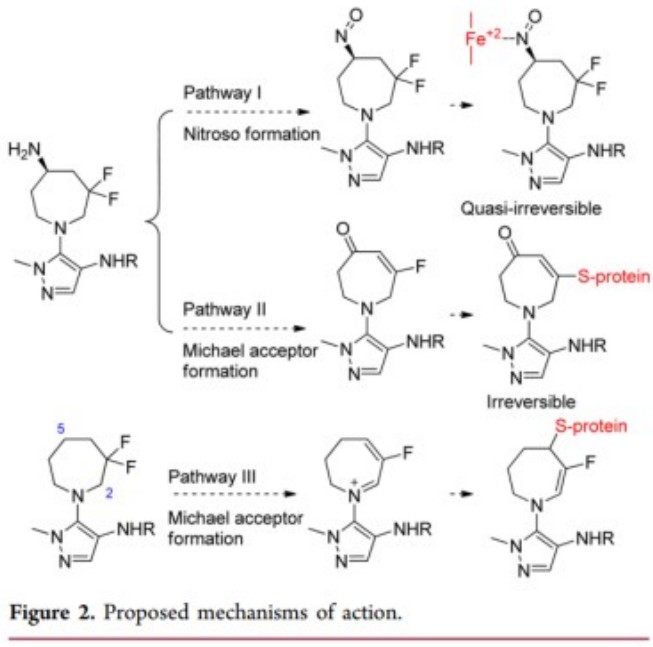


Figure 13. Metabolic displacement of a difluoromethylene group (Wang *et al* (2015))

4.5. (Trifluoromethyl)imidazole groups

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

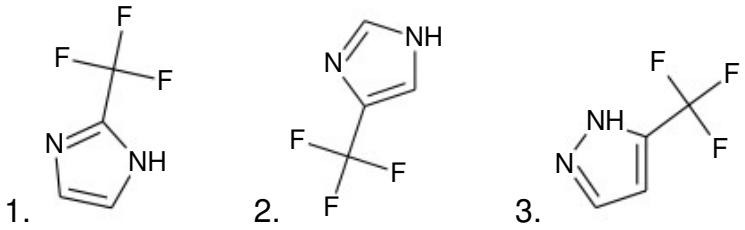


Figure 14. Model structures 1) 2-(trifluoromethyl)-1H-imidazole, 2) 4-(trifluoromethyl)-1H-imidazole, 3) 5-(trifluoromethyl)-1H-pyrazole

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.**

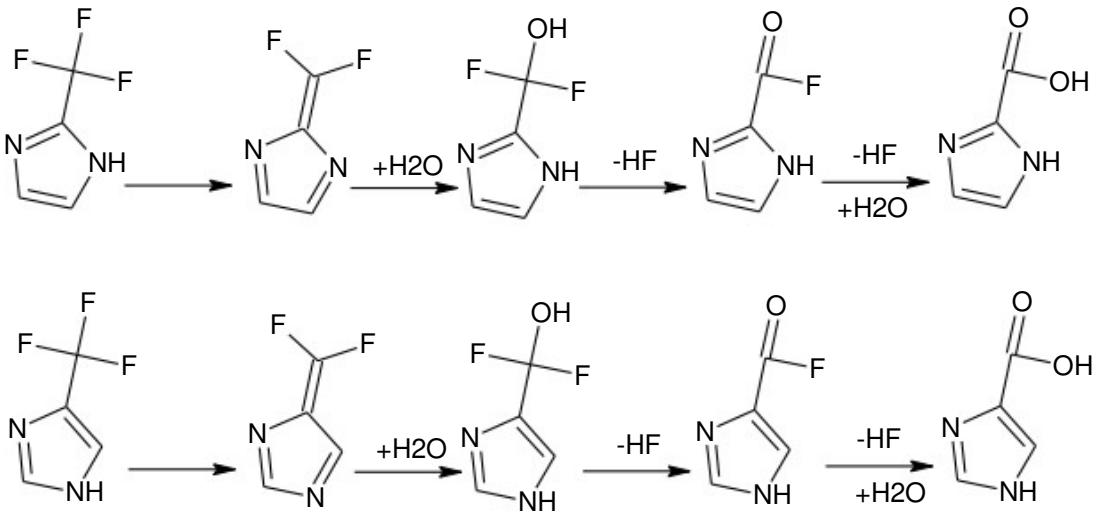


Figure 15. Hydrolysis of 2 and 4-trifluoromethylimidazole according Hayakawa et al (1998) under alkaline laboratory conditions. At pH=9 (30°C) 2-(trifluoromethyl)-1H-imidazole has a half-life of 80h, and 4-trifluoromethylimidazole a half-life of 200h.

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.

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

Buszek, R. J. & Francisco, J. S. (2009): The Gas-Phase Decomposition of CF3OH with Water: A Radical-Catalyzed Mechanism. Journal of Physical Chemistry A, 113, 5333–5337.

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

Ermolenko, M.S., Guillou, S., Janin, Y.L. (2012) Pyrazole-3/5-carboxylic acids from 3/5-trifluoromethyl NH-pyrazoles. Tetrahedron; 69: 257-263.

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

Fischer, G.W. (1993) Tetrazole compounds. 8[1]. Synthesis of tetrazolylpyrimidines from tetrazolyl substituted enamino ketones. J. Heterocyclic Chem.; 30: 1517-1519.

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

Hayakawa, Y., Kimoto, H., Cohen L.A., Kirk, K.L. (1998) Synthesis of (trifluoromethyl)imidazoles with additional electronegative substituents. An approach to receptor-activated affinity labels. J. Org. Chem.; 63: 9448-9454.

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

P17 , W. F. et al. (1995) Atmospheric Chemistry of CF3OH: Is Photolysis Important? Environ. Sci. Technol. 29(1), 247–250.

P17 , 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. Georg Thieme Verlag.

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

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