MINISTERIO
PARA LA TRANSICIÓN ECOLÓGICA
Y EL RETO DEMOGRÁFICO

SUBSTANCE EVALUATION CONCLUSION and

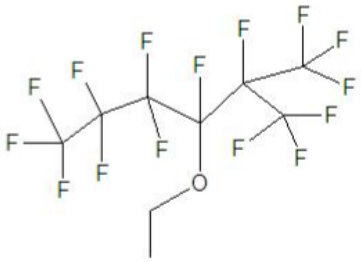
EVALUATION REPORT

for

3-ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)-hexane

EC No 435-790-1/List 608-415-4

CAS No 297730-93-9



Evaluating Member State Competent Authority:
Spain

Dated: 29 April 2024

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2018

Before concluding the substance evaluation a Decision to request further information was issued on: 21 August 2018

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

3-ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)-hexane (HFE-7500) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected PBT/vPvB
- Exposure of environment
- Wide dispersive use

During the evaluation no other concern was identified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table 2-1. Overview of other processes / EU legislation

No other processes	CCH	TPE	GMT	Previously on CoRAP	Annex VI (CLP)	Annex XVII (Restriction)	Candidate List/Annex XIV (Authorisation)
☐	☒	☐	☐	☐	☒	☐	☐

Other EU legislation	Previous legislation	Stockholm convention	Other
PPP/BPR	NONS/RAR	POP	(e.g., UNEP)
☐	☐	☐	☐

HFE-7500 is included in the Annex VI of the Regulation (EC) Nº 1272/2008 (CLP Regulation) with the index number 603-224-00-2.

ECHA conducted a comprehensive compliance check on the Substance registration dossier, which was concluded in 2022 with no decision issued.

The German, Dutch, Swedish, Danish and Norwegian Member State Competent Authorities (MCSAs) have submitted a proposal for a universal restriction on per- and polyfluoroalkyl substances (PFASs) under REACH[2]. It addresses the manufacture, placing on the market, as well as all uses of PFASs as such and as constituents in other substances, in mixtures and in articles above a certain concentration unless a specific derogation has been formulated for a use. The Substance and its uses fall in the scope of the restriction proposal. The restriction proposal process is still ongoing.

3. CONCLUSION OF SUBSTANCE EVALUATION

The above concerns identified for substance evaluation were analysed. The evaluation of the available information on the Substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

[2] https://echa.europa.eu/documents/10162/f605d4b5-7c17-7414-8823-b49b9fd43aea

Table 3-1. Conclusion and regulatory follow-up action

Initial and additional concern	Conclusion on concern	Regulatory follow-up action
PBT/vPvB	Concern confirmed (vPvB)	Restrictions
Exposure of environment	Inconclusive	Restrictions
Wide dispersive use	Concern removed (Registrant actions to ensure safety)	No need for regulatory follow-up at EU level

vPvB. The vP criterion is considered to be fulfilled based on a requested OECD TG 308 assay and the vB criterion is considered to be fulfilled for aquatic organisms as the BCF is greater than 5000 L/kg in fish. It is not possible to conclude on whether the T criterion is fulfilled.

Exposure of environment. According to the consideration of a vPvB substance minimisation of emissions and exposure must be ensured for the Substance. In the current registration dossier, only industrial use in closed systems is reported. However, due to the high volatility of the Substance, emissions to air cannot be excluded during use, equipment charging and cleaning.

Wide dispersive use. According to information in the initial registration dossier (2010) the Substance was used as a functional fluid at industrial sites and by professional workers. Furthermore, article service-life in vehicles covered by the End-of-Life Vehicles (ELV) directive and in machinery, mechanical appliances, electrical/electronic articles covered by the Waste Electrical and Electronic Equipment (WEEE) directive was reported. However, according to the latest updated dossier only industrial uses in closed systems are registered.

Due to the high persistence and bioaccumulation of the Substance, and the fact that the Substance and its degradation product perfluorobutyric acid (PFBA) belong to the group of extremely persistent per- and polyfluorinated alkyl substances (PFAS), the eMSCA considers that it cannot be ensured that risks are adequately controlled and therefore, information confirming minimization of exposure should be provided. Such information may be obtained through another regulatory process. The Substance will likely be covered by the universal PFAS restriction currently under development.

Therefore, the eMSCA concludes that no further information is requested under this Substance Evaluation.

4. Regulatory follow up actions at EU level

4.1. Harmonised Classification and Labelling

As explained in Section 16, the vP and vB criteria are fulfilled. An update of the existing harmonised classification is proposed considering the new environmental hazard class vPvB in the CLP Regulation, updated in the Commission delegated Regulation (EU) 2023/707[3].

The following hazard class needs to be added after the publication of the Commission Delegated Regulation 2023/707[3]: vPvB with the hazard statement:

> Strongly accumulates in the environment and living organisms including in humans; EUH441

4.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not proposed at the moment. As the vPvB identification can be done under the CLP Regulation and the Substance is expected to be covered by the generic PFAS restriction, it is not foreseen that an identification as SVHC is needed for the Substance.

4.3. Restriction

Restrictions may be introduced, when there is an unacceptable risk to human health or the environment arising from the manufacture, placing on the market and use of a substance, and the risk needs to be addressed on a Community-wide basis. The Substance, with concluded vPvB properties, and its uses fall in the scope of the proposed universal restriction of PFAS currently under development at EU level. The eMSCA supports this risk management option for the Substance. In case the Substance or its uses will not be covered by the final PFAS restriction, an RMOA will be proposed.

4.4. Other EU-wide regulatory risk management measures

No other EU regulatory measures are considered to be needed at this stage.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Not applicable for this substance. See section 4 for the proposed regulatory actions.

5.2. Other actions

Not applicable.

[3] COMMISSION DELEGATED REGULATION (EU) 2023/707 of 19 December 2022 amending Regulation (EC) No 1272/2008 as regards hazard classes and criteria for the classification, labelling and packaging of substances and mixtures.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions (RoI).

Table 6-1. Follow-up actions

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Harmonised classification	To be decided	Depending on the outcome of the universal PFAS restriction proposal, the eMSCA may submit a RoI for CLH.
Restriction	ongoing	The Substance is expected to be covered by the universal restriction of PFAS proposed by DE, NL, SE, DK and NO MSCAs and which is currently under development.
RMOA	To be decided	In case the Substance or its uses will not be covered by the final universal PFAS restriction, an RMOA will be proposed by the eMSCA.

Part B. Substance evaluation report

7. Overview of the Substance Evaluation Performed

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to suspected PBT/vPvB, exposure of the environment and wide dispersive use, the Substance, 3-ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)-hexane (or HFE-7500) was included in the Community rolling action plan (CoRAP) for substance evaluation pursuant to Article 44(2) of REACH to be evaluated in 2018. The Competent Authority of Spain was appointed to carry out the evaluation.

Pursuant to Article 45(4) of REACH, the Competent Authority of Spain initiated the substance evaluation for Reaction mass of 3-ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)-hexane, (EC No 435-790-1) based on registration(s) submitted by the Registrant(s) and other relevant and available information.

The evaluating MSCA considered that further information was required to clarify the suspected PBT/vPvB concern. Therefore, it prepared a draft decision pursuant to Article 46(1) of REACH to request further information.

A unanimous agreement of the Member State Committee on the draft decision was reached in its MSC-70 meeting. ECHA notified the registrant(s) of the decision pursuant to Article 51(6) of REACH on 10 September 2020 requesting an aerobic/anaerobic water-sediment persistency study (OECD TG 308).

In accordance with Article 46(2) of REACH, the registrant(s) updated their dossier on 15 April 2023 with an aerobic/anaerobic water-sediment study applying measures to avoid volatilisation of the substance. In accordance with Article 46(3) of REACH, the evaluating Member State started the second round of the evaluation without undue delay.

In accordance with Article 46(4) of REACH, the evaluating Member State finished its evaluation activities within 12 months of the information being submitted by registrants. The eMSCA concluded that the Substance is vPvB after the analysis of the information requested in the decision issued on 10 September 2020 and other available information.

8. Substance identity

The information on the Substance, including identifiers and structural formula, can be found on the cover page. For more details see ECHA: https://echa.europa.eu/home

Synonyms:

HFE-7500

8.1. Type of substance

Based on analytical information in the registration dossier, HFE-7500 is identified as a mono constituent substance.

8.2. Other relevant information

In the OECD TG 308 study, perfluorobutyric acid (PFBA) and 1H-heptafluoropropane (HFC-227) were identified as degradation products of the Substance.

1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)hexan-3-yl acetate and 1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)hexan-3-yl formate were identified as transformation products for HFE-7500 in photo transformation kinetics laboratory studies (Goto et al. 2002, Rodriguez et al. 2014).

Table 8-1. 2,2,3,3,4,4,4-heptafluorobutanoic acid

DEGRADATION PRODUCT	
Public name:	2,2,3,3,4,4,4-heptafluorobutanoic acid
EC number:	206-786-3
CAS number:	375-22-4
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	$C_4HF_7O_2$
Molecular weight range:	214.039 g/mol
Smiles	C(=O)(C(C(C(F)(F)F)(F)F)(F)F)O
Synonyms:	Perfluorobutyric acid (PFBA) Heptafluorobutyric acid

Structural formula:

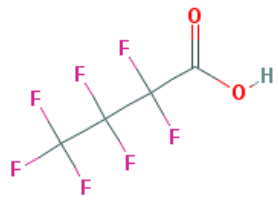


Table 8-2. 1H-heptafluoropropane (HFC-227)

DEGRADATION PRODUCT	
Public name:	1H-heptafluoropropane (HFC-227)
EC number:	811-906-8
CAS number:	2252-84-8
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C3HF7
Molecular weight range:	170 g/mol

Smiles	

Structural formula:

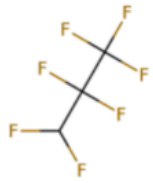


Table 8-3. 1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)hexan-3-yl acetate

DEGRADATION PRODUCT	
Public name:	1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)hexan-3-yl acetate
EC number:	
CAS number:	
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C9H3F15O2
Molecular weight range:	428.097 g/mol
Smiles	CC(=O)OC(F)(C(F)(F)C(F)(F)C(F)(F)F)C(F)(C(F)(F)F)C(F)(F)F

Structural formula:

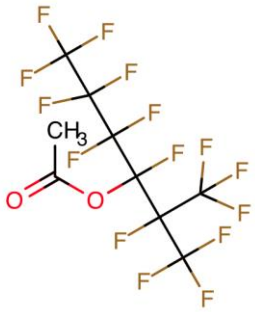
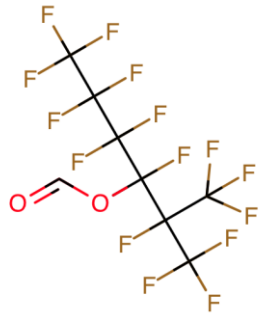


Table 8-4. 1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)hexan-3-yl formate

DEGRADATION PRODUCT	
Public name:	1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)hexan-3-yl formate
EC number:	

CAS number:	
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C8HF15O2
Molecular weight range:	414.07 g/mol
Smiles	C(=O)OC(F)(C(F)(F)C(F)(F)C(F)(F)F)C(F)(C(F)(F)F)C(F)(F)F

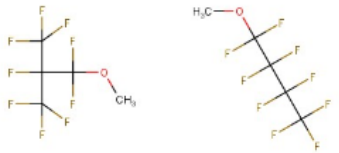
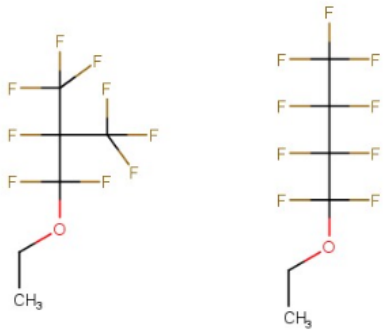
Structural formula:

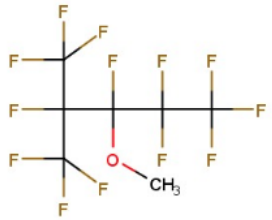
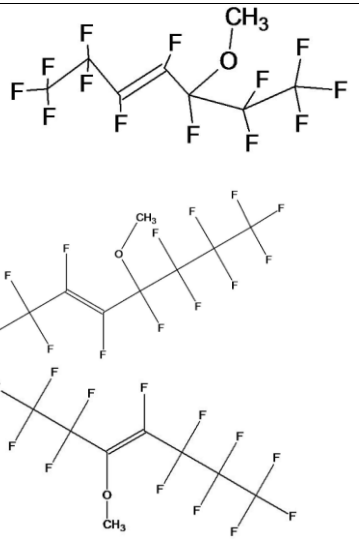


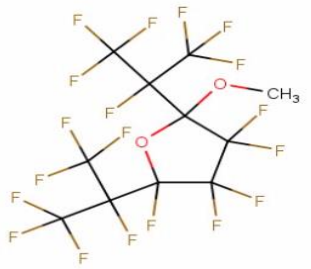
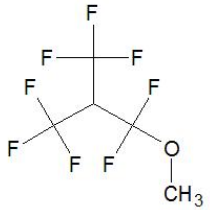
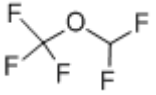
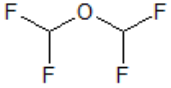
8.3. Analogue substance (read-across)

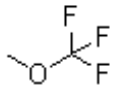
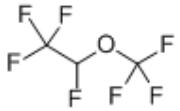
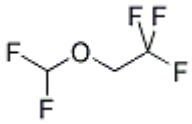
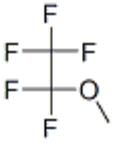
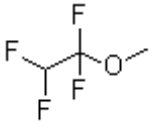
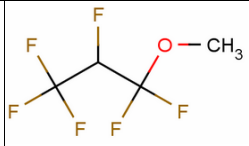
HFE-7500 is a segregated hydrofluoroether with a completely fluorinated region and a hydrocarbon region. It belongs to the hydrofluoroethers (HFEs) group (see below table).

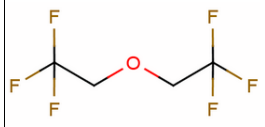
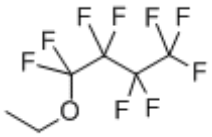
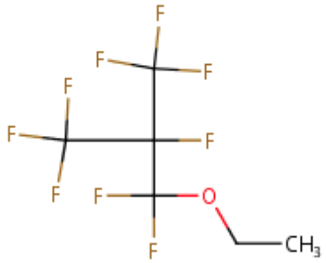
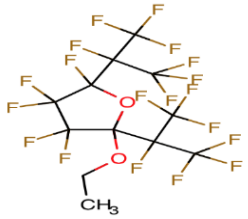
Table 8-5. Identified HFEs.

IUPAC name	HFEs	CAS number	EC number	Mol formula	MW	Mol structure/smiles	Principal probable uses
8.3.1.1.1.1. Registered under REACH							
3M(TM) NOVEC(TM) ENGINEERED FLUID HFE-7000			484-450-7				
Propane, 2-(difluoromethoxymethyl)-1,1,1,2,3,3,3-heptafluoro-	HFE-7100	163702-08-7	422-270-2	C4F9OCH3	250		Cleaning solvent
reaction mass of: 1-ethoxy-1,1,2,3,3,3-hexafluoro-2-(trifluoromethyl)propane 1-ethoxy-1,1,2,2,3,3,4,4,4-nonafluorobutane	HFE-7200	-	425-340-0	C6H5F9O	264	 CCOC(C(C(C(F)(F)F)(F)F)(F)F)(F)F	

IUPAC name	HFEs	CAS number	EC number	Mol formula	MW	Mol structure/smiles	Principal probable uses
						C(OC(F)(F)C(F)(C(F)(F)F)C(F)(F)F)C	
1,1,1,2,2,3,4,5,5,5-decafluoro-3-methoxy-4-(trifluoromethyl)pentane	HFE-7300	132182-92-4	459-520-5	C7H3F13O	350	 COC(F)(C(F)(F)C(F)(F)F)C(F)(C(F)(F)F)C(F)(F)F	Cleaning solvent, heat transfer fluid
Reaction mass of (3E)-1,1,1,2,2,3,4,5,6,6,7,7,7-tridecafluoro-5-methoxyhept-3-ene and (2E)-1,1,1,2,3,4,5,5,6,6,7,7,7-tridecafluoro-4-methoxyhept-2-ene and (3E)-1,1,1,2,2,4,5,5,6,6,7,7,7-tridecafluoro-3-methoxyhept-3-ene	-	-	700-755-2	C8H3F13O	362		Cleaning solvent, heat transfer fluid

IUPAC name	HFEs	CAS number	EC number	Mol formula	MW	Mol structure/smiles	Principal probable uses
2,3,3,4,4-pentafluoro-5-methoxy-2,5-bis[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]tetrahydrofuran		957209-18-6	812-244-2	C11H3F19O2	528	 COC1(C(C(C(O1)(C(C(F)(F)F)(C(F)(F)F)F)F)(F)F)(F)F)C(C(F)(F)F)(C(F)(F)F)F	Heat transfer fluid
2-[difluoro(methoxy)methyl]-1,1,1,3,3,3-hexafluoropropane	-	382-26-3	609-534-4	C5H4F8O	232	 **8.3.1.1.1.2.** FC(F)(F)C(C(F)(F)F)C(F)(F)OC	Intermediate use only
8.3.1.1.1.3. Not registered under REACH							
pentafluorodimethyl ether	HFE-125	3822-68-2	-	CF3OCF2H	136	 O(C(F)F)C(F)(F)F	Refrigerant
1,1,3,3-tetrafluorodimethyl ether	HFE-134	1691-17-4	-	CHF2OCHF2	118	 O(C(F)F)C(F)F	Refrigerant, blowing agent

IUPAC name	HFEs	CAS number	EC number	Mol formula	MW	Mol structure/smiles	Principal probable uses
1,1,1-Trifluoromethyl methyl ether	HFE-143a	421-14-7	-	CF3OCH3	100	 COC(F)(F)F	Refrigerant
1,1,1,2-tetrafluoro-2-(trifluoromethoxy)ethane	HFE-227me	2356-62-9	-	CF3OCFHCF3	186	 FC(C(F)(F)F)OC(F)(F)F	Dry etching agent, refrigerant
difluoromethyl-2,2,2-trifluoroethyl ether	HFE-245mf	1885-48-9	413-830-7	CF3CH2OCF2H	150	 C(C(F)(F)F)OC(F)F	Blowing agent, refrigerant
Pentafluoroethyl methyl ether	HFE-245mc	22410-44-2	-	CF3CF2OCH3	150	 COC(C(F)(F)F)(F)F	Refrigerant, blowing agent
1,1,2,2-tetrafluoroethyl methyl ether	HFE-254pc	425-88-7	207-039-4	CHF2CF2OCH3	132	 COC(C(F)F)(F)F	Refrigerant, blowing agent
1,1,2,3,3,3-Hexafluoropropyl Methyl Ether	HFE-356mec	382-34-3	609-536-5	CF3CHFCF2OCH3	182	 COC(C(C(F)(F)F)F)(F)F	Blowing agent, refrigerant

IUPAC name	HFEs	CAS number	EC number	Mol formula	MW	Mol structure/smiles	Principal probable uses
Bis(2,2,2-trifluoroethyl) Ether	HFE-356mff	333-36-8	626-793-9	CF3CH2OCH2CF3	182	 C(C(F)(F)F)OCC(F)(F)F	Refrigerant
Butane, 1-ethoxy-1,1,2,2,3,3,4,4,4-nonafluoro-	HFE-7200 (HFE-569mccc)	163702-05-4	922-358-5	C6H5F9O	264	 CCOC(C(C(C(F)(F)F)(F)F)(F)F)(F)F	
Ethyl nonafluoroisobutyl ether	HFE-7200 (HFE-569mccc) Novec 7200	163702-06-5	639-027-3	C6H5F9O	264	 C(OC(F)(F)C(F)(C(F)(F)F)C(F)(F)F)C	Cleaning solvent
2-Ethoxy-3,3,4,4,5-pentafluoro-2,5-bis[(1,2,2,2-tetrafluoro-1-trifluoromethyl)ethyl] tetrahydrofuran	HFE-7800	-	484-410-9	C12H5F19O2	542		

IUPAC name	HFEs	CAS number	EC number	Mol formula	MW	Mol structure/smiles	Principal probable uses
						CCOC1(OC(F)(C(F)(C(F)(F)F)C(F)(F)F)C(F)(F)C1(F)F)C(F)(C(F)(F)F)C(F)(F)F	

9. Physico-chemical properties

Table 9-1. Physico-chemical properties

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Clear liquid
Vapour pressure	0.847 kPa at 20° C (OECD TG 104)
Water solubility	21.3 µg/L at 23° C (ETS-8-172.3, similar to OECD TG 105)
Partition coefficient n-octanol/water (Log Kow)	6.0 at 23°C (shake flask method, OPPTS 830.7550) 5.75 at 30°C (HPLC method, OECD 117) There is uncertainty in the measured log Kow values as the Shake Flask Method, according to the OECD 107, is applicable for substances with log Kow up to 4, and the OECD 117 study had several deviations from the guideline.
Melting point	<-81ºC (ECHA dissemination website)
Boiling point	129ºC (at 101.3kPa) (ECHA dissemination website)

10. Manufacture and uses

10.1. Quantities

The aggregated tonnage (per year) of the Substance is 10 - 100 tonnes.

10.2. Overview of uses

Based on the updated (2023) registration information, HFE-7500 is used as functional fluid (heat transfer fluid) only at industrial sites in closed systems. Previously, uses by professional workers and article service-life were also reported in the registration dossiers.

Hydrofluoroethers (HFEs) are being used as third generation replacements to chlorofluorocarbons (CFCs), hydrochlorofluorocarbons (HCFCs), hydrofluorocarbons (HFCs) and perfluorocarbons (PFCs) because of their nearly zero stratospheric ozone depletion and relatively low global warming potential (Tsai, 2005). However, there are other properties (*i.e.*, high volatility and long atmospheric lifetime) that should also be considered.

HFEs have been developed for commercial and industrial uses as refrigerants, cleaning solvents, foaming agents and dry etching agents:

- Refrigerants: HFCs have been used in domestic refrigerators, freezers and air conditioners as replacements for CFCs and HCFCs (phase out under the Montreal Protocol). As HFCs have been targeted as greenhouse gases (GHGs) in the Kyoto Protocol and are included for phase-down under the Montreal Protocol, HFEs will

gradually increase in use with more extensive applications because of their lower cost than HFCs.

- Cleaning solvent: it is necessary to use HFCs or HFEs as cleaning solvents in some precision processes or equipment. HFE 7500 among others HFEs could be termed as dense non-aqueous phase liquid (DNAPL), examples of which could include trichloroethylene and perchloroethylene, from a leakage or illegal dumping perspective.
- Blowing agent: According to the thermal conductivity, some HFEs are potential alternatives to traditional blowing agents (CFCs).
- Dry etching agent (process of removing exposed SiO2 thin-film in the pattern formed by photoresist exposure and development): used in substitution of PFCs in semiconductor industry.
- Other applications: carrier solvents for coatings, and lubricants or friction- reduction agents on devices such as surgical knife blades.

Table 10-1. Overview of uses

USES	
Uses as intermediate	-
Formulation	-
Uses at industrial sites	Use in closed systems
Uses by professional workers	-
Consumer Uses	-
Article service life	-

11. Classification and Labelling

Table 11-1. Classification of the Substance

Harmonised classification (Annex VI of CLP)	Self-classification in registrations	Self-classification in C&L notifications[4]
Aquatic Chronic 4 (H413)	No additional hazard classes compared to the harmonised classification	No additional hazard classes compared to the harmonised classification

12. Environmental fate properties

12.1. Degradation

12.1.1. Abiotic degradation

There is no experimental data on hydrolysis due to the low water solubility of the Substance. EPISuite HYDROWIN (v2.00) predictions were not performed as the substance falls outside the applicability domain of the model. A hydrolysis study (EU Method C.7) is available for the similar substance HFE-7100 (EC 422-270-2) and hydrolysis half-lives above one year at 25°C and at pH 4, 7 and 9 are reported.

[4] Checked on 25 April 2024 https://echa.europa.eu/information-on-chemicals/cl-inventory-database

Regarding photo transformation in air, three published articles addressing the degradation of HFE-7500 by indirect photo transformation using hydroxyl radical and/or atomic chlorine in laboratory experiments were found. Goto et al. (2002) examined the degradation rate of the substance relative to reference substances with known degradation rate. Direct photodegradation was not observed. The rate constant for reaction with hydroxyl radicals was (2.6 ± 0.6) x 10^{-14} cm^3 $molecule^{-1}$ s^{-1} at 295 K and ~200 torr of total pressure and with chlorine radicals (2.3 ± 0.7) x 10^{-12} cm^3 $molecule^{-1}$ s^{-1} at 295 K and ~700 torr of total pressure. By comparison with the accepted atmospheric half-life of 1,1,1-trichloroethane, which has a rate constant of 1.0 x 10^{-14} cm^3 $molecule^{-1}$ s^{-1} for reaction with hydroxyl radicals, the authors estimated for HFE-7500 a lifetime of 2.2 years in the atmosphere. Based on this, a half-life of 1.5 years can be calculated[5].

Rodriguez et al. (2014) studied the atmospheric degradation with OH radicals of HFE-7500 at atmospheric pressure as a function of temperature (271-333 K) in a reaction chamber using GC/FID and GC/MS techniques for the analysis. The relative-rate experiment gave a rate constant of (1.37 ± 0.29) x 10^{-13} cm^3 $molecule^{-1}$ s^{-1} for the substance. The rate constant was found to increase with increasing temperature following Arrhenius plots. The authors estimated a local atmospheric lifetime of 0.30 years (at 275 K and ~760 torr) for HFE-7500, which can be converted to a half-life of 0.21 years[5]. This is significantly lower than the half-life calculated based on the study by Goto et al. (2002). Different total pressures were used in the studies but based on studies on other HFEs the H-abstraction reactions usually seem to be independent of the total pressure (Diaz-de-Mera et al. 2009). Therefore, the factors causing the difference in the lifetimes and half-lives estimated in the two studies are not clear.

Diaz-de-Mera et al. (2009) examined temperature dependence of the reaction of HFE-7500 with chlorine radicals. The second order rate constant was (2.2 ± 0.6) x 10^{-12} cm^3 $molecule^{-1}$ s^{-1} at 298 K, which is very similar to the rate constant estimated for the chlorine reaction in the Goto et al. (2002) study, and (1.5 ± 0.3) x 10^{-12} cm^3 $molecule^{-1}$ s^{-1} at 273 K. The estimated atmospheric lifetimes were 2.9 and 4.5 years at 298 and 273 K, respectively.

Transformation products

In the publications by Goto et al. (2002) and Rodriguez et al. (2014), degradation pathways are proposed for the reactions with either hydroxyl or chlorine radical, using infrared spectroscopy or GC-mass spectrometry/GC-FID, respectively, and reactivity characteristics. According to both studies, the first step is oxidation of the non-fluorinated ethyl ether group to either an acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ (major product) or formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$ (minor product).

Goto et al. (2002) also examined the indirect photolysis of these fluorinated formate and acetate esters using chlorine radicals. The acetate ester was not observed to degrade while the formate ester had a rate constant of 9.7 x 10^{-15} cm^3 $molecule^{-1}$ s^{-1}. Based on the molecular structure, the esters could be susceptible to hydrolysis and degrade into the corresponding carboxylic acid and fluorinated alcohol. However, due to the low water solubility of the transformation products, hydrolysis may not be relevant in the atmosphere. Hence, the photo transformation products of HFE-7500 could be more persistent than the parent substance in the atmosphere.

According to the registrants, the ultimate degradation products are perfluorobutyric acid (PFBA), hydrofluoric acid (HF) and trifluoroacetic acid (TFA). In the publications by Goto et al. (2002) and Wang et al. (2014), the authors suggest that the acetate and formate ester transformation products will likely be hydrolysed by moist air and form C3F7CF(OH)CF(CF3)2, which can likely be further oxidized to C3F7C(O)CF(CF3)2. According to Wang et al. (2014), by analogy with the atmospheric degradation of

[5] half-life= 0.693 x lifetime, if first-order kinetics apply

C2F5C(O)CF(CF3)2 and CF3COCF3, it is expected that C3F7C(O)CF(CF3)2 can further undergo direct photolysis or hydrolysis to yield PFBA.

However, the proposed degradation pathway in these publications is based on theoretical assumptions and there is no experimental information indicating that PFBA or any other of the mentioned ultimate degradation products are formed by abiotic degradation processes at relevant quantities in the environment. Furthermore, due to the low water solubility and high HLC of the primary transformation products (fluorinated acetate ester and formate ester), hydrolysis in the atmosphere is not likely to be a significant degradation pathway for them.

12.1.2. Biodegradation

Estimated data

HFE-7500 (Parent substance)

According to the REACH Guidance R.11: PBT/vPvB assessment (ECHA, 2023), the output of the models BIOWIN 2, BIOWIN 3 and BIOWIN 6 of the software BIOWIN can be used to give a screening assessment of persistence. The following outcomes indicate that a substance may be persistent: BIOWIN 2 <0.5 and BIOWIN 3 <2.25 or BIOWIN 6 <0.5 and BIOWIN 3 <2.25. EPISuite BIOWIN v4.10 models were performed for HFE-7500 and the results are shown in the below table. Based on the BIOWIN predictions, HFE-7500 fulfils the screening criteria for P or vP.

Table 12-1. Results of the BIOWIN QSAR predictions for HFE-7500.

Model	Result
BIOWIN 1 (linear model prediction)	-2.09 (Does not biodegrade fast)
BIOWIN 2 (non-linear model prediction)	0.00 (Does not biodegrade fast)
BIOWIN 3 (ultimate biodegr. timeframe)	-0.11 (Recalcitrant)
BIOWIN 4 (primary biodegr. timeframe)	1.80 (Months)
BIOWIN 5 (MITI linear model prediction)	0.06 (Does not biodegrade fast)
BIOWIN 6 (MITI non-linear model prediction)	0.00 (Does not biodegrade fast)

For evaluation of the BIOWIN predictions it is noted that the models are not very well suited for predicting biodegradation of perfluorinated carbon chains. In particular, there is no fragment coefficient for a non-terminal perfluorinated carbon in the BIOWIN models. For example, the perfluorinated carbon chains of the HFEs are contributing to the predicted biodegradability scores by the fragments of "carbon with 4 single bonds & no hydrogens", and the BIOWIN 1-4 predictions include a specific fragment for a trifluoromethyl group, while the BIOWIN 5 and 6 include fluoride as a fragment, which remarkably has a positive influence on biodegradability in BIOWIN 5 but a (strongly) negative influence on the biodegradability in BIOWIN 6.

It should also be noted that in BIOWIN 1-4 the trifluoromethyl fragment is based on only one compound in the training set (3'-Methyl-4'-chloro-2,2,2-trifluoroacetophenone, CAS 286017-71-8, which is not a perfluorinated alkyl substance). Furthermore, the number of trifluoromethyl fragments in HFE-7500 exceeds the maximum number of fragments in the training set compound. Predictions may therefore also be less accurate according to BIOWIN User's Guide. Based on these observations the BIOWIN models cannot be expected to predict the biodegradability of perfluorinated alkyl chains with high reliability.

Considering that the perfluorinated carbon chain is expected to be very stable but not properly included in the model it can be concluded that the persistence of poly- and perfluorinated substances, including HFE-7500, will be underestimated by the BIOWIN predictions.

CATALOGIC (301C v11.15) model was run to get information on potential degradation pathways of HFE-7500 (see Figure 1). Based on the model results, the degradation is initiated by the oxidation of the ethyl group. However, the model predicts HFE-7500 to be stable as both the probabilities for the first predicted transformation steps as well as the quantities of the predicted transformation products are very low (Prob < 0.05 and Q < 0.04)[6].

The EAWAG-BBD Pathway Prediction System[7] was not used for predicting the biodegradation pathway because according to the EAWAG website the rules used by the model do not accurately predict the unique characteristics of per- and highly- fluorinated chemicals, and hence, the model should not be used for these substances.

[6] "Prob" means overall probability (probability from parent to specific degradation product); "Q" means quantity (mol/mol parent).

[7] http://eawag-bbd.ethz.ch/predict/

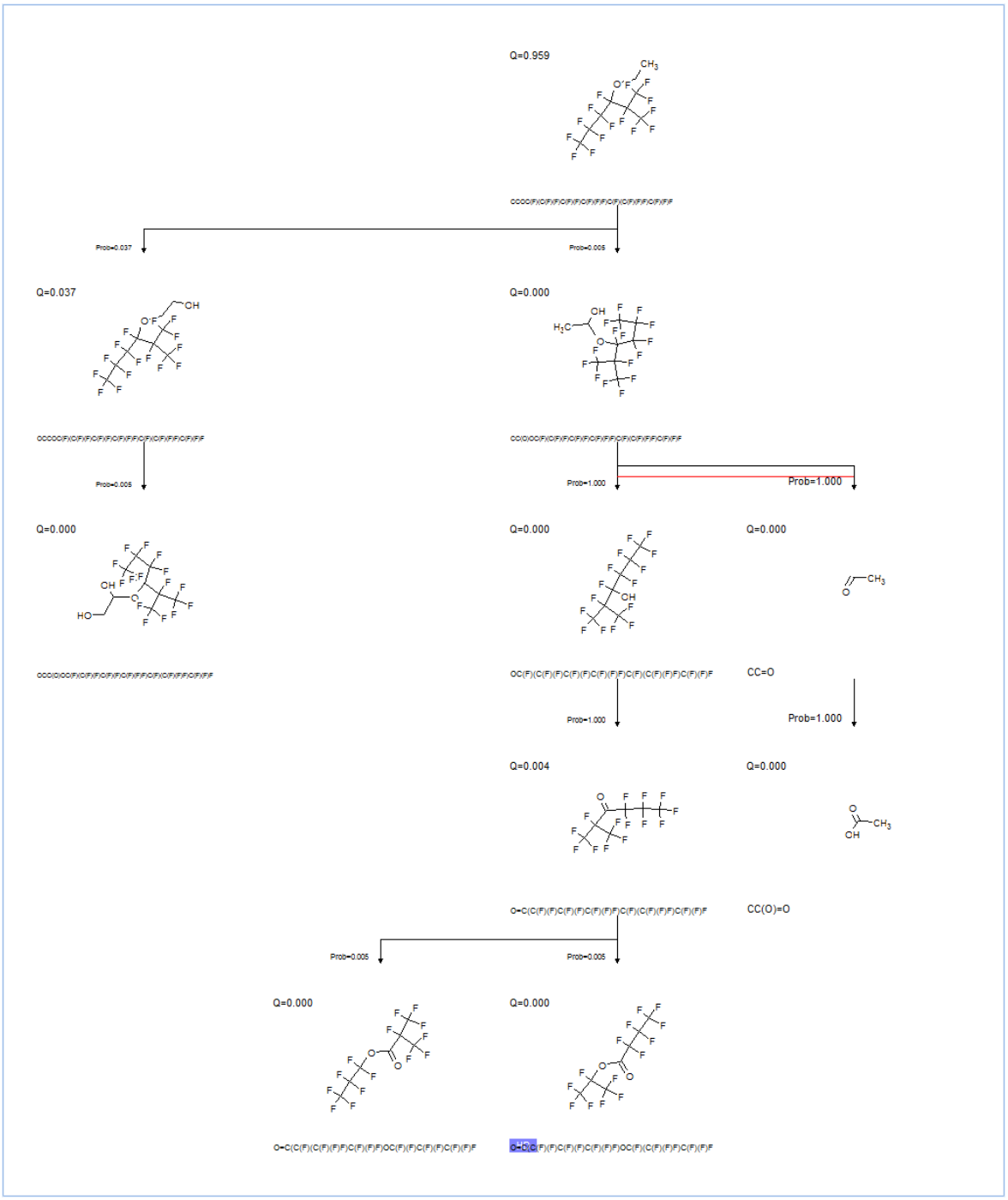


Figure 1. Catalogic (301C v11.15) model prediction for the degradation pathway of HFE-7500. "Prob" means overall probability (probability from parent to specific degradation product); "Q" means quantity (mol/mol parent).

Transformation products

EPISuite BIOWIN models were also performed for the two photo transformation products identified in the studies by Goto et al. (2002) and Rodriguez et al. (2014); fluorinated acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$, fluorinated formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$ and perfluorobutyric acid (PFBA). Based on these predictions the transformation products meet the screening criteria for P/vP. The same considerations on the reliability of BIOWIN models to predict persistence of perfluorinated carbon chains that are mentioned above for the parent substance are also relevant for the transformation products. As the transformation products also have perfluorinated fragments, the BIOWIN models may underestimate their persistence. However, as the results of the BIOWIN

models clearly fulfil the screening criteria for potentially P/vP, this is not considered a problem.

PFBA is a perfluorinated carboxylic acid and longer-chained substances of that group are known to be very persistent. The length of the fluorinated carbon chain is not considered to significantly affect the persistence, and hence, PFBA is expected to be very persistent.

Table 12-2. Results of the BIOWIN QSAR predictions for the transformation/degradation products.

	Fluorinated acetate ester	Fluorinated formate ester	PFBA
Model	Results		
BIOWIN 1 (linear model prediction)	-1.58 (Does not biodegrade fast)	-1.57 (Does not biodegrade fast)	-1.16 (Does not biodegrade fast)
BIOWIN 2 (non-linear model prediction)	0.00 (Does not biodegrade fast)	0.00 (Does not biodegrade fast)	0.00 (Does not biodegrade fast)
BIOWIN 3 (ultimate biodegr. timeframe)	0.01 (Recalcitrant)	0.04 (Recalcitrant)	2.15 (months)
BIOWIN 4 (primary biodegr. timeframe)	2.02 (Months)	2.04 (Months)	3.34 (days-weeks)
BIOWIN 5 (MITI linear model prediction)	0.31 (Does not biodegrade fast)	0.36 (Does not biodegrade fast)	0.51 (Does not biodegrade fast)
BIOWIN 6 (MITI non-linear model prediction)	0.00 (Does not biodegrade fast)	0.00 (Does not biodegrade fast)	0.00 (Does not biodegrade fast)

Screening tests

HFE-7500 (Parent substance)

A closed bottle ready biodegradation screening test following OECD TG 301D is available for HFE-7500. The test substance at an initial concentration of 9.13 mg/L (ThOD, 0.75 mg O2/mg) was inoculated in oxygen-saturated medium for 28 days using secondary effluent of a domestic sewage treatment plant. Aniline was used as a reference substance, and the test included also inoculum blank and abiotic controls. After 28 days the degradation of the test substance was 1 % based on O2 consumption and 0-1 % based on test material analysis.

Based on this information the substance meets the screening criteria for P/vP.

Information on similar substances

Several other HFEs have been registered under REACH (see Table 8-5. Only screening tests on biodegradation are available for these substances (Table 12-3).

Table 12-3 Availability of biodegradation studies for other HFEs registered under REACH (see Table 8.3-1 for the chemical structures).

substance	Screening test
EC 484-450-7	OECD 301D:

	Degradation after 28d: 24 % (test mat.) 45 % (BOD)
HFE 7100 EC 422-270-2	OECD 301D: Degradation after 28d: -6-13 % (test mat.) -7-22 % (BOD)
HFE-7200 EC 425-340-0	OECD 301D: Degradation after 28d: 0 % (test mat.), 0 % (BOD)
HFE-7300 EC 459-520-5	OECD 301D: Degradation after 28d: 0 % (test mat.), 0 % (BOD)
List 812-244-2	OECD 301C: Degradation after 28d: 0 % (test mat.), 17-25 % (BOD)
HFE-7800 EC 484-410-9	OECD 301C: Degradation after 28d 0 % (test mat.) 22 % (BOD)
List 700-755-2	OECD 301D: Degradation after 28d 0 % (test mat.) 0 % (BOD) OECD 302C: Degradation after 28d 44% (test mat.) 39 % (BOD)

HFE-7500 is a segregated hydrofluoroether that includes a perfluorinated region and a hydrocarbon region which are connected via an ether bond. The stability of organic fluorine compounds has been described in detail by Siegemund et al. (2000). When all valences of a carbon chain are satisfied by fluorine, the zig-zag- shaped carbon skeleton is twisted out of its plane in the form of a helix. This situation allows the electronegative fluorine substituents to envelope the carbon skeleton completely and shield it from chemical attack. Also the polarisability and high bond energies, which increase with increasing substitution by fluorine, of the carbon- fluorine bond contribute to the high stability of fluorinated compounds. The influence of fluorine is greatest in highly fluorinated and perfluorinated compounds. According to Wang et al. (2015), under environmentally relevant conditions, perfluoroether chains are similarly resistant to abiotic (photolysis, reactions with OH radicals, and hydrolysis) and biotic degradation as the perfluoroalkyl chains.

Several perfluorinated carboxylic and sulphonic acids (as well as their precursor substances) have already been identified as SVHCs due to their PBT and/or vPvB properties (e.g. ECHA 2012a, 2012b, 2012c, 2013, 2016, 2017) and there is extensive experimental information on the persistence of some of these substances.

Furthermore, 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoic acid, its salts and its acyl halides (covering any of their individual isomers and combinations thereof), further denoted as HFPO-DA, were identified as SVHCs in accordance with Article 57(f) of REACH due to, among other properties, their vP properties. According to the Annex XV report of

HFPO-DA, the ether bond in HFPO-DA is not expected to decrease the persistence of the substance compared to the other PFAS already concluded as SVHCs. It is further noted that QSAR models in BIOWIN v4.10 of EpiSuite include a negative fragment contribution of the aliphatic ether bond on the degradation potential. This indicates that the ether bond in HFPO-DA is not expected to decrease the environmental persistence, although it is neither likely to increase the environmental persistence in comparison to the perfluorinated carboxylic acids, which are already very persistent.

However, a direct read across from the other perfluorinated substances already concluded to be P/vP to HFE-7500 does not seem possible as HFE-7500 contains, besides the perfluorinated region, also a hydrocarbon region. Furthermore, the ether bond in HFE-7500 is not located between two per- or polyfluorinated fragments (which is the case e.g. in HFPO-DA), but instead it connects the perfluorinated and the hydrocarbon fragments of the substance.

Simulation studies

OECD TG 308 Aerobic test:

Following the Substance Evaluation decision, an aerobic water-sediment simulation study following OECD TG 308 and in accordance with GLP was performed for the Substance.

Study design

Sediments and freshwater were collected from two locations in Minnesota, US, in Fish Lake (S1) and North Goose Lake (S2). The sediment S1 consisted of 100% sand and 0.06 % of gravel and had an organic carbon (OC) content of 0.1 %. The sediment S2 consisted of 11% of clay+silt, 89% of sand and 0.28 % of gravel, and had 2.4 % of OC. It is noted that the sediment characteristics did not fully comply with the specifications of the OECD TG 308. According to the OECD TG 308, one sediment should have a high organic carbon content (2.5-7.5%) and a fine texture (clay+silt > 50%) , and the other sediment should have a low organic carbon content (0.5-2.5%) and a coarse texture (clay+silt < 50%). Furthermore, the guideline indicates that the difference between the OC content and the [clay + silt] content of the two selected sediments should normally be at least 2% and 20 %, respectively. That would mean that in practice both sediments would be in line with the characteristics of the "coarse" sediments with low OC content according to the information provided in the OECD TG 308. However, results can be applied to a best-case scenario in which low potential NER fraction expected.

After collection the sediments and freshwaters were stored refrigerated (4 ± 2°C) in the laboratory for a maximum 2 days. Before preparation of the test vials, the sediments were wet-sieved through a sterilized metal sieve. Bioactive sediment samples were characterized for pH, OC and total C content, redox potential, and nitrogen and phosphorous content as well as micro-organism communities at several points throughout the study: post-handling/start of acclimation, start of the test and end of the test. At the start of acclimation further properties were measured, e.g. regarding moisture content, texture, density and microbial biomass. Lake water samples were characterized at the same time points for OC content and micro-organism communities.

Sterilised sediment and water were prepared for the sterile controls. For the sediment, a 3-step autoclave-freeze-autoclave procedure was used in which subsamples of the bulk sediment were autoclaved first for 60 minutes, then frozen for a nominal 2 hours or more, then autoclaved again for 60 minutes. Additionally, sodium azide (NaN3) was supplemented as a microbial inhibitor. For the lake water, a 60 minute autoclave cycle was used and then the water was spiked with a sodium azide solution to achieve a nominal concentration of 500 ppm in the final sterilized water. Sterile sediment and lake water were also characterized throughout the study at each of these time points.

HFE-7500 was administered to the test vessels by applying the analyte onto sterilised, dry "control" sediment from Goose River (North Dakota). Then that dried material was dosed

into the test vessels by blending it with the freshwater sediment and lake water contained in the test vials. The dosing sediment was treated with HFE-7500 by incubating the dry matrix with a known amount of an HFE-7500 gas standard in a sealed container. The container was thoroughly mixed to homogenize the HFE-7500 adsorbed to the sterile sediment. The prepared dosing sediment was then stored at room temperature in a sealed vessel. The dosing sediment was tested for homogeneity and stability. All the homogeneity acceptance criteria were met, and the dosing sediment was found to be stable for at least 21 weeks under ambient conditions. The theoretical dosing amount, which was used to determine mass balance, was also determined using the homogeneity test samples prior to dosing the test cultures. The theoretical dosing amount was determined to be the average quantified amount of HFE-7500 delivered using the 1-mL scoop of dosing sediment. For sediment S1 the initial amount was 61900 ng/test vessel and for S2 66700 ng/test vessel.

40-ml glass volatile organics analysis (VOA) vials (actual volume 42.5-mL) with silicone rubber-bonded septum screw caps were used as closed system test vials. Test vials consisted of matrix sediment, an overlay of lake water collected with the sediment, an addition of dry control sediment treated with HFE-7500, and headspace (ambient air). Each test culture was prepared by loading wet sediment to 2 cm mark in the VOA vial (equal to 20.7 g for S1 and 15.5 g for S2 in wet weight). This was followed by 20 mL of associated overlying water from the same site. Vials were then loosely sealed, placed under incubation conditions and allowed to acclimate for 1 week in dark at 12 ± 2°C. Then 1 mL (equal to 1.09 g with a relative standard deviation (RSD) of 1.74% for S1 and 1.12 g with RSD of 1.51% for S2) of dosing sediment was added to each test culture and/or other spikes as needed. Once all components of the culture (matrix sediment, dosing sediment, overlay water and additional liquid spikes, as needed) had been added to the culture vials, the vials were tightly sealed and inverted several times to thoroughly mix the vial contents. The vials were then loosely sealed, and stored inside a cardboard box (dark) inside the study incubators at 12 ± 2°C for one week to acclimate the test cultures to the study conditions.

Additional liquid spikes (sodium dodecyl sulfate (SDS), perfluorohexanesulfonate (PFHS) or perfluorobutyric acid (PFBA)) were added as aqueous solutions immediately prior to the addition of the non-treated blank or HFE-7500 treated dried sediment. The water to sediment volume ratio was 1.8:1 in the final test vessels. This is not in line with the 3:1 to 4:1 ratio indicated in the OECD TG 308. The height of the sediment layer was just in the acceptable range (2.5 ± 0.5 cm) but the weight of the sediment differed from that recommended in the guideline (minimum 50 g in dry weight).

Two types of sterile controls were prepared. One with sterilised sediment and lake water and another one with only sterilised water. The water-sediment sterile controls were prepared the same way as the biotic vessels using spiked sediment for dosing. The sterile controls with only water were dosed using a solution of HFE-7500 in methanol. The concentration of the HFE-7500 was nominally 36 µg per culture. The HFE-7500 dosing solution was prepared in methanol at nominally 1200 µg/mL and dosed by adding 30 µL of HFE-7500 solution to each culture.

Two replicate test vials were prepared for each sediment for each sampling time point on nominal times 0, 3h, 6h, 12h, 24h and on days 7, 14, 28, 56, 120 and 160. In addition, a series of other test vials were prepared for the time points on days 0, 7, 14, 28, 56, 120 and 160:

- Inoculum blank(1): Test cultures prepared in single replicates for all timepoints with field sediment and overlying water but without addition of test item (called "bioactive blank" in report).
- Abiotic sterile control (2): Two types of sterile controls prepared:
    - one with sterilized sediment and lake water and
    - another one with only sterilized lake water.
- Toxicity control (1): Dosed with test item and sodium dodecyl sulfate (SDS).

- Other(7):
    1. sterile blank with sterilized sediment and water, no test item
    2. sterile blank with sterilized water only, no sediment and no test item
    3. bioactive PFBA control
    4. bioactive positive control (SDS)
    5. sterile positive control (SDS)
    6. bioactive negative control (perfluorohexanesulfonate, PFHS)
    7. sterile negative control (PFHS)
- Laboratory matrix spike (LMS) cultures (5): prepared for bioactive culture, bioactive blank, toxicity control, sterile culture, sterile blank
- Characterization cultures (2): prepared for bioactive culture and sterile culture for monitoring pH in water and sediment and oxygen in water and headspace (one culture for each timepoint >24 hours).

Culture sets were incubated at 12±2°C with orbital shaking at nominal 50 rpm in incubator-shakers and away from direct light. There is no information on whether appropriate settling and stratification of the sediment and water layers were maintained during the study. The shaking speed was half of the of the continuous shaking at approx. 100 rpm suggested in the OECD TG 309 to maintain particles and microorganisms in suspension. Therefore, full suspension of the two phases is not expected but some mixing of the phases especially at the interface of the sediment and water layer may have occurred. This may have increased the diffusion of oxygen to the lower layers of the sediment.

The oxygen levels were checked every 7 days (±5 days). This was conducted using indicator cultures (for bioactive and sterile cultures) prepared for each time pull, but without test material, and that were co-incubated with test cultures. First, the gas-phase O2 concentration was evaluated without opening the designated indicator culture test vessel. If O2 concentration was ≤10% in the headspace, the headspace of all cultures was then captured for analysis of HFE-7500 and volatile biotransformation products, then the cap was removed and left open for approximately 60 seconds. The cap was then replaced and tightly sealed, the oxygen level in the headspace had now been replenished to appropriate levels. As a demonstration of recovery for the headspace sampling procedure, two control samples were included for each time pull (total of 12 control samples per sediment type). Instead of sampling a culture vial's headspace, a known concentration of HFE-7500, HFC-227 and HFPP from a gas standard, was added to the control samples every time the other oxygen replenishment samples were processed. For the test vessels with S1, replenishment was done once for the test vessels sampled on timepoints Day 56 and 120, and twice for the test vessel for Day 160. For S2, replenishments were done for all test vessesl at least once, and for some (vessels for Day 56, 120 and 160) several times. It is not fully clear whether the replenishment procedure was perfomed also for sterile controls as it is not specifically mentioned. But since in the report it is said that "all cultures" were replenished at each occasion, it can be assumed that this involved also the sterile controls, although the headspace oxygen levels of the sterile indicator culture remained above 10% throughout the study.

Sample analysis

The sediment, water and headspace were sampled for chemical analysis on HFE-7500 and potential transformation products on 11 timepoints: 0, 3, 6, 12, 24 hours and 7, 14, 28, 56, 120 and 160 days. Each culture was prepared for sampling analysis by first centrifuging at ~1000 rpm for at least 20 minutes to form a clear separation of the aqueous and sediment layers. Second, an aliquot of the headspace was removed using a syringe inserted through the cap's bonded septum and transferred to a VOA vial for analysis of HFE-7500, HFC-227 and HFPP by purge and trap GC/MS. Third, the water was decanted into another vial from which 10 mL was transferred to an analysis vial and analyzed for HFE-7500, HFC-227 and HFPP by purge and trap GC/MS. An aliquot of the remaining water was transferred to an autovial and fortified with the appropriate internal standards for analysis of PFBA (test samples) and positive and negative controls by LC/MS/MS. Lastly, the isolated

sediment phase was solvent extracted using methanol for analysis of HFE 7500 by GCMS and PFBA and positive and negative controls by LC/MS/MS. The methanol used for extraction contained internal standards: d8-toluene for GCMS analysis and [$^{13}C_4$]- PFBA and [$^{13}C_3$]- PFHS for LC/MS/MS analysis. An aliquot of the extract was then diluted with MiliQ water for analysis of PFBA and positive and negative controls by LC MS/MS. Timepoints 3-24 hours were used to evaluate the partitioning of the parent substance across the three phases - sediment, water and headspace, and hence only HFE-7500 was measured in these samples.

In order to have as complete mass balance as possible, the possible formation of other degradation products besides PFBA, HFC-227 and HFPP was investigated using two approaches. First, evaluation of the full scan data from headspace GC/MS analysis, sediment solvent extract by direct injection GC/MS, and water phase by purge and trap GC/MS, did not show any detectable fluorinated volatile or semi-volatile products. Second, additional qualitative HPLC with time-of-flight (LC-qTOF) analysis was used to acquire sensitive high-resolution mass spectrometric data using a non-targeted analysis approach.

Selected vials of water fractions used for LC/MS/MS analysis of PFBA were analyzed for free fluoride (inorganic fluoride) using combustion ion chromatography (CIC) using the procedures outlined in ETS-8-093 "Analysis of Total Organic Fluoride by Ion Chromatography – Combustion Ion Chromatography – Method for Water and Wastewater". It should be noted that total fluoride was not measured, only inorganic free fluoride using ion chromatography.

The quality control included adding reference substances to calibration standards at variable concentrations and analyzed for instrument calibration and quantitation purposes. In addition, reference substances were added to culture-specific quality controls which were identified as laboratory matrix spike (LMS) cultures. The inclusion of laboratory matrix spike (LMS) samples was conducted to evaluate for any effect of the test culture matrix may have on target analyte recovery and to ensure HFE-7500, HFPP, and HFC-227 were stable throughout the sample preparation process and during storage prior to analysis. Each LMS culture was prepared for analysis by a three-step process, first involving sampling of the headspace gas, secondly decanting the water phase off with extraction of the water phase, and then extraction of the sediment phase. After that, the reference substances were spiked to the different phases. Gas standard of HFE-7500 was spiked to headspace and water, and HFE-7500 in methanol standard solution to the sediment phase. PFBA standard solution was spiked to the water and sediment phases. Gas standards of HFC-227 and HFPP were spiked to the headspace and water phases. After spiking, the headspace, water and sediment samples were analysed for the substance concentrations and the recoveries were determined. The recoveries were mostly in the acceptable range (100 ± 30%) for HFE-7500, HFC-227 and HFPP. For PFBA in water the recoveries were also in the acceptable range but in sediment the recoveries of PFBA had higher variation and in several timepoints they were below 70% and in some cases well above 130%.

The water and sediment phases of biotic and sterile test vessels were tested for microbial biomass (total plate count) and total organic carbon at the start of acclimation, start of the study (day 0) and end of the study (day 160). Based on the reported results, the sterilisation of the water samples was successful and they remained sterile throughout the study (< 10 CFU/ml of actinomycetes and bacteria in the plate counts). The sterilised sediment samples contained more microorganisms and they increased during the study, especially in the sediment S2 (300-960 CFU/ml actinomycetes and 4600-8200 CFU/ml bacteria). However, the amounts were one or two orders of magnitude lower than in the bioactive sediment samples of sediments S1 and S2 (actinomycetes 4700-9000 CFU/g on day 0 and 17000-17900 CFU/g on day 160, bacteria 11000-15000 CFU/g on day 0 and 22000-23000 CFU/g on day 160). It is also noted that in the sterile controls of S1 and S2 with the positive reference substance SDS, only some dissappearance of SDS occured while in the bioactive controls of SDS very fast total disappearance occurred. Therefore, even though the sterilisation of the sediments may not have been complete, the microbial

activity was significantly decreased and low biodegradation potential can be assumed for the sterile controls.

Aerobic Study results

The positive reference substance SDS was completely degraded by Day 7 in both the positive substance and toxicity control cultures. The degradation of the SDS in these cultures demonstrated the cultures were healthy and ultimately bioactive and that HFE-7500 did not have toxic effects in the degrading microorganisms. Only slight decrease of SDS was observed in the sterile controls during the 160 days study period.

The negative control substance PFHS showed no loss in the bioactive cultures over 160 days, indicating the likelihood of false positive results during the study was low.

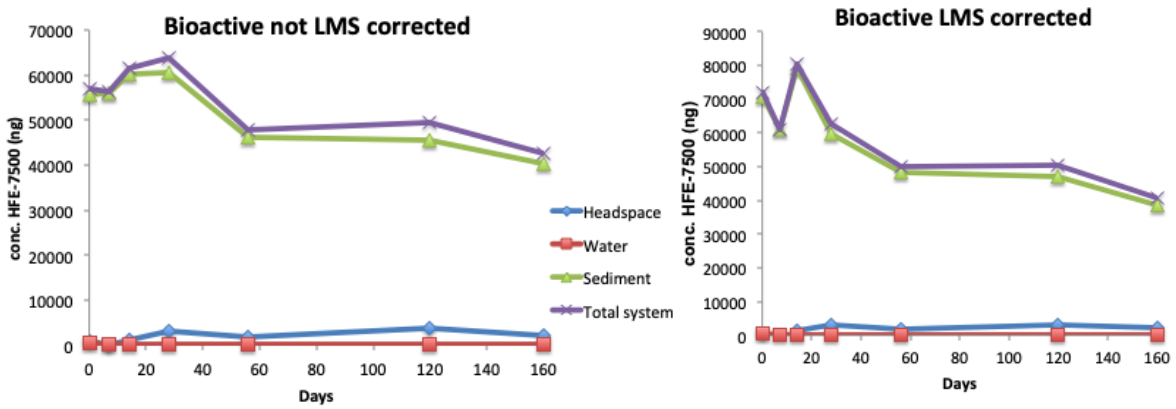
PFBA was an expected persistent biodegradation product of HFE-7500. Bioactive PFBA Controls were included with each time pull to ensure proper recoveries were being obtained and to verify that false negative results did not affect the results of this study. PFBA was dosed into bioactive PFBA control cultures at 197 ng per culture. PFBA remained stable over the 160 days study, with an average recovery (overall time points) of 103 and 98.2 % of the initial amount for S1 and S2, respectively, and the resulting RSD% of 9.24 and 5.71 %, respectively. This indicates that PFBA was not degraded during the study.

The results of the first timepoints at 0, 3, 6, 12 and 24 hours for both sediments S1 and S2 showed that HFE-7500 rapidly partitioned between the three phases and Day 0 was confirmed as the appropriate starting point.

In the full study report, the results for HFE-7500 concentrations are not given for each replicate at each time point, only a mean value is given per time point and treatment. The kinetic analyses reported in the study report also seem to be based on the mean values instead of the values for each replicate. Therefore, due to the lack of information on the replicate values, the eMSCA also performed the kinetic analysis with the mean values given per time point and treatment.

The concentration of HFE-7500 decreased during the study in the bioactive and bioactive toxicity control test vessels for S1 and in the bioactive test vessels for S2 (Figure 2 and Figure 3, respectively). However, a similar decrease was also observed in the sterile control vessels for both sediments. Most of the captured HFE-7500 was in the sediment with only small amounts captured in the headspace and water phases.

In the additional sterile control containing only water, the recovery of HFE-7500 was only 65% at day 0 and remained in similar levels (51-74%) during the whole study duration. With the exception of the day 0, HFE-7500 was detected almost exclusively in the headspace in these sterile water controls.



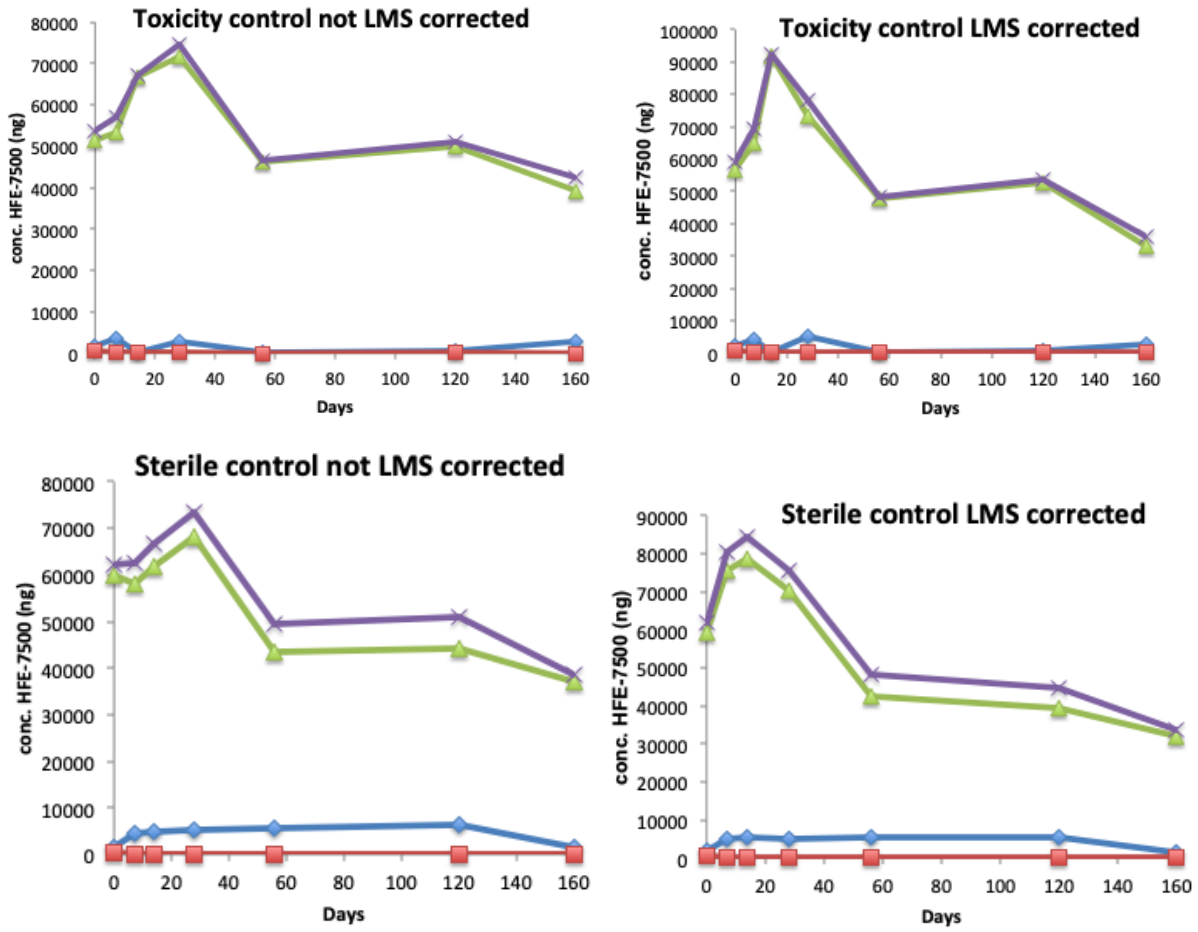
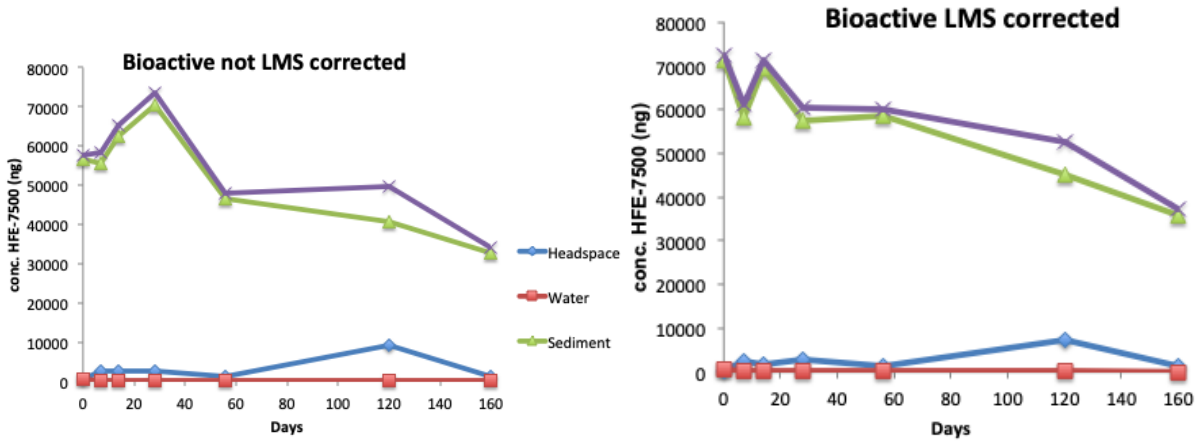


Figure 2. Amount of HFE-7500 present in the bioactive, toxicity and sterile control test vessels with the sediment S1 in the different time points of the study period based on non-corrected and LMS-corrected data (figures prepared by the eMSCA based on the raw data available in the study report). The initial nominal amount was 61900 ng/test vessel.



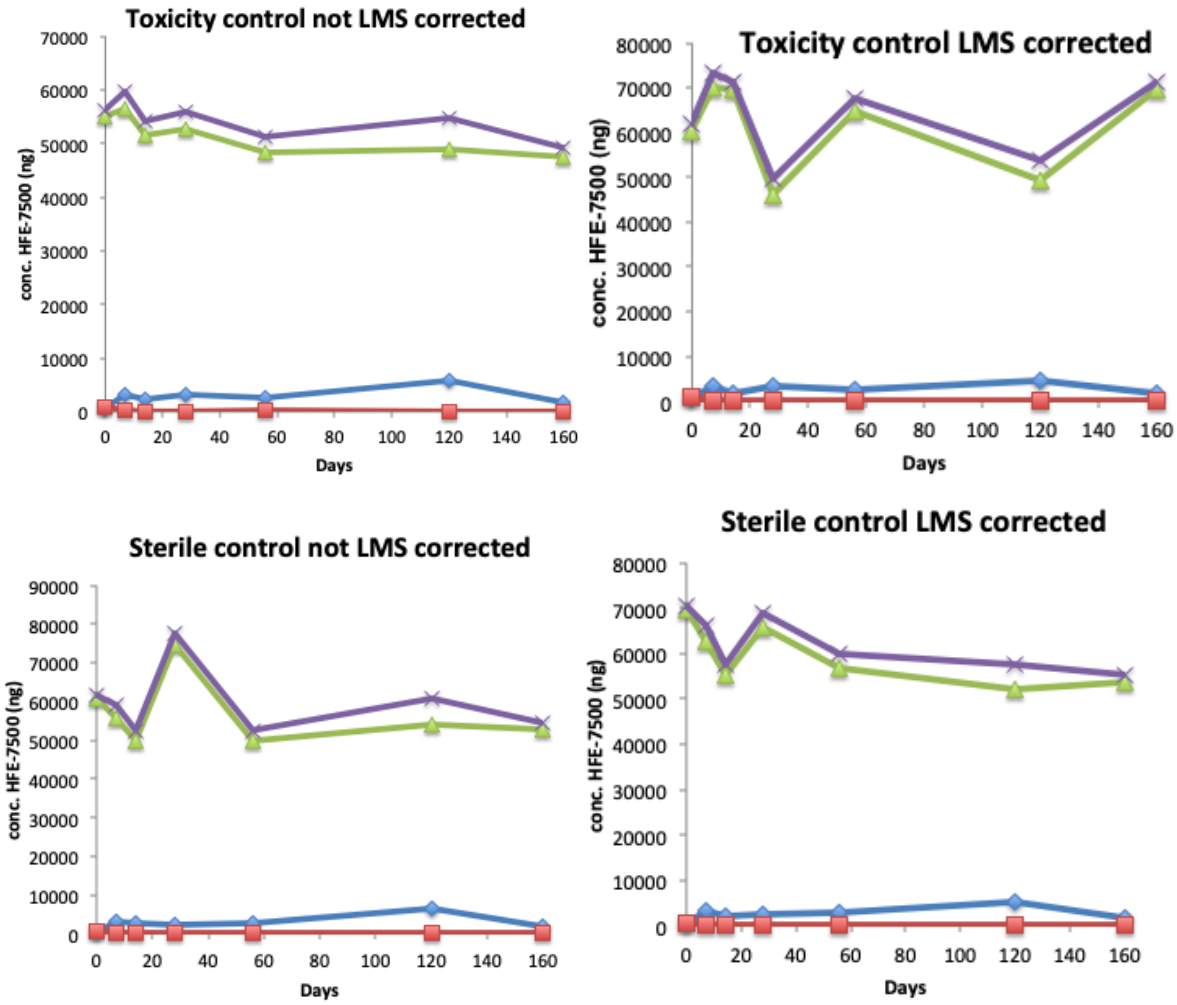


Figure 3. Amount of HFE-7500 present in the bioactive, toxicity and sterile control test vessels with the sediment S2 in the different time points of the study period based on non-corrected and LMS-corrected data (figures prepared by the eMSCA based on the raw data available in the study report). The initial nominal amount was 66700 ng/test vessel.

In the study, an initial increase in the concentration of HFE-7500 is observed in both types of sediments including in the sterile controls. It is not clear whether it could be due to a lack of appropriate settling and stratification after mixing the vial contents after the week of acclimation period. As the test substance was introduced to the test vessels using a small amount of spiked dry control sediment, potentially it could have taken some time for the test substance to be released from the control sediment and mix with the rest of the sediment. This could have led to lower measured/extractable concentrations and higher variation in the first part of the study.

Low levels of PFBA were observed throughout the course of the incubation in bioactive cultures for both sediments (<1% of initial HFE-7500 amount) but also in the sterile controls and sterile blanks (Figure 4). PFBA levels in the bioactive cultures were generally higher than the levels measured in the sterile controls and the sterile blanks. PFBA maximum observed in the bioactive test cultures was 0.244% at 160 days in S1 and 0.375% at 120 days in S2 (results adjusted by LMS recovery). In the S2 sterile control, an increase of PFBA is observed at the latter part of the study. This could potentially be due to the increase of microorganisms observed in the S2 sterile controls as abiotic degradation of HFE-7500 is not expected under the test conditions. However, it should be noted that the amount of measured PFBA is very low, less than 0.2 % of the initial amount of HFE-7500.

A) B)

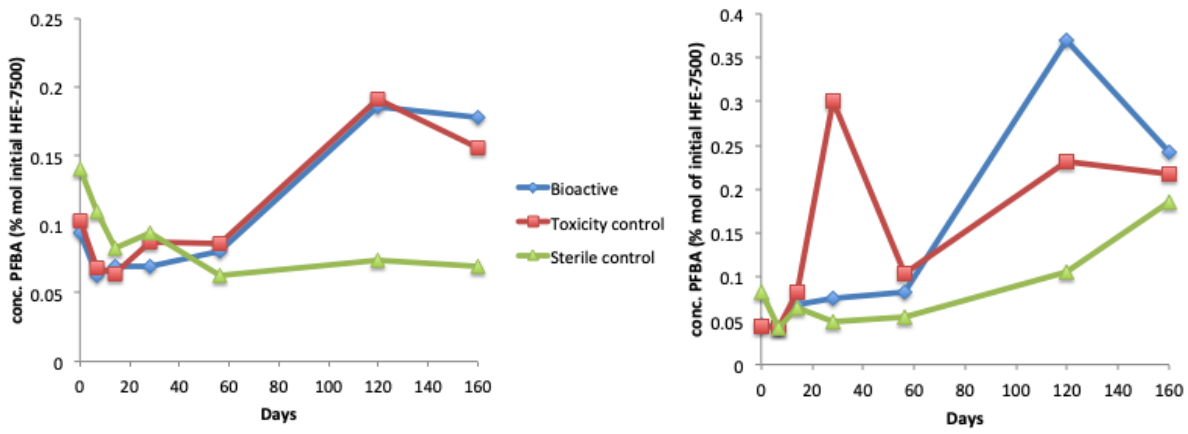


Figure 4. Amount of PFBA (% mol of initial HFE-7500 concentration, not LMS corrected) present in the test vessels with sediment A) S1 and B) S2 at different time points (figures prepared by the eMSCA based on the raw data available in the study report).

A possible pathway for PFBA formation involves metabolism of the ethoxy group to acetyl or formyl, with subsequent hydrolysis to secondary perfluoroalcohol. Such chemistries are known to undergo dehydrofluorination, in this case forming a well-characterized branched perfluoroketone which is unstable in water. The products of the putative metabolic intermediate are expected to be PFBA, along with 1H-heptafluoropropane (HFC-227) and/or hexafluoropropene (HFPP). One mol of each PFBA, HFC-227 and HFPP can be formed out of one mol of HFE-7500. However, while PFBA was observed to form in cultures at trace levels, HFPP was not observed above the limit of quantitation. HFC-227 was occasionally (already on day 0) detected at low amounts both in the bioactive and sterile test vessels (<0.1 % of initial HFE-7500 amount) but without a clear trend with time and later timepoints were also affected by an increase in LOQ due to the oxygen replenishment procedure.

In the study report, HFE-7500 recovery was calculated using the mass of HFE-7500 (ng) recovered from the total test culture compared to the theoretical mass of HFE-7500 (ng) dosed into each culture. In addition, mass balance was calculated using all quantifiable amounts (pmol) of HFE-7500 and the relevant biotransformation products determined to be present in the total test culture versus actual dosed HFE-7500. The mass balance ranged from 69.1% (day 160) to 103% (day 28) for S1, and from 51.2% (day 160) to 110% (day 28) for S2 (Table 12-4 and Table 12-5). As only very small amounts of transformation products were observed, the mass balance was practically the same as the HFE-7500 recovery at each time point. In the bioactive S2 test vessels the recovery of HFE-7500 was lower (51%) on day 160 than in the toxicity and sterile controls. However, on day 120 the recovery was still above 70 % which was similar to the recoveries measured in the controls. Also, no higher concentrations of PFBA or other transformation products were detected. Therefore, the low recovery on day 160 was likely due to losses of the parent substance during sampling or leakage from the test system.

The results of the analysis used to investigate the possible formation of other degradation products besides PFBA, HFC-227 and HFPP did not show any other water-soluble products present in the culture extracts for day 0, day 56 or day 160. Therefore, the low mass balance on day 160 in bioactive and sterile control cultures was not attributed to degradation of HFE-7500 to unknown degradation products. Rather, the loss of HFE-7500 from the test system was presumed to be due to potential volatile losses over time and/or non-extractable residues in sediment solids.

Table 12-4. Measured amounts of HFE-7500 and the degradation products, HFE-7500 recovery and mass balance in S1. The initial dosed amount was 149000 pmol HFE-7500.

Treatment	Day	HFE-7500 (pmol)	HFPP[a] (pmol)	HFC-227[a] (pmol)	PFBA[b] (pmol)	HFE-7500 Recovery (%)	Mass balance (%)
Bioactive							
	0	138000	≤37.6	71.8	139	92.10%	92.60%
	7	136000	≤37.6	≤41.8	≤98.6	91.00%	91.30%
	14	149000	≤113	≤50.4	≤99.5	99.50%	100%
	28	154000	≤37.6	80.6	≤105	103%	103%
	56	116000	≤800	≤794	≤121	77.40%	77.90%
	120	120000	≤800	≤806	276	80.00%	80.50%
	160	103000	≤800	≤794	263	68.80%	69.10%
Toxicity control							
	0	129000	≤37.1	71.2	154	86.60%	86.60%
	7	138000	≤37.1	74.7	101	92.20%	92.60%
	14	163000	≤112	≤42.7	95.3	109%	109%
	28	180000	≤37.1	60.6	129	121%	121%
	56	113000	≤787	≤782	127	75.30%	75.80%
	120	123000	≤787	≤788	284	82.20%	82.60%
	160	102000	≤787	≤782	231	68.30%	68.50%
Sterile control							
	0	150000	≤40.6	71.2	155	100%	101%
	7	151000	≤40.6	72.9	161	101%	101%
	14	161000	≤122	79.4	124	108%	108%
	28	177000	≤40.6	81.2	139	119%	119%
	56	119000	≤887	≤876	≤98.6	79.80%	79.90%
	120	123000	≤887	≤876	109	82.10%	82.60%
	160	93000	≤887	≤876	103	62.20%	62.50%

[a]The headspace LOQ increased after the Day 28 time pull due to the oxygen replenishment process. The lower limit of quantification (LLOQ) for HFPP was further adjusted to compensate for the low recoveries observed for HFPP in the Oxygen Replenishment Control Sample.

[b] Total PFBA present in the culture was obtained by adding the PFBA present in the sediment extractions to the PFBA present in the aqueous samples. If either value was determined to be <LOQ, the corresponding LOQ was used in the summation, as a result these values were denoted as approximate high-end values by using the "≤" symbol.

Table 12-5. Measured amounts of HFE-7500 and the degradation products, HFE-7500 recovery and mass balance in S2. The initial dosed amount was 161000 pmol HFE-7500.

Treatment	Day	HFE-7500 (pmol)	HFPP[a] (pmol)	HFC-227[a] (pmol)	PFBA (pmol)	HFE-7500 Recovery (%)	Mass balance (%)
Bioactive							
	0	140000	≤37.7	≤54.8	72.3	86.70%	87.00%
	7	141000	≤37.7	58.1	68.5	87.60%	87.60%
	14	158000	≤113	57	109	97.90%	98.10%

	28	177000	≤780	≤782	110	110%	110%
	56	116000	≤780	≤782	133	72.10%	72.00%
	120	120000	≤780	≤782	530	74.70%	75.20%
	160	82100	≤780	≤782	391	51.00%	51.20%
Toxicity control							
	0	136000	≤37.3	≤55.5	69.9	84.30%	84.50%
	7	144000	≤37.3	54.8	68.1	89.70%	89.40%
	14	130000	≤112	65.9	134	81.00%	80.70%
	28	135000	≤773	≤782	405	83.70%	83.90%
	56	124000	≤773	≤770	167	76.80%	77.00%
	120	132000	≤773	≤765	374	82.00%	82.00%
	160	119000	≤773	≤770	349	73.80%	73.90%
Sterile control							
	0	149000	≤37.4	≤52.5	132	92.50%	92.50%
	7	143000	≤37.4	44.5	66.7	88.80%	88.80%
	14	127000	≤113	42.8	105	78.90%	78.90%
	28	188000	≤773	≤765	77.9	116%	117%
	56	127000	≤773	≤765	87.3	78.90%	78.90%
	120	147000	≤773	≤765	169	91.50%	91.30%
	160	132000	≤773	≤765	300	81.90%	82.00%

[a] The headspace LOQ increased after the Day 14 time pull due to the oxygen replenishment process. The LLOQ for HFPP was further adjusted to compensate for the low recoveries observed for HFPP in the Oxygen Replenishment Control Sample.

As previously indicated, selected vials of water fractions used for LC/MS/MS analysis of PFBA were analyzed for free fluoride (inorganic fluoride). The average free fluoride concentration for all samples analyzed was 24.7 ng/mL (15% RSD – relative standard deviation), which has been calculated by the eMSCA to be equivalent to 60 pmol and considered negligible in the view of the amount of other degradation products. No appreciable difference in free fluoride was observed between culture samples dosed with HFE-7500 and blank cultures.

The registrants performed kinetic analysis for the data using PestDF biotransformation kinetic software (source: U.S. EPA). The registrants calculated DT50 values for HFE-7500 for the disappearance of the parent substance from the total system by fitting the data to single first-order (SFO) kinetics and DFOP kinetics. The recovered quantities of HFE-7500 adjusted using the relevant LMS recoveries were used for the fitting. SFO kinetics gave the best fit to the data and hence it was chosen for the determination of DT50 values. This resulted in DT50 values of 198, 181 and 131 days for the bioactive, toxicity and sterile controls with sediment S1, respectively, and DT50 values of 218, 7907 and 568 days for the bioactive, toxicity and sterile controls with sediment S2, respectively (Table 12-6). These DT50 values are for dissipation and are not representative for degradation half-lives as they are based on the mass balance calculations and volatilization and leakage from the test system seemed to occur. Also, part of the parent substance may be present as non-extractable bound residue which was not measured in the test. Hence, the degradation half-lives of HFE-7500 are higher than the estimated DT50 values.

The registrants also report half-lives for HFE-7500 determined based on the formation of PFBA (Table 12-6) for the bioactive and toxicity controls (but not for the sterile controls). To do this, the observed quantities of PFBA (in pmol) were also adjusted using the relevant LMS recoveries and the adjusted amounts of PFBA (in pmol) were then subtracted from the theoretical amounts of HFE-7500 dosed into the test cultures (in pmol) and the residual HFE-7500 amount was plotted and fitted with SFO kinetics and DFOP kinetics. One mol of PFBA is expected to be formed of one mol of HFE-7500. As indicated above, based on the results of the PFBA biotic controls, PFBA did not degrade during the study and hence the

amount of PFBA measured on each timepoint can be considered as the accumulated amount of PFBA on each timepoint. SFO kinetics were chosen for the determination of half-lives (DT50) of HFE-7500 in the various test cultures. This resulted in half-lives of 187 and 224 years for the sediment S1 and 91 and 150 years for the sediment S2 for the bioactive and toxicity control vessels, respectively. These half-lives values are conservative estimates of the real (primary) degradation half-lives as part of the initial amount of HFE-7500 added to the system was lost by volatilization and leakage and was hence not available for degradation. Also, although not detected by the analytical measurements performed in the study, it cannot be completely excluded that other degradation products than PFBA may have formed, and these are not considered in these half-life calculations. On the other hand, all PFBA formed in the test systems does not necessarily come from degradation of HFE-7500 as there could potentially be other reactants, too.

Table 12-6. DT50 and half-life values determined by the registrant for HFE-7500 using SFO kinetics in PestDF biotransformation kinetic software.

Test culture	DT50 based on parent substance disappearance	Half-live based on formation of PFBA
Sediment S1		
Bioactive	198 days	187 years
Toxicity	181 days	224 years
Sterile	131 days	-
Sediment S2		
Bioactive	218 days	91 years
Toxicity	7907 days	150 years
Sterile	568 days	-

The eMSCA re-calculated the DT50 values for the disappearance of the parent substance from the total system using CAKE Software. In CAKE the input data should be concentrations in percentages (%), and therefore, the non-corrected and LMS corrected total amounts of HFE-7500 for each time point were compared with the initial nominal amount of HFE-7500 added to each test culture and the results were multiplied by 100%. These percentage values were then used in the fitting. This resulted in very similar DT50 values based on SFO kinetics as the ones reported by the registrant

Table 12-7). The best fits were obtained with SFO kinetics. The fits were generally better for the data of the bioactive test vessels than for the data of the toxicity control vessels based on the visual fit (Figure 5) and χ^2 error % and t-test statistical metric (Table 12-7). In the S2 toxicity control with LMS corrected data and the sterile control with not corrected data, the estimated disappearance rates (k) were statistically not significantly different from zero (t-test p>>0.05).

Table 12-7. DT50 values determined using the not corrected and LMS corrected data by the eMSCA for HFE-7500 using SFO kinetics in CAKE software.

Test culture	χ^2 error %	disappearance rate (k) (95% Confidence interval)	t-test probability value	DT50 (days)
Sediment S1 non-corrected data				
Bioactive	5.98	0.0020 (0.00029-0.004)	0.015	352
Toxicity	11.9	0.0021 (-0.0012-0.005)	0.08	324
Sterile	8.49	0.0030 (0.00045-0.006)	0.015	233
Sediment S1 LMS corrected data				
Bioactive	8.86	0.0035 (7.71E-004 - 0.006)	0.011	198
Toxicity	15.7	0.0038 (-0.001-0.009)	0.051	181
Sterile	12	0.005 (0.0009-0.009)	0.013	139
Sediment S2 not corrected data				
Bioactive	10.5	0.0031 (-0.00006-0.006)	0.027	224
Toxicity	3.3	0.00074 (-0.0001-0.002)	0.039	931
Sterile	10.3	0.00053 (-0.002-0.003)	0.32	13100
Sediment S2 LMS corrected data				
Bioactive	5.93	0.0032 (0.0014-0.005)	0.003	219
Toxicity	10.8	8.72E-005 (-0.00264-0.003)	0.469	7950
Sterile	4.8	0.0012 (-0.00009-0.002)	0.031	578

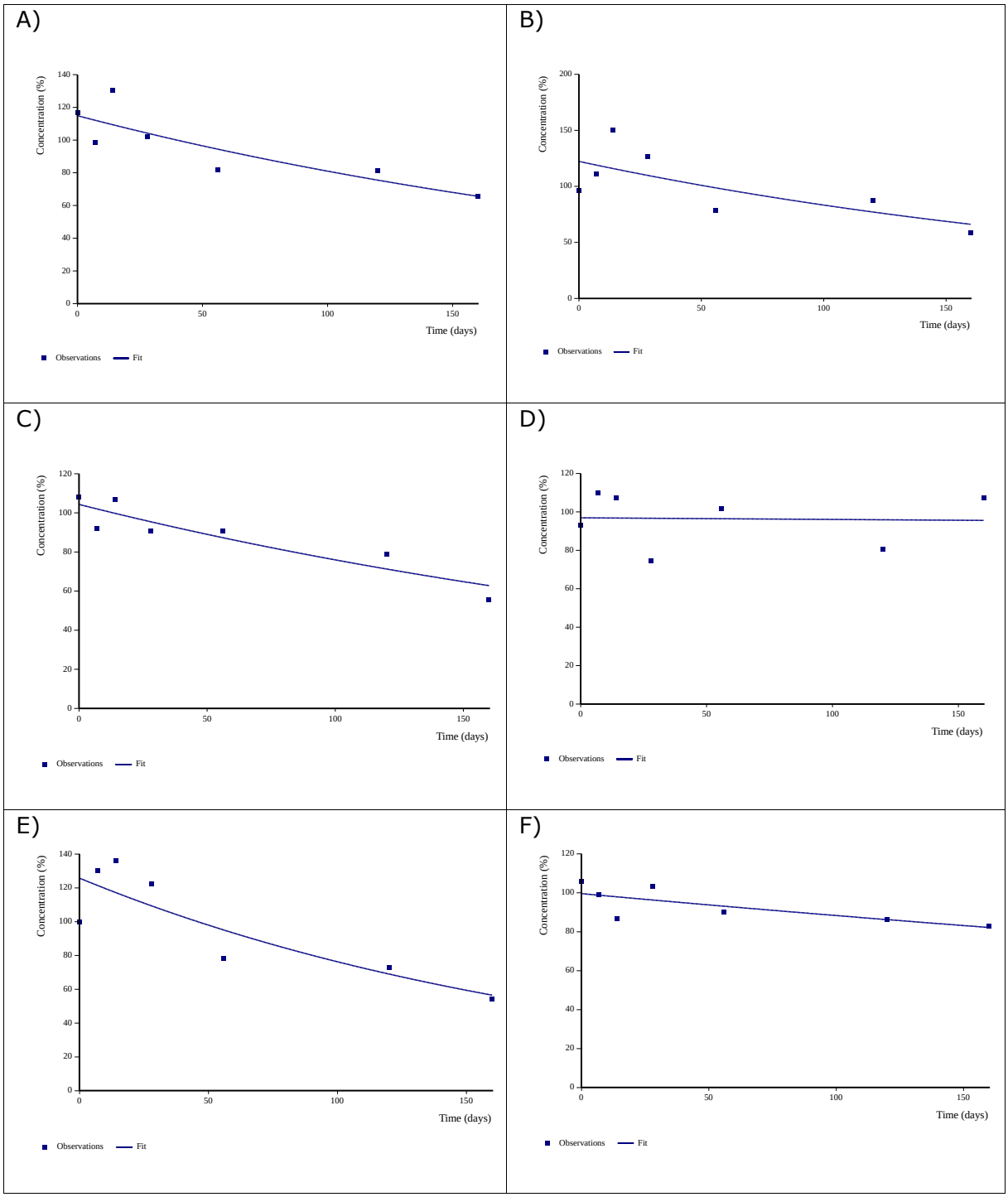


Figure 5. Observations and fitted SFO models for LMS-corrected data using CAKE for A) S1 bioactive, B) S1 toxicity control, C) S2 bioactive, D) S2 toxicity control, E) S1 sterile control and F) S2 sterile control test cultures.

As there was an increase in the measured amounts of HFE-7500 in the first timepoints in almost all test vessels and no clear explanation was found for this, additional kinetic analysis was done by the eMSCA (using CAKE) considering only the values from the highest concentration measured onwards. These DT50 values (Table 12-8) represent the best case DT50 values as they only take into account the data points from the highest concentration onwards and hence the slope of the curve will be more inclined than if taking into account all time points from the beginning of the test where lower concentrations were measured.

For the sterile control of S2 when using the LMS corrected data, the highest concentration corresponds to the day 0 and hence, no further kinetic analysis was done for that. For S1, the DT50 values of the bioactive vessel and toxicity control are above the vP criteria

whereas the DT50 of the sterile control is slightly lower. With the LMS corrected data all DT50 values are below 180 days but the value of the bioactive test vessel is close to it. In the case of S2, the bioactive vessel has clearly the lowest DT50 values, below 180 days with uncorrected data and above 180 days with LMS corrected data. The toxicity and sterile controls have very high DT50 values indicating very slow disappearance of the Substance. Some of the fits were not good, as indicated by the p-value above 0.05 and quite high χ^2 error %. If the first days of the test where the initial increase occurred are considered as lag phase they can be added to the calculated best case DT50 values (Table 12-8).

Table 12-8. Best case DT50 values calculated by the eMSCA based on the data from the timepoints after the initial increase in HFE-7500 observed in all test vessels. The timepoints that were considered for each treatment are indicated in the first column.

Test culture	χ^2 error %	disappearance rate (k) (95% Confidence interval)	t-test probability value	DT50 (days)	DT50 with lag phase included (days)
Sediment S1 non-corrected data					
Bioactive (days 28-160)	7.17	0.0025 (-0.0028-0.008)	0.091	279	306
Toxicity (days 28-160)	12.4	0.0036 (-0.0058-0.013)	0.12	191	218
Sterile (days 28-160)	10.2	0.0041 (-0.0037-0.012)	0.076	168	195
Sediment S1 LMS corrected data					
Bioactive (days 14-160)	9.32	0.0041 (-0.0003-0.009)	0.030	168	181
Toxicity (days 14-160)	12.2	0.006 (-0.0004-0.012)	0.029	115	128
Sterile (days 14-160)	9.02	0.006 (0.0016-0.011)	0.012	108	121
Sediment S2 non-corrected data					
Bioactive (days 28-160)	11.2	0.0048 (-0.004-0.014)	0.072	145	172
Toxicity (days 7-160)	3.6	0.0008 (-0.0004-0.002)	0.065	899	905
Sterile (days 28-160)	10.4	0.0019 (-0.006-0.009)	0.20	372	399
Sediment S2 LMS corrected data					
Bioactive (days 14-160)	5.55	0.0035 (0.00095-0.006)	0.011	197	210
Toxicity (days	11.4	0.00024 (-	0.43	2900	2906

7-160)		0.0033-0.004)			

Based on the results of the study, there was difference between the disappearance of HFE-7500 in the S1 and S2 sediments. In S1 test vessels, the disappearance of HFE-7500 in the bioactive vessels and toxicity controls was similar and slower than in the sterile control. In contrast, in S2, the disappearance was fastest in the bioactive vessel and almost negligible in the toxicity and sterile controls.

It is not clear what could explain the differences between the sterile and toxicity controls of S1 and S2. Based on the measurements of microbial communities, in the sediment phase of the S2 sterile control there were more microorganisms present during the test than in the S1 sterile control. Hence, the sterilization appeared to be more successful in the S1 sediment and the faster disappearance of the parent substance in the S1 sterile control compared to S2 cannot be explained by a lower success in the sterilization of S1 sediment. This is also supported by the results of both S1 and S2 sterile controls with the positive reference substance SDS which showed slow disappearance of SDS, thus, confirming that both sediments were successfully sterilised. Therefore, the differences in the disappearance of the parent substance in the S1 and S2 sediments are likely mostly caused by other dissipation processes than degradation.

The sterile sediment of S2 has a higher organic carbon content (3.0-4.5%) than S1 (0.1 %) which could result in higher adsorption and consequently lower volatilization of HFE-7500 in the sterile S2 sediments. In the bioactive S2 sediment the organic carbon content was a bit lower (2.4 % at the start of acclimation, 3.0% on day 0 and 1.5 % on day 160) than in the sterile sediment. This could lead to lower adsorption and potentially higher losses due to volatilization.

It is also noted that several oxygen replenishments (up to 6 times for the day 160 vessels) were done for the S2 vessels, while for the S1 vessels this was done only once for the day 56 and 120 vessels and twice for the day 160 vessels. In the study report it is indicated that replenishments were done for "all cultures" still remaining at each replenishment occasion. However, it is not fully clear whether it was done only for the biotic vessels or also for the sterile vessels. If only done for the biotic vessels and not for sterile controls, this could partly explain the significantly lower DT50 in the biotic vessels.

The significant differences in the biotic and toxicity controls of S2 is not expected to be caused by toxicity of HFE-7500 to microorganisms as the reference substance SDS was degraded as expected in the toxicity controls.

When taking into account data from all time points in the kinetic analysis, all DT50 values of the biotic and toxicity controls are above 180 days. The best case DT50 values of the biotic and toxicity control vessels, calculated based on data only from the time points after the initial increase in parent substance concentration, are also above 180 days except when using LMS corrected data for S1 and in the case of the bioactive vessel of S2 when using the non-corrected data.

Considering that only very low amounts of PFBA and HFC-227 were observed and no other transformation/degradation products were detected, it appears likely that the disappearance of HFE-7500 was mainly due to other processes than degradation, e.g. volatilisation or adsorption and NER formation. This is especially true for S1 sediment as the sterile control has even lower DT50 than the biotic vessel and toxicity control. The differences observed in the different treatments and sediments could be at least partly explained by differences in volatilization and adsorption e.g. due to different organic carbon contents, sediment texture and different handling such as air replenishment. Even though part of the initial parent substance is lost by volatilization and is hence not available for degradation, the very low amount of transformation/degradation products observed throughout the study indicates that the parent substance that was available for

microorganisms had very slow degradation. At the end of the test, between 51 and 74% of the initial amount of HFE-7500 remained in the bioactive and toxicity control systems but the amount of detected degradation products was less than 1% of the initial amount of HFE-7500.

OECD TG 308 Anaerobic test

An OECD TG 308 study (GLP compliant) under anaerobic conditions was also performed following the Substance Evaluation decision.

Study design

The test design and procedure were the same as in the aerobic study with only some exceptions. The sediments and overlying water were collected from anaerobic zone of two surface water bodies from two locations in Minnesota, US (1) South Goose Lake (~15 ft water depth, referred to as S3) and (2) Fish Lake (~13.5 ft water depth, referred to as S4). The sediment S3 had a coarse texture (sand, silt and clay contents not reported) and a high OC content (15.4 %) . The sediment S4 was a sandy loam (66 % sand/32 % silt/2% clay) with an OC content of 6.3 %. In order to create the anaerobic conditions in the closed volatile organics analysis (VOA) test vessels, the sediment handling and the culture preparation was done in the glove box under an atmosphere of nitrogen. HFE-7500 was added to the test vials in the same way as in the aerobic test. The initial amount of HFE-7500 was 68400 ng/test vial (165000 pmol) for both sediments. The culture vials were then capped and incubated at 12°C outside of the glove box, and with no orbital shaking. Sampling of the test vials was done in the same timepoints and the parent substance and the same transformation/degradation products were analysed using the same analytical methods as in the aerobic OECD TG 308 test. 2,4,6 trichlorophenol (TCP) instead of SDS was used as positive control substance. TCP was expected to be biotransformed in anaerobic sediments via methanogenic microbial populations. TCP and its expected degradation product 4-CP were analysed using the LC/MS/MS method.

The results for control cultures showed that TCP (at initial concentration of 20800 ng/test culture) was removed from bioactive positive control cultures, but was stable in equivalent sterile control cultures, demonstrating that test cultures were biologically active, and the sterile cultures were sufficiently inhibited by the sterilization procedures implemented. TCP completely disappeared by day 63 in both bioactive and toxicity controls. The concentration of its expected degradation product 4-CP increased and later decreased during the study indicating that TCP was degraded. The negative control PFHS showed no loss in bioactive cultures over 160 days, indicating the likelihood of false positive results during the study was low.

Redox potential measurements of the overlying water taken at each sampling timepoint showed some variation and no clear trend with time (-78.1 to 84.2 mV for S3 and -195 mV to 114 mV for S4). Redox potential measurements of the sediments were done post collection, on day 0 and day 160. Day 0 and day 160 redox sediment measurements showed a decrease relative to post collection (from 113 mV at start of acclimation to 82 mV at day 160 for S3 and 119 mV to 55 mV respectively for S4). Although these values do not strictly fall within the anaerobic range stated in OECD 308 (Eh range of -80 to -190 mV), the observed degradation of the positive control TCP suggest that the cultures are consistent with an anaerobic environment.

Anaerobic Study results

PFBA was observed at trace levels in the bioactive and toxicity cultures for both sediments over 160 days (<0.3 mole %). However, PFBA was also observed in sterile controls. The highest concentration of PFBA was observed on day 160 in S3 bioactive cultures with average of 0.160 mole percent (mol%) relative to dosed concentration of HFE-7500, and in S4 at 0.250 mol% on day 160. These levels were similar to the PFBA in sterile controls, which showed maximum concentrations of 0.293 mol% in S3 on day 120 and 0.150 mol%

in S4 on day 63. In the sterile and bioactive blanks, PFBA was generally below the limit of quantitation or detected at lower levels than the test cultures.

HFC-227 was detected at trace levels in bioactive, toxicity control and sterile control cultures (<0.2 mol%), and below limit of quantitation in sterile water control, bioactive blank and sterile blank. The highest concentration of HFC-227 was observed on day 160 in the bioactive cultures: 0.12 mole % for S3 and 0.19 mole % for S4. In the sterile controls, HFC-227 was measured at 0.10 mole % for S3 and 0.10 mole % in S4. HFPP was consistently below limit of quantitation in all test cultures. The possible formation of other degradation products besides PFBA, HFC-227 and HFPP was not investigated because the mass balance at the 160 day completion of the study was within the requirement of 70 to 110 % specified by OECD 308 for a study done with nonlabelled test item.

HFE-7500 remained stable in both sediments throughout the study (Figure 6). In the bioactive cultures of S3 the recovery ranged from 75.3 to 83.5,% and 76% of the initial added amount of HFE-7500 remained in the culture on day 160. In the bioactive cultures of S4, the recovery of HFE-7500 ranged from 74 to 101.2%, the highest recovery measured on day 160. Similar recoveries were observed in the toxicity and sterile controls. The substance was found mostly in the sediment phase with only small amounts in headspace (<5%) and water (<1%). Based on these results, HFE-7500 was very stable under the anaerobic conditions.

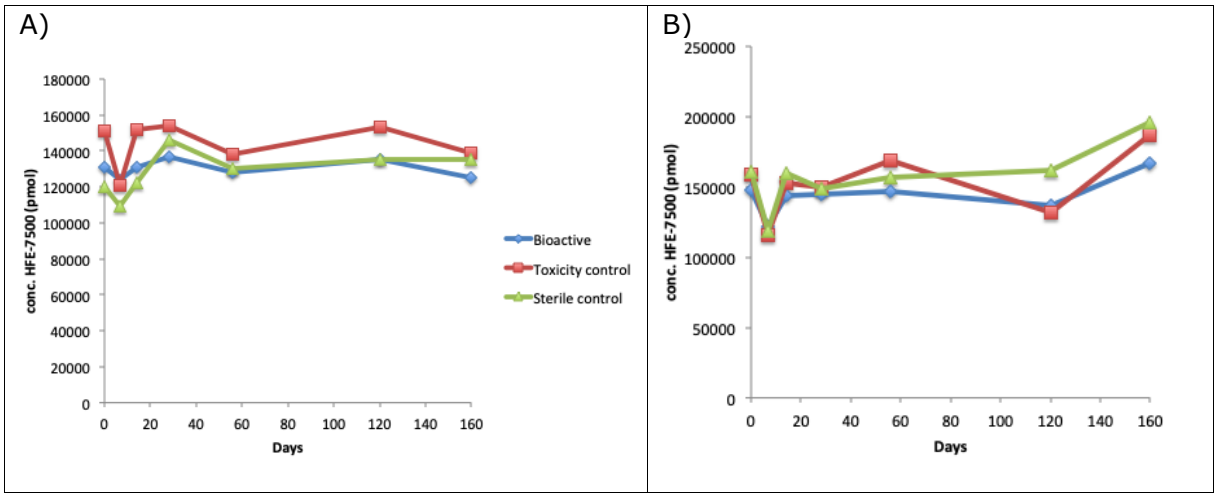


Figure 6. Amount of HFE-7500 (pmol/test culture) in total system of test cultures with A) sediment S3 and B) sediment S4.

In the sterile controls including only water, the recovery of HFE-7500 was lower, 56.9 and 49.2 % on day 160, and after the first day the substance was found almost exclusively in the headspace.

For the anaerobic study, the registrants report only half-lives of HFE-7500 determined based on the formation of PFBA. These were determined in the same way as in the aerobic study, i.e., the observed quantities of PFBA (adjusted for LMS recoveries) were subtracted from the initial amounts of HFE-7500 dosed into the test cultures and the residual HFE-7500 amount was plotted and fitted with SFO kinetics and DFOP kinetics. SFO kinetics gave the best fit and were chosen for the determination of half-lives (DT50) of HFE-7500 in the bioactive S3 and S4 cultures as well as in the sterile control of S3. This resulted in half-lives of 415 and 189 years for the bioactive cultures of S3 and S4, respectively, and 197 years for the sterile control of S3. For the toxicity controls and sterile control of S4 no half-life could be determined due to poor fit of the data. As already mentioned above for the aerobic study, these half-lives values are conservative estimates of the real (primary) degradation half-lives as part of the initial amount of HFE-7500 added to the system was lost by leakage and was hence not available for degradation, and also because although not detected by the analytical measurements performed in the study, other degradation

products than PFBA may also have formed and these are not considered in these half-life calculations.

12.1.3. Summary and discussion on degradation

Parent substance

No experimental information on hydrolysis is available. Based on the structure of the substance and the available information on a similar substance, hydrolysis is not expected.

Based on the available publications on the photo transformation in air, HFE-7500 has an atmospheric half-life in the range of 0.21-1.5 years. However, these are based on laboratory kinetic studies and therefore the half-lives may be different under environmental conditions.

In an OECD TG 301 D test, negligible degradation of HFE-7500 was observed. Hence, the substance is not readily biodegradable and screens potentially P/vP.

Also the BIOWIN QSAR models predict slow or no degradation of the substance. Based on CATALOGIC biodegradation pathway predictions, the probabilities of the first transformation steps of HFE-7500 are very low.

HFE-7500 has a perfluorinated region consisting of a branched C7 chain where all the carbons are perfluorinated except the one where the oxygen of the ether bond is connected. On the other side of the ether bond, there is an ethyl group. Hence, HFE-7500 is a highly fluorinated substance and due to the known high stability of C-F bond and the slow or negligible degradation observed for other per- and polyfluorinated substances, HFE-7500 is also expected to show very slow biodegradation in the environment. Especially mineralisation will be negligible due to the perfluorinated region, although some primary transformation in the hydrocarbon region cannot be excluded.

The substance has low water solubility (0.021 mg/L) and high volatility. Therefore, the substance may disappear rapidly from surface water and soil via volatilisation, and hence, these compartments may not be the most relevant for the persistence assessment. However, based on the high log Koc value (4.88), part of the substance may adsorb to suspended material and end up in the sediment. Based on distribution modelling (see section 12.2.3), air and sediment are the most relevant compartments for the substance.

In the aerobic OECD TG 308 study performed with unlabelled HFE-7500 following the Substance Evaluation decision, all the DT50 values estimated for dissipation of HFE-7500, when including all time points in the kinetic analysis, are above 180 days.

The best-case DT50 values, calculated based on time points after the initial increase of HFE-7500 concentrations observed in the test vessel, have more variation. For sediment S1, when using non-corrected data, the DT50 values of the bioactive vessel and toxicity control are above the vP criteria whereas the DT50 of the sterile control is slightly lower. With the LMS corrected data all DT50 values are below 180 days but the value of the bioactive test vessel is close to it. In the case of sediment S2, the bioactive vessel has clearly the lowest DT50 values, below 180 days with uncorrected data and above 180 days with LMS corrected data. The toxicity and sterile controls of S2 have very high DT50 values indicating very slow disappearance of the Substance.

In conclusion, none of the determined DT50 values are fully reliable. However, most of the different determined DT50 values, even the best-case DT50 values, are above the 180 days and the degradation half-lives of HFE-7500 are expected to be even higher than these as, based on the results of the sterile controls and the very low levels of transformation/degradation products observed in the biotic vessels, most of the

disappearance of the parent substance was likely due to other dissipation processes than degradation. Based on the similar decrease of parent substance observed in the sterile water-sediment controls and in the sterile water only control, leakage from the test system appeared to occur. Furthermore, presence of the parent substance in NER cannot be excluded either.

The conservative half-life values of HFE-7500 estimated based on the formation of the degradation product PFBA are in the range of tens and hundreds of years. The study had some deviations from the OECD TG 308 guideline and some of them may have favoured degradation (e.g. shaking after acclimation and during incubation) and others may have disfavoured degradation (lower bioavailability due to spiking of sediment, different water-sediment volume ratio, occasionally decreased oxygen levels). However, the study is considered reliable with restrictions and the high DT50 values and very low formation of transformation products during the 160 day study duration are considered sufficiently reliable information to demonstrate that HFE-7500 is a very persistent substance.

In the anaerobic OECD TG 308 study, HFE-7500 remained stable during the 160 days study duration and very low levels of PFBA were detected. Hence, the substance is very persistent also under anaerobic conditions.

Transformation products

Based on the information in the available photo transformation studies (Goto et al 2002, Rodriguez et al 2014), the degradation of HFE-7500 in air is initiated by indirect photolysis of the hydrocarbon region leading to formation of segregated C7-perfluoroalkyl ester. The identified transformation products are an acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ (major product) and a formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$ (minor product). These transformation products have low water solubility and high HLC, and hence, they are expected to mainly remain in the atmosphere.

According to Goto et al. (2002) these products are more resistant to photodegradation than the parent substance. Based on the EPISuite BIOWIN predictions, the acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ and formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$ fulfill the screening criteria for P/vP. However, Goto et al (2002) and Wang et al. (2014) propose a degradation pathway for these products starting from hydrolysis and finally leading to formation of PFBA, which is known to be a highly persistent perfluorinated substance, but there is no experimental information supporting this proposed pathway. Due to the low water solubility of the acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ and formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$, hydrolysis in the atmosphere may not be significant. Therefore, further information would be needed to confirm which degradation products are relevant for HFE-7500 in the environment.

PFBA belongs to the group of perfluorinated carboxylic acids, which in general are known to be highly persistent, and the length of the perfluorinated alkyl chain is not expected to significantly affect the persistence. In the OECD TG 308 with the Substance, bioactive PFBA controls were included and no significant decrease of PFBA was observed during the 160 days study. Hence, it is likely to fulfill the criteria for P/vP.

In the OECD TG 308 (2023) it is speculated that the slow biotransformation of HFE-7500 could follow a degradation pathway which might involve a diol intermediate which could be expected to hydrolyze to form PFBA, along with 1H-heptafluoropropane (HFC-227) and/or hexafluoropropene. PFBA and HFC-227 were observed to form in the test cultures at trace levels, and hence, can be considered to be transformation/degradation products of HFE-7500.In contrast, hexafluoropropene was not observed in the test cultures.

12.2. Environmental distribution

12.2.1. Adsorption

A log Koc of 4.88 at 35 °C is reported for HFE-7500 in a study following OECD TG 121 (HPLC method). At lower, environmentally more relevant temperatures, the log Koc is expected to be even higher. Hence, the substance is expected to adsorb to organic material in soil and sediment.

12.2.2. Volatilisation

The Henry's Law constant (HLC) of HFE-7500 was determined by the ratio of gas-phase concentration over aqueous phase concentration for a given test system vessel at equilibrium conditions and at ambient temperature (~23°C) and pressure. The overall average HLC for HFE-7500 is 19100 (%RSD = 21, n=22). The dimensionless HLC can be converted to 4.7E+07 Pa·m3/mol or 464 atm·m3/mole. This study was conducted under GLP compliance with an accepted method. However, there were several samples that had high %RPD (relative percent difference) for the duplicate measurements. Therefore, the study is considered reliable with restrictions.

Based on the high HLC, HFE-7500 is highly volatile.

12.2.3. Distribution modelling

Based on Level III distribution modelling in EPISUITE using the measured physico-chemical parameters of HFE-7500 as input, it is estimated that the majority of the substance released to the environment will partition either into air or sediment.

Based on the registration information on the uses of HFE-7500, most of the emissions can be expected to be released to air. However, based on the available information, release to other compartments cannot be ruled out for some of the uses.

Table 12-9. Results of the EPISuite Level III distribution modelling for the partitioning of HFE-7500 in the different environmental compartments assuming equal emissions to all compartments or emissions only to one of the compartments.

Compartment	Equal emissions to all compartments	Emissions only to air	Emissions only to water	Emissions only to soil
Air	4.2 %	100 %	0.9 %	95.3 %
Water	5.4 %	<< 0.01 %	5.5 %	<< 0.01 %
Soil	0.08 %	< 0.01 %	<< 0.01 %	4.7 %
Sediment	90.3 %	< 0.01 %	93.6 %	< 0.01 %

The EPISuite STP Fugacity Model using the measured physico-chemical parameters of HFE-7500 as input predicts that 58.4 % will partition to sludge, 41.4 % to aeration off gas, 0 % to effluent water and < 1 % is biodegraded.

12.2.3.1. Other distribution data

The registration dossier includes information from a study that was performed to examine the volatilisation of HFE-7500 from soil/sand and soil/sand/water mixtures used to represent aquatic sediment in order to address the feasibility of testing of bioconcentration in Oligochaete worms under OECD TG 315. The test was conducted using materials equivalent to those described in OECD TG 315 and 207. Analysis was by purge & trap GC/MS according to USEPA method 8260.

The study consisted of a series of experiments with spiked sand, soil/sand and soil/sand/water mixtures that were either capped or left open. The substance could be maintained in tightly capped vials, but in open systems the recovery of the substance was lower. A half-life of 13.7 ± 64.8 minutes was roughly estimated for volatilisation from uncapped artificial sediment. The substance was lost more slowly from uncapped moist soil. HFE-7500 injected to the gas phase above artificial sediment could not be detected in the water phase. However, neither the vial headspace nor the suspended material was analysed. The substance partitioned to moist soils when injected to the gas phase in a sealed container, however in open containers the flux was out of the soil.

The registration dossier also includes information from an experiment examining the volatilisation of HFE-7500 from water solution in both open containers and closed containers having approximately equal volumes of water and air. The test was done using a purge and trap GC/MS method according to USEPA method 8260, under GLP criteria. Closed containers were either shaken or left still. Vials were loaded with a fixed volume of water saturated with the test substance and incubated for up to 24 hours. Concentrations in the water at each time point were compared to initial concentrations in samples drawn from the same stock. Volatilisation followed first order kinetics. Rate constants for volatilisation were 0.0798/hour for open vials, 0.108/hour for closed but unshaken vials, and 0.279/hour for closed and shaken vials, through an interfacial area in the range of 2.4 cm^2 to 4.5 cm^2.

Potential for long range transport

The measured and estimated atmospheric half-lives of HFE-7500 are above 2 days and hence the substance has potential for long-range atmospheric transport.

The OECD Pov and LRTP screening tool also indicates potential for long-range transport for HFE-7500 with predicted overall environmental persistence (Pov) of 790 days, characteristic travel distance (CTD) of 227065 km and transport efficiency (TE) of 29.5 % (the screening criteria indicated in the manual of the tool are Pov > 195 days, CTD > 5097 km, TE > 2.248 %). This conclusion is in agreement with registrants.

12.3. Bioaccumulation

12.3.1. Aquatic bioaccumulation

HFE-7500 (Parent substance)

Table 12-10. Available bioconcentration studies on HFE-7500.

Method	Results	Remarks	Reference
Cyprinus carpio aqueous (freshwater) flow-	BCF: 5200 (whole body w.w.) (Time of plateau: 35 d)(steady state)	2 (reliable with restrictions) experimental result	ECHA dissemination website

through Total uptake duration: 56 d Total depuration duration: 36 d OECD Guideline 305 (Bioconcentration: Flow-through Fish Test)	(Test substance conc. 5 µg/L) Elimination: DT50: 10.8 d Lipid content: 2.89 — 4.65 %	Test material (IUPAC name): 3- ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)-hexane	
Cyprinus carpio aqueous (freshwater) Total uptake duration: 70 d Total depuration duration: 42 d OECD Guideline 305 C (Bioaccumulation: Test for the Degree of Bioconcentration in Fish)	BCF: 3150 — 8530 (whole body w.w.) (Time of plateau: 8 wk)(steady state) (Test substance conc. 50 µg/L and 500 µg/L) Elimination: DT50: 39 d Lipid content: 4.1 %	3 (not reliable) experimental result Test material (IUPAC name): 3- ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)-hexane	ECHA dissemination website

Log Kow values of 5.75 (at 30°C) and 6.0 (at 23°C) are measured for the substance using the HPLC method (OECD TG 117) and shake flask method (U.S EPA OPPTS 830.7550), respectively. Hence, the substance screens as B/vB.

In the registration dossier two bioconcentration in fish studies following OECD TG 305 are available for HFE-7500. Due to the low solubility of the substance, HCO-20 (Polyoxyethylene Hydrogenated Castor Oil) and 2-methoxyethanol were used as dispersant and cosolvent, respectively, in both studies.

In one of the studies, both test substance concentrations (50 and 500 µg/L) were well above the water solubility limit of 21 µg/L reported for the substance. Hence, this study is not considered reliable.

In the other study, only one substance concentration was tested. The nominal and mean measured test substance concentrations were 5 and 4.61 µg/L, respectively, which are both below the measured water solubility of the substance. In the uptake phase common carp (*Cyprinus carpio*) were exposed to the test substance under flow-through conditions during 56 days. The depuration phase was 36 days.

Analysis of test organisms was performed six times at each exposure concentration during the exposure period (after 7, 14, 28, 35, 49 and 56 days) and four times during the depuration period (after 7, 14, 28, and 36 days). Four test organisms were removed at each sample period. Analysis of control test organisms was performed before test initiation and after test completion. Six test organisms were also taken at test initiation and after

test completion to determine lipid content. Each analytical sample was made by combining tissues from two test organisms due to the small size of the test organisms. Analysis of the test substance in test water was conducted once before the first analysis of test organisms and at the same time as that for test organisms thereafter.

A steady-state BCF of 5200 and a depuration half-life of 10.8 days are reported in the registration dossier. The BCF was calculated based on the results of days 35, 49 and 56 of the uptake phase. The half-life was calculated by plotting the residual rate (%) of the sampled fish relative to the time using the regression log y = -0.0278x + 2.12.

The mean lipid content of the fish at the beginning of the test was 2.89 % and at the end of the test 4.65 %. There is some uncertainty on with which fish the lipid content was determined as in the robust study summary it is indicated that the number of control fish was 16. It is indicated that 4 control fish were sampled both at the start and end of the test for analysis of test substance concentration, and 6 fish were sampled at the start and end of the test for lipid content measurements. However, this would result in 20 control fish in total.

A kinetic BCF is not reported, and hence, growth correction is not applied. The length of the fish was in the range of 5.9 - 11.0 cm during the study, and the weight in the range of 6.01-13.1 g during exposure and 13.0 - 24.0 g during depuration. Hence, the fish grew significantly during the study, and therefore, a growth corrected BCF value could be higher than the one reported in the study.

It is noted that in the OECD TG 305 the use of any dispersants or solvents is generally not recommended. However, the use of solubilising agents may be acceptable in order to produce a suitably concentrated stock solution (OECD, 2012). The solvent concentration in the final test medium should not exceed its toxicity threshold and a maximum solvent concentration is 100 mg/L (or 0.1 mL/L). Some solvents and solubilising agents are mentioned in the OECD TG 305 (OECD, 2012). HCO-40 is one of the designated solvents. However, HCO-20, instead of HCO-40, was used in the study available for HFE-7500. HCO-20 and HCO-40 are both hydrogenated castor oils which differ in the number of ethoxylated groups. No information on toxicity of HCO-20 is available. However, in the study summary included in the registration dossier there is no mentioning of any possible toxic effects caused by the dispersant. In addition, HCO-20 was only used in a low concentration of 0.100 mg/L. Thus, it can be expected that HCO-20 was probably not toxic to fish in this bioaccumulation study.

2-methoxyethanol was used in a very low concentration of 0.4 µL/L in the final test solution. The use of this solvent is not mentioned in the current version of the OECD 305 guideline (OECD 2012) but its use was allowed in the previous version of the guideline (OECD 1996) which was the existing version when the study with HFE-7500 was performed. The concentration of 2-methoxyethanol was well below the known 96 hours LC50 or predicted Ch values available for the substance (10000 mg/L and 2 472 mg/L) for different fish species, e.g. Lepomis macrochirus or Oncorhynchus mykiss (ECHA dissemination site, 2018). Thus, 2-methoxyethanol probably was not toxic to fish in the test.

Hence, considering that the study is well conducted following the OECD TG 305 guideline and under GLP principles, the solubilising agents were used at low concentrations which are not expected to be toxic to fish, the test substance concentration was below the water solubility limit of the substance and that is indicated that no sublethal effects were observed in the test groups, the eMSCA considers the bioconcentration study reliable for the B assessment of the substance.

The eMSCA recalculated the steady state BCF and normalised it to 5% lipid content using the average value of 3.77 % calculated based on the mean lipid content at the start and end of the test. The steady state seemed to be reached already on day 28 and hence the

results of days 28, 35, 49 and 56 of the uptake phase were considered. This resulted in a steady state BCF_{SS} of 5317 L/kg and a 5% lipid normalised BCF_{SSL} of 7052 L/kg.

The eMSCA performed kinetic analysis on the raw data available in the robust study summary included in the registration dossier using the bcmfR R-Package programme (Version 0.4-18). All fits with untransformed data, Box-Cox transformed data and ln-transformed data gave very similar results. Untransformed data was selected for the final results as it gave a good fit (Figure 7). This resulted in a BCFk of 5874 L/kG. The estimated depuration rate (k_2) and half-life were 0.056 day^{-1} and 12.3 days, respectively. Lipid normalisation was done based on the average lipid content of 3.77 % and this resulted in a 5% lipid normalised BCFkL of 7790 L/kg. Growth correction could not be done as raw data on the fish weights was not available. However, as indicated above, based on the average weights of fish at the start and end of the test, the fish grew significantly. Therefore, the growth corrected kinetic BCF would be even higher.

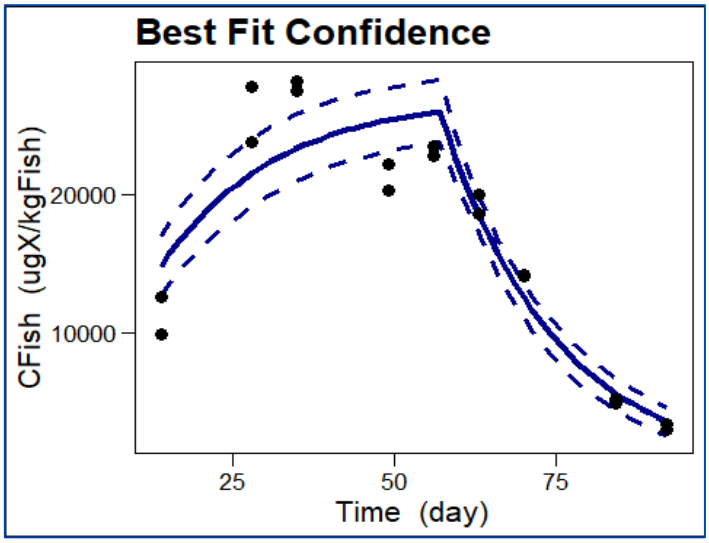


Figure 7. The measured concentrations of HFE-7500 in fish and the best fit (with 95% CI) with untransformed data in the OECD TG 305 study (Unnamed 2002), analysis performed by the eMSCA.

Newsted et al. (2002) estimated "food chain multipliers" for wildlife species in the range of 2.1-2,7 for HFE-7500, which would indicate potential for biomagnification of HFE-7500.

Transformation products

Based on the EPISuite KOWWIN predictions, the acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ and formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$ have a log Kow of 5.58 and 5.04, respectively. Hence, they fulfil the screening criteria for B/vB.

PFBA has a predicted log D of -0.36 at pH 7 using ACD Labs / log D QSAR model (EPISuite KOWIN prediction of 2.14). Hence, it is not likely to bioaccumulate in aquatic organisms via lipophilicity. However, other longer-chained perfluorinated carboxylic acids are known to bioaccumulate through protein binding.

12.3.2. Terrestrial bioaccumulation

Parent substance

KOAWIN (v1.10) predicts a log Koa of 1.72 for HFE-7500 when using the measured log Kow of 6.0 and measured HLC of 464 atm m^3/mole as input. According to the ECHA guidance R11 (ECHA, 2023), an efficiently absorbed, non-biotransformed neutral organic substance with a log Koa ≥ 5 in combination with a log Kow ≥ 2 has the potential to

biomagnify in terrestrial food chains and air-breathing marine wildlife as well as in humans. Based on the predicted log Koa, HFE-7500 does not fulfill these criteria.

The substance does not match the structural criteria specified in the boundaries of the profiler for protein binding in the QSAR-ToolBox v3.4. However, the model gives similar results for perfluorooctane sulfonates (PFOS) which are well known bioaccumulative substances.

No experimental data on toxicokinetics in mammals is available for the Substance.

Transformation products

KOAWIN (v1.10) predicts log Koa values of 2.5 and 1.8 for the acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ and formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$, respectively. Hence, they do not fulfill the screening criteria for terrestrial bioaccumulation.

PFBA may have potential for terrestrial bioaccumulation since it is a perfluorinated carboxylic acid and some longer-chained PFCAs are known to bioaccumulate through protein binding in air-breathing organisms.

13. Environmental hazard assessment

13.1. Aquatic compartment (including sediment)

Regarding aquatic toxicity, only two acute studies on fish (considered not reliable) are available for HFE-7500. The Registrant has provided an adaptation for further aquatic toxicity testing indicating that there is no aqueous exposure due to low solubility, high volatility and use pattern with release anticipated primarily to air. While the primary emissions may indeed be to air there are uses for which exposure to other compartments cannot be ruled out. Additionally, there is no data provided to demonstrate the lack of exposure to other compartments.

13.1.1. Fish

Table 13-1. Available fish toxicity studies on HFE-7500

Method	Results	Remarks	Reference
Oryzias latipes freshwater semi-static Japanese Industrial Standard (JIS K 0102-1998-71), "Testing methods for industrial waste water, Acute toxicity test with fish".	LC50 (96 h): > 10 mg/L test mat. (nominal)	key study experimental result Test material (IUPAC name): 3- ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)-hexane	ECHA dissemination website
Oryzias latipes	LC50 (48 h): > 50 mg/L test mat.	3 (not reliable) supporting study	ECHA dissemination

freshwater semi-static Japanese Industrial Standard Method "JIS K0102-1993, Industrial Waste Water Testing Method, 71, Acute toxicity study using fish".	(nominal)	experimental result Test material (IUPAC name): 3- ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-(trifluoromethyl)-hexane	website

Two acute studies using *Oryzias latipes* (high-eyes medaka or orange-red killifish) are available for HFE-7500. Both tests were conducted following the Japanese test guideline JIS K 0102- 1998-71 ("Testing methods for industrial waste water, Acute toxicity test with fish"). In the key study the fish were exposed to the test substance for 96 hours, with replacement of test medium every 8 to 16 hours, using a limit concentration of 10 mg/L test substance (nominal concentration). 2-methoxyethanol and HCO-20 were used as solubilising agents at concentrations of ca. 1000 mg/L and 200 mg/L, respectively. No mortality was observed during the test. A LC50 of > 10 mg/L based on nominal concentration is reported. This is well above the water solubility limit of the substance and the exposure concentrations were not analytically verified. Therefore, the study is not considered reliable.

The other study is also considered not reliable due to its short duration (48 hours) as well as the high nominal concentration used and the lack of analytical confirmation of the exposure concentration.

Hence, there is no reliable information on the toxicity of HFE-7500 to fish.

ECOSAR (v1.11) predicts a chronic value of 0.013 mg/L for fish. No specific class is included in the ECOSAR for per- and polyfluorinated alkyl substances, and hence, the prediction is for neutral organics ECOSAR class and is only based on the log Kow value. The ECOSAR QSAR model predictions have uncertainties and can only be used as supporting information.

13.1.2. Aquatic invertebrates

No relevant experimental information is available.

ECOSAR (v1.11) predicts a chronic value of 0.019 mg/L for Daphnia. The same considerations on the reliability of ECOSAR predictions as those indicated above for fish apply for Daphnia.

13.1.3. Algae and aquatic plants

No relevant experimental information is available.

ECOSAR (v1.11) predicts a chronic value of 0.146 mg/L for algae. In the case of algae, ECOSAR estimate chronic toxicity at 72 or 96h. The exposure time considered is not indicated in this estimation which means that the Chr result could be a higher value. The same considerations on the reliability of ECOSAR predictions as those indicated above for fish apply for algae.

13.1.4. Sediment organisms

No relevant experimental information is available.

13.1.5. Other aquatic organisms

No relevant experimental information is available.

13.2. Terrestrial compartment

No relevant data is available.

13.3. Microbiological activity in sewage treatment systems

One study on the toxicity of HFE-7500 to activated sludge microorganisms performed following OECD TG 209 is available. A 30min-EC50 of >100 mg/L and a 30min-NOEC of 100 mg/L based on respiration rate are reported.

13.4. PNEC derivation and other hazard conclusions

Not evaluated during this substance evaluation.

13.5. Conclusions for classification and labelling

The Substance has a harmonised classification as Aquatic Chronic 4. The eMSCA supports this classification as there is a concern for aquatic toxicity. No long-term tests on aquatic organisms are available but the Substance is not rapidly degradable in accordance with Section 4.1.2.9.5 of CLP and has an experimentally determined BCF ≥ 500.

The Substance also fulfils the criteria for classification as vPvB (EUH441) according to the criteria in the amended CLP Regulation[3].

14. Human Health hazard assessment

Human health endpoints were not evaluated.

15. Assessment of endocrine disrupting (ED) properties

Not evaluated during this substance evaluation.

16. PBT /vPvB and PMT/vPvM assessment

16.1. Persistence

Parent substance:

No experimental information on hydrolysis is available. Based on the structure of the substance and the available information on a similar substance, hydrolysis is not expected.

Based on the available publications on the phototransformation in air, HFE-7500 has an atmospheric half-life in the range of 0.21-1.5 years. However, these are based on laboratory kinetic studies and therefore the half-lives may be different under environmental conditions.

In an OECD TG 301 D test, negligible degradation of HFE-7500 was observed. Hence, the substance is not readily biodegradable and screens as potentially P/vP.

Also the BIOWIN QSAR models predict slow or no degradation of the substance. Based on CATALOGIC biodegradation pathway predictions, the probabilities of the first transformation steps of HFE-7500 are very low.

HFE-7500 has a perfluorinated region consisting of a branched C7 chain where all the carbons are perfluorinated except the one where the oxygen of the ether bond is connected. On the other side of the ether bond there is an ethyl group. Hence, HFE-7500 is a highly fluorinated substance and due to the known high stability of C-F bond and the slow or negligible degradation observed for other per- and polyfluorinated substances, HFE-7500 is also expected to show very slow biodegradation in the environment. Especially mineralisation will be negligible due to the perfluorinated region, although some primary transformation in the hydrocarbon region cannot be excluded.

Due to its low water solubility (0.021 mg/L) and high volatility, HFE-7500 may disappear rapidly from surface water and soil via volatilisation, and hence, these compartments may not be relevant for the persistence assessment. However, based on the high log Koc value (4.88), part of the substance may adsorb to suspended material and end up in the sediment. Based on distribution modelling (see section 12.2.3), air and sediment are the most relevant compartments for the substance.

In the aerobic OECD TG 308 study performed with unlabelled HFE-7500 following the Substance Evaluation decision, all the DT50 values estimated for dissipation of HFE-7500, when including all time points in the kinetic analysis, are above 180 days. Also most of the best case DT50 values of the bioactive and toxicity control vessels, calculated based on time points after the initial increase of HFE-7500 concentrations observed in the test vessel, are above or very close to 180 days. The degradation half-lives of HFE-7500 are expected to be even higher than these as based on the results of the sterile controls and the very low levels of transformation/degradation products observed in the biotic vessels, most of the disappearance of the parent substance was likely due to other dissipation processes than degradation. Based on the similar decrease of parent substance observed in the sterile water-sediment controls and in the sterile water only control, leakage from the test system appeared to occur. Furthermore, presence of the parent substance in NER cannot be excluded either. The conservative half-life values of HFE-7500 estimated based on the formation of the degradation product PFBA in the OECD TG 308 study are in the range of tens and hundreds of years.

The study had some deviations from the OECD TG 308 guideline and some of them may have favoured degradation (e.g. shaking after acclimation and during incubation) and others may have disfavoured degradation (lower bioavailability due to spiking of sediment, different water-sediment volume ratio, occasionally decreased oxygen levels). In conclusion, none of the determined DT50 values are fully reliable. However, most of the DT50 values for bioactive and toxicity controls, even the best case DT50 values, are above the 180 days. The study is considered reliable with restrictions and the high DT50 values and very low formation of transformation products during the 160 day study duration are considered sufficiently reliable information to demonstrate that HFE-7500 is a very persistent substance.

In the anaerobic OECD TG 308 study, HFE-7500 remained stable during the 160 days study duration and very low levels of PFBA were detected. Hence, the substance is very persistent also under anaerobic conditions.

Transformation/degradation products

Based on the information in the available photo transformation studies (Goto et al 2002, Rodriguez et al 2014), the degradation of HFE-7500 in air is initiated by indirect photolysis of the hydrocarbon region leading to formation of segregated C7-perfluoroalkyl ester. The identified transformation products are an acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ (major product) and a formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$ (minor product). These transformation products have low water solubility and high HLC, and hence, they are expected to mainly remain in the atmosphere.

According to Goto et al. (2002) these products are more resistant to photodegradation than the parent substance. Based on the EPISuite BIOWIN predictions, the acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ and formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$ fulfill the screening criteria for P/vP. However, Goto et al (2002) and Wang et al. (2014) propose a degradation pathway for these products starting from hydrolysis and finally leading to formation of PFBA, but there is no experimental information supporting this proposed pathway. Due to the low water solubility of the acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ and formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$, hydrolysis in the atmosphere may not be significant. Therefore, further information would be needed to confirm which degradation products are relevant for HFE-7500 in the environment.

In the OECD TG 308 (2023) it is speculated that the slow biotransformation of HFE-7500 could follow a degradation pathway which might involve a diol intermediate which could be expected to hydrolyze to form PFBA, along with 1H-heptafluoropropane (HFC-227) and/or hexafluoropropene. PFBA and HFC-227 were observed to form in cultures at trace levels and are confirmed to be transformation/degradation products of HFE-7500. Hexafluoropropene was not observed in the test cultures.

PFBA belongs to the group of perfluorinated carboxylic acids which in general are known to be highly persistent. Based on BIOWIN QSAR models the substance screens P/vP. In the OECD TG 308 with the Substance, bioactive PFBA controls were included and no significant decrease of PFBA was observed during the 160 day study. Hence, it is likely to fulfill the criteria for P/vP.

16.2. Bioaccumulation

Parent substance:

HFE-7500 has measured log Kow values in the range of 5.75-6.0, and hence, it screens as B/vB.

A steady-state BCF of 5200 for carp is reported in a bioconcentration in fish study following OECD TG 305 (Unnamed 2002). Although solubilising agents (HCO-20 and 2-methoxyethanol) were used due to the low solubility of the substance, the concentrations of these agents were low and well below the maximum limits indicated in the OECD TG 305 and the known toxicity values for fish. Therefore, the study is considered adequate for the B assessment of the substance.

The eMSCA recalculated the steady state BCF and normalised it to 5% lipid content using the average value of 3.77 % calculated based on the mean lipid content at the start and end of the test. This resulted in a steady state BCF_{SS} of 5317 L/kg and a 5% lipid normalised BCF_{SSL} of 7052 L/kg.

The eMSCA determined also a kinetic BCF of 5874 L/kg and a 5% lipid normalised BCFkL of 7790 L/kg based on the raw data available in the robust study summary. The estimated depuration rate (k_2) and half-life were 0.056 day^{-1} and 12.3 days, respectively. Growth correction could not be done as raw data on the fish weights was not available. However, based on the average weights of fish at the start and end of the test indicated in the robust

study summary, the fish grew significantly. Therefore, the growth corrected kinetic BCF would be even higher.

In conclusion, HFE-7500 fulfils the criteria for B and vB.

Transformation/degradation products

The identified phototransformation products of HFE-7500, acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ and formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$ screen for B/vB based on their predicted log Kow values.

PFBA is a perfluorinated carboxylic acid (PFCA) and some longer-chained PFCAs are known to bioaccumulate through protein binding in air-breathing organisms.

16.3. Mobility

Not assessed.

16.4. Toxicity

HFE-7500 is not classified as Carcinogenic 1A or 1B, Mutagenic 1A or 1B, Toxic to reproduction 1A, 1B or 2 or STOT RE 1 or 2.

Regarding aquatic toxicity, there is no reliable experimental acute data and no experimental chronic data for the substance. Based on ECOSAR predictions the chronic values are close to the 0.01 mg/L threshold.

No information is available on the toxicity of the phototransformation products acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ and formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$.

Therefore, no conclusion can be drawn on toxicity.

16.5. Conclusions of the PBT/vPvB/PMT/vPvM assessment and related classification and labelling

Based on the available information, HFE-7500 fulfils the criteria for P/vP and B/vB. No conclusion can be drawn on toxicity based on the available information. Therefore, the substance is concluded to be vPvB.

The phototransformation products acetate ester *n*-$C_3F_7CF(OC(O)CH_3)CF(CF_3)_2$ and formate ester *n*-$C_3F_7CF(OC(O)H)CF(CF_3)_2$, screen for P/vP and B/vB.

PFBA is likely to be P/vP and it may potentially be B/vB in air-breathing organisms. The Danish MSCA is preparing a RMOA on the potential CMR and PBT properties of PFBA and its salts and precursors.

Mobility of HFE-7500 was not assessed.

17. Exposure assessment

Not evaluated in this assessment.

The Substance is concluded to be vPvB. Therefore, exposure of the environment should be minimised. Only industrial use in closed systems is currently registered. However, due to the high volatility of the Substance, emissions to air cannot be excluded during use, charging and cleaning of the equipment. As the Substance is very persistent and bioaccumulative and belongs, together with its highly persistent degradation product PFBA, to a wide group of per- and polyfluorinated alkyl substances (PFAS) even low emissions of the Substance add up to the total PFAS pollution in the environment.

The Substance and its use are covered by the current universal PFAS restriction proposal that is under development in the EU. Further assessment of exposure, taking into account all relevant PFAS and their uses, may be performed under that process.

18. Risk characterisation

Not applicable as no exposure assessment performed in this evaluation.

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20. Abbreviations

BPR	Biocidal products regulation (EU) 528/2012
BAF	bioaccumulation factor
BCF	bioconcentration factor
CLP	Classification, labelling and packaging
CoRAP	Community rolling action plan
CCH	Compliance check
CFC	chlorofluorocarbon
CFU	Colony-forming unit
CMR	Carcinogenic, mutagenic and toxic for reproduction
DFOP	Double First-Order in Parallel
DT50	degradation half-life

ECHA	European chemicals agency
EC	European community
EC50	50% effect concentration
EU	European union
GC	Gas chromatography
GC-FID	Gas chromatography - Flame ionization detector
GC/MS	Gas chromatography Mass spectrometry
HCFC	hydrochlorofluorocarbon
HCO-20/40	Polyoxyethylene Hydrogenated Castor Oil
HFC	hydrofluorocarbon
HFC-22	1H-heptafluoropropane
HFE	hydrofluoroether
HFPO-DA	2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoic acid
HFPP	hexafluoropropene
HLC	Henry's Law Constant
HPLC	high-performance liquid chromatography
Koc	organic carbon-water partition co-efficient
Kow	n-Octanol/Water Partition coefficient
LC50	50% lethal concentration
LC MS/MS	Liquid chromatography tandem mass spectrometry
LOQ	Limit of quantification
LLOQ	Lower limit of quantification
LMS	Laboratory matrix spike
MSCA	Member state competent authority
NER	Non-extractable residues
NOEC	No observed effect concentration
NONs	Notification of new substances
OC	Organic carbon
OECD	Organisation for Economic Cooperation and Development
PBT	Persistent, bioaccumulative and toxic

PFBA	Perfluorobutyric acid
PFAS	Per- and polyfluoroalkyl substances
PFC	perfluorocarbon
PFHS	perfluorohexanesulfonate
POP	Persistent organic pollutants
PPP	Plant protection products regulation EC 1107/2009
PNEC	Predicted no-effect concentration
QSAR	(quantitative) structure activity relationships
REACH	Regulation No 1907/2006 concerning registration, evaluation, authorisation, and restriction of chemicals
RAR	Risk assessment report
RMOA	Risk management options analysis
RoI	Registry of Intentions
RSD	relative standard deviation
SDS	sodium dodecyl sulfate
SFO	single first-order
STOT RE	Specific target organ toxicity – repeated exposure
SVHC	Substances of very high concern
TG	Test guideline
ThOD	Theoretical oxygen demand
TPE	Testing proposal examination
UNEP	United nations environment program
vPvB	Very persistent and very bioaccumulative
VOA	Volatile organics analysis