

Annex XV report

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

Substance Name: reaction mass of 2,2,3,3,5,5,6,6-octafluoro-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)morpholine and 2,2,3,3,5,5,6,6-octafluoro-4-(heptafluoropropyl)morpholine

EC Number: 473-390-7

CAS Number: -

Submitted by: Belgium

Date: August 2022

This document has been prepared according to template: TEM-0049.04

CONTENTS

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57	6
PART I.....	8
JUSTIFICATION	8
1. IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES ..	8
1.1. Name and other identifiers of the substance	8
1.2 Composition of the substance	8
1.3 Identity and composition of degradation products/metabolites relevant for the SVHC assessment.....	9
1.4 Identity and composition of structurally related substances (used in a grouping or read-across approach).....	9
1.5 Physicochemical properties	11
2. HARMONISED CLASSIFICATION AND LABELLING	12
3. ENVIRONMENTAL FATE PROPERTIES	13
3.1 Degradation.....	13
3.1.1 Abiotic degradation.....	13
3.1.2 Biodegradation	14
3.1.3 Field data.....	16
3.1.4 Summary and discussion of degradation.....	16
3.2 Environmental distribution	17
3.2.1 Adsorption/desorption	17
3.2.2 Volatilisation.....	17
3.2.3 Distribution modelling	18
3.2.4 Field data.....	21
3.2.5 Summary and discussion of environmental distribution	21
3.3 Data indicating potential for long-range transport	21
3.4 Bioaccumulation	21
3.4.1 Bioaccumulation in aquatic organisms (pelagic & sediment organisms).....	21
3.4.2 Bioaccumulation in terrestrial organisms (soil dwelling organisms, vertebrates)	25
3.4.3 Field data.....	26
3.4.4 Summary and discussion of bioaccumulation	26
4. HUMAN HEALTH HAZARD ASSESSMENT	26
5. ENVIRONMENTAL HAZARD ASSESSMENT	27
5.1 Aquatic compartment (including sediment).....	27
5.1.1 Fish	27
5.1.2 Aquatic invertebrates	27
5.1.3 Algae and aquatic plants	28
5.1.4 Sediment organisms	28
5.1.5 Other aquatic organisms	28
5.2 Terrestrial compartment.....	28
5.3 Atmospheric compartment	28
5.4 Microbiological activity in sewage treatment systems.....	28

5.5 Toxicity to birds	29
5.6 Mammalian wildlife	29
5.7 Endocrine disruption (Environment)	29
5.8 Other effects	29
5.9 Summary and discussion of the environmental hazard assessment	29
6. CONCLUSIONS ON THE SVHC PROPERTIES	30
6.1 CMR assessment.....	30
6.2 PBT and vPvB assessment.....	30
6.2.1 <i>Assessment of PBT/vPvB properties</i>	30
6.2.2 <i>Summary and overall conclusions on the PBT and vPvB properties</i>	32
6.3 Assessment under Article 57(f)	33
PART II.....	34
7. REGISTRATION AND C&L NOTIFICATION STATUS	34
7.1 Registration status.....	34
7.2 CLP notification status.....	34
8. TOTAL TONNAGE OF THE SUBSTANCE.....	34
9. INFORMATION ON USES OF THE SUBSTANCE	35
10. INFORMATION ON STRUCTURE OF THE SUPPLY CHAIN.....	36
11. ADDITIONAL INFORMATION.....	36
11.1 Substances with similar hazard and use profiles on the Candidate List	36
11.2 Alternatives.....	36
11.3 Existing EU legislation.....	36
11.4 Previous assessments by other authorities/ongoing regulatory activities.....	36
REFERENCES FOR PART I	37
REFERENCES FOR PART II	39

TABLES

Table 1: Substance identity	8
Table 2: Constituents other than impurities/additives	9
Table 3: Structurally related substance 1 identity	9
Table 4: Structurally related substance 2 identity	10
Table 5: Structurally related substance 3 identity	11
Table 6: Overview of physicochemical properties.....	12
Table 7: EPI Suite distribution modelling (Level III Fugacity model)	19
Table 8: NewEQC Level III Fugacity modelling.....	19
Table 9: EUSES environmental distribution modelling	21
Table 10: Test conditions in OECD TG 305 study	23
Table 11: Measured tissue and water concentrations.....	24
Table 12: Registration status	34
Table 13: CLP notifications	34
Table 14: Tonnage status	34
Table 15: Uses.....	35

ABBREVIATIONS

ASTM :	American Society for Testing and Materials
B :	Bioaccumulative
BCF :	Bioconcentration factor
CA :	Competent Authority
CLP :	Classification, Labelling and Packaging
EC ₅₀ :	Concentration that causes 50% of the effect
ECHA :	European Chemicals Agency
ED :	Endocrine disruption
EU :	European Union
EUSES :	European Union System for the Evaluation of Substances
GLP :	Good Laboratory Practice
K _{aw} :	Air-water partition coefficient
K _{oa} :	Octanol-air partition coefficient
K _{oc} :	Organic carbon normalized adsorption coefficient
K _{ow} :	n-octanol/water partition coefficient
LC ₅₀ :	Concentration that is lethal for 50% of the organisms
LD ₅₀ :	Dose that is lethal for 50% of the organisms
NOAEL :	No Observed Adverse Effect Level
OECD :	Organisation for Economic Co-operation and Development
P :	Persistent
PBT :	Persistent, bioaccumulative and toxic
PFCA :	Perfluorocarboxylic acid
PFHxS :	Perfluorohexane-1-sulphonic acid
PFOA :	Perfluorooctanoic acid
QSAR :	Quantitative Structure-Activity Relationship
REACH :	Regulation No 1907/2006 concerning Registration, Evaluation, Authorisation and Restriction of Chemicals
STOT RE :	Specific target organ toxicity – repeated exposure
SVHC :	Substance of Very High Concern
T :	Toxic
TG :	Test Guideline
TGD :	Technical Guidance Document
TOC :	Total organic carbon
vB :	Very bioaccumulative
vP :	Very persistent
vPvB :	Very persistent and very bioaccumulative

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

Substance name: reaction mass of 2,2,3,3,5,5,6,6-octafluoro-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)morpholine and 2,2,3,3,5,5,6,6-octafluoro-4-(heptafluoropropyl)morpholine

EC number: 473-390-7

CAS number: -

- It is proposed to identify the substance as very persistent and very bioaccumulative (vPvB) according to Article 57(e) of Regulation (EC) No 1907/2006 (REACH).

Summary of how the substance meets the criteria set out in Article 57 of the REACH Regulation

A weight-of-evidence determination according to the provisions of Annex XIII of REACH has been used to identify reaction mass of 2,2,3,3,5,5,6,6-octafluoro-4-(1,1,1,2,3,3,3-heptafluoro-propan-2-yl)morpholine and 2,2,3,3,5,5,6,6-octafluoro-4-(heptafluoropropyl)morpholine (referred to as 'EC 473-390-7' in this document) as vPvB. All available information such as the results of standard tests, information from the application of the analogue approach (read-across) and (Q)SAR results was considered together in a weight-of-evidence approach.

EC 473-390-7 is a substance that consists of two main constituents that are structural isomers. Their chemical structures are very similar. Therefore, the vPvB assessment performed for EC 473-390-7 is also valid for the two individual constituents.

Persistence

Based on a weight-of-evidence approach and considering assessment information in accordance with REACH Annex XIII Section 3.2.1.(d), it is concluded that EC 473-390-7 is very persistent due to its C-F bonds which cannot be broken under environmental conditions, and the abundant presence of fluorine atoms shields the carbon skeleton from other transformation reactions. This is supported by a ready biodegradation study (OECD TG 310; reliable with restrictions) which showed no degradation of EC 473-390-7 and by QSAR predictions (low reliability). No abiotic degradation is expected for this substance. Based on structural similarity, persistence in the air compartment is expected for EC 473-390-7 as analogous substances like perfluorocyclobutane show half-lives of more than 1000 years.

In summary, EC 473-390-7 is considered to be very persistent in all environmental compartments as no indications are found that it can undergo abiotic or biotic degradation under relevant environmental conditions. Half-lives are expected to largely exceed the triggers for 'persistence' (P) and 'very persistent' (vP) criteria (degradation half-life

>60 days in water and degradation half-lives >180 days in sediment or soil) of REACH Annex XIII, exhibiting extreme persistence beyond current regulatory criteria.

Bioaccumulation

The substance screens as bioaccumulative according to REACH Guidance Chapter R.11 based on its $\log K_{ow} > 4.5$. Based on the results from an experimental bioaccumulation study (reliable with restrictions) with EC 473-390-7, a kinetic BCF_k and a steady-state BCF_{ss} were determined. Detailed analysis of the available test data leads to a kinetic BCF_k of 9585 with a 95% confidence interval of 5492–16726. Assuming that steady-state was reached in the study and applying the least conservative mathematical approach a BCF_{ss} of 8418 L/kg is calculated. Taking into account the underlying assumption, it is concluded that the real BCF_{ss} can only be greater than 8418 L/kg, and that this value represents a minimal estimation. The very low depuration rate constant (k_2 of 0.0633 d^{-1}) derived from this bioaccumulation test further confirms the bioaccumulation potential of EC 473-390-7.

Using a weight-of-evidence approach and considering that the lower limit of the 95% confidence interval for the kinetic BCF_k (i.e., 5492) and the estimation of the minimal steady-state BCF_{ss} (i.e., 8418 L/kg) are greater than 5000 and the low depuration rate constant (k_2 of 0.0633 d^{-1}) of EC 473-390-7 is indicative of a $BCF > 5000$, it is concluded that EC 473-390-7 meets the 'bioaccumulation' criterion (B) and the 'very bioaccumulative' criterion (vB) in accordance with Annex XIII, points 1.2.1. and 1.2.2. of the REACH Regulation.

Conclusion on the P and B properties

Based on the information available and using a weight-of-evidence determination, it is concluded that EC 473-390-7 meets the criteria for a vPvB substance in accordance with Annex XIII of the REACH Regulation, and thereby it fulfils the criteria set out in REACH Article 57(e).

Registration dossiers submitted for the substance: Yes

PART I

Justification

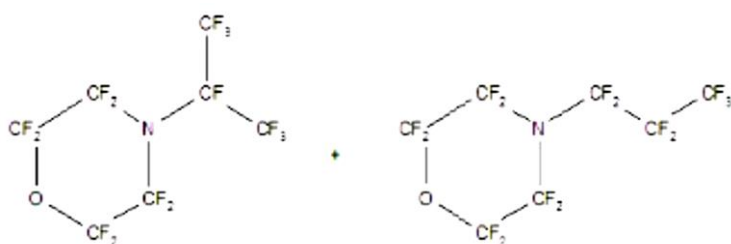
1. Identity of the substance and physical and chemical properties

1.1. Name and other identifiers of the substance

Table 1: Substance identity

EC number:	473-390-7
EC name:	n.a.
CAS number (in the EC inventory):	n.a.
CAS number:	n.a.
IUPAC name:	reaction mass of 2,2,3,3,5,5,6,6-octafluoro-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)morpholine and 2,2,3,3,5,5,6,6-octafluoro-4-(heptafluoropropyl)morpholine
Index number in Annex VI of the CLP Regulation:	n.a.
Molecular formula:	C ₇ F ₁₅ NO
Molecular weight range:	399.0 g/mol
Synonyms:	perfluoro-4-isopropylmorpholine and perfluoro-4-propylmorpholine

Structural formula:



1.2 Composition of the substance

Name: reaction mass of 2,2,3,3,5,5,6,6-octafluoro-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)morpholine and 2,2,3,3,5,5,6,6-octafluoro-4-(heptafluoropropyl)morpholine

Description: EC 473-390-7 is a substance consisting of 2 isomeric perfluorinated substituted propyl morpholines as main constituents

Substance type: multi-constituent

Table 2: Constituents other than impurities/additives

Constituents	Typical concentration	Remarks
2,2,3,3,5,5,6,6-octafluoro-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)morpholine	≥10% - <80%	name: perfluoro-4-isopropylmorpholine
2,2,3,3,5,5,6,6-octafluoro-4-(1,1,2,2,3,3,3-heptafluoropropyl)morpholine	≥10% - <80%	name: perfluoro-4-propylmorpholine

1.3 Identity and composition of degradation products/metabolites relevant for the SVHC assessment

Not relevant for this SVHC dossier.

1.4 Identity and composition of structurally related substances (used in a grouping or read-across approach)

Table 3: Structurally related substance 1 identity

EC number:	206-841-1
EC name:	2,2,3,3,5,5,6,6-octafluoro-4-(trifluoromethyl)morpholine
SMILES:	<chem>FC(F)(F)N1C(F)(F)C(F)(F)OC(F)(F)C1(F)F</chem>
CAS number (in the EC inventory):	382-28-5
CAS number:	382-28-5
IUPAC name:	2,2,3,3,5,5,6,6-octafluoro-4-(trifluoromethyl)morpholine
Index number in Annex VI of the CLP Regulation	n.a.
Molecular formula:	C ₅ F ₁₁ NO
Molecular weight range:	299.0 g/mol
Synonyms:	perfluoro-4-methylmorpholine

Substance type: mono-constituent

Structurally related substance structural formula:

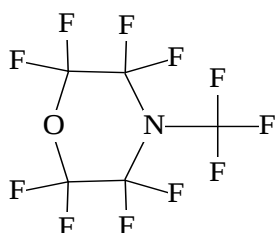


Table 4: Structurally related substance 2 identity

EC number:	204-075-2
EC name:	octafluorocyclobutane
SMILES:	<chem>FC1(F)C(F)(F)C(F)(F)C1(F)F</chem>
CAS number (in the EC inventory):	115-25-3
CAS number:	115-25-3
IUPAC name:	1,1,2,2,3,3,4,4-octafluorocyclobutane
Index number in Annex VI of the CLP Regulation	n.a.
Molecular formula:	C ₄ F ₈
Molecular weight range:	200.0 g/mol
Synonyms:	perfluorocyclobutane

Substance type: mono-constituent

Structurally related substance structural formula:

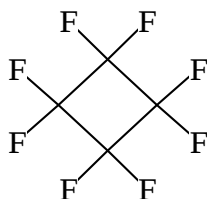
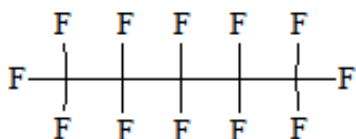


Table 5: Structurally related substance 3 identity

EC number:	211-647-5
EC name:	dodecafluoropentane
SMILES:	<chem>FC(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)F</chem>
CAS number (in the EC inventory):	678-26-2
CAS number:	678-26-2
IUPAC name:	1,1,1,2,2,3,3,4,4,5,5,5-dodecafluoropentane
Index number in Annex VI of the CLP Regulation	n.a.
Molecular formula:	C ₅ F ₁₂
Molecular weight range:	288.0 g/mol
Synonyms:	perfluoropentane

Substance type: mono-constituent

Structurally related substance structural formula:



1.5 Physicochemical properties

Values for physicochemical properties were experimentally determined for the substance as a whole and not for the individual constituents. Considering the very similar chemical structures, namely an isopropyl side chain in one constituent and a n-propyl side chain in the other, it is reasonable to accept that the numerical values for the individual constituents will hardly differ. This is underpinned by the EPI Suite estimations (US EPA, 2000) for the two constituents that indicate that only the log K_{ow} values differ to a small extent.

Table 6: Overview of physicochemical properties

Property	Description of key information	Value [Unit]	Reference/source of information
Physical state at 20 °C and 101.3 kPa		Liquid	ECHA dissemination website
Melting/freezing point		-127 °C at 101.3 kPa	ECHA dissemination website
Boiling point	According to OECD TG 103	96 °C at 101.3 kPa	ECHA dissemination website
Vapour pressure	According to OECD TG 104 ASTM E-1719-97	Key: 6750 Pa at 20 °C 5070 Pa at 20 °C	ECHA dissemination website
Density	According to OECD TG 109	1.80 kg/L at 20 °C	ECHA dissemination website
Water solubility	Equivalent to OECD TG 105	66.2 µg/L at 23 °C	ECHA dissemination website
Partition coefficient n-octanol/water (log value)	Applying solubility ratio method	5.7 at 23 °C	ECHA dissemination website

2. Harmonised classification and labelling

EC 473-390-7 is not listed in annex VI to the CLP Regulation.

3. Environmental fate properties

3.1 Degradation

3.1.1 Abiotic degradation

3.1.1.1 Hydrolysis

A hydrolysis study has not been performed with EC 473-390-7. Based on the chemical functionalities of the two main constituents of the substance, it is considered that hydrolysis does not take place. During manufacture of the substance, very harsh reaction conditions are applied and the substance as the end product of the synthesis is demonstrated to be very stable. Therefore, any chemical transformation under environmental conditions (e.g., ring opening or hydrolysis) is highly unlikely to occur.

It is also noted that the substance does not contain functional groups for which hydrolysis can be estimated by the QSAR model HYDROWIN v2.00 of the EPI Suite tool (US EPA, 2000).

3.1.1.2 Oxidation

Experimental data on oxidation of EC 473-390-7 are not available.

Taking into account the perfluorinated character of the two constituents it is estimated that under environmental conditions the substance is oxidatively very recalcitrant and that degradation by such a process is highly unlikely.

3.1.1.3 Phototransformation/photolysis

3.1.1.3.1 Phototransformation in air

The susceptibility of the substance to phototransformation in air has not been experimentally examined. On the contrary, the structural analogue perfluoro-N-methylmorpholine (PNMM) was examined and appeared to be resistant to direct photolysis under medium pressure mercury lamp irradiation as well as to indirect photolysis by hydroxyl radicals and singlet oxygen atoms (ECHA, Disseminated dossier, 2022). The dissipation half-life of PNMM was calculated to be >1000 years. PNMM differs from the substance only in the length of the alkyl chain attached to the morpholinic nitrogen. Comparison of the UV spectra of the substance and PNMM shows very little difference in the absorption cross sections and therefore similar susceptibility to direct photolysis is assumed. Further, it is considered that perfluoroalkyl chains are inert to oxidative processes. Therefore, it is appropriate to conclude that the substance is very stable in the air compartment with a half-life assessed to be 1000 years or longer. In publicly available literature (Prather *et al.*, 2001), atmospheric lifetimes of 3200 and 4100 years are reported for perfluorocyclobutane and perfluoropentane. These data confirm that in general perfluorinated compounds are extremely stable in the atmosphere and there is no reason to assume that the substance behaves differently.

It is also noted that the substance does not contain functional groups that allow the QSAR model AOP v1.92 of the EPI Suite tool (US EPA, 2000) to estimate a reaction rate constant or a half-life for reaction with hydroxyl radicals or ozone.

3.1.1.3.2 Phototransformation in water

Phototransformation in water is not experimentally tested. There are no indications that this type of degradation process is relevant for the substance.

3.1.1.4 Summary on abiotic degradation

Experimental data on the abiotic degradation of EC 473-390-7 itself are not available. Nevertheless, based on a read-across approach with the structural analogue perfluoro-N-methylmorpholine, no indications are found that the substance can degrade to a relevant extent by abiotic processes under environmental conditions. Based on structural similarity, persistence in the air compartment is expected for EC 473-390-7 as analogous substances like perfluorocyclobutane show half-lives of more than 1000 years.

It is to be noted that many perfluorinated substances have been extensively examined (e.g., PFCAs and PFSAs) and for none of them a relevant abiotic degradation process was found. The covalent C-F bonds are so strong that they resist to acids, bases, oxidation, reduction and high temperatures (Kissa, 2001). There are no indications that in this respect EC 473-390-7 behaves differently.

3.1.2 Biodegradation

In general, the stability of organic fluorine compounds has been described by Siegemund *et al.* (Siegemund, 2012). This author concludes that *"when all valences of a carbon chain are satisfied by fluorine, the zigzag-shaped carbon skeleton is twisted out of its plane in the form of a helix. This situation allows the electronegative fluorine substituents to envelop the carbon skeleton completely and shield it from chemical attack. Several other properties of the C-F bond contribute to the fact that highly fluorinated compounds belong to the most stable organic compounds. These include polarizability and high bond energies, which increase with increasing substitution by fluorine. The influence of fluorine is greatest in highly fluorinated and perfluorinated compounds."*

The fluorine atoms of EC 473-390-7 completely envelop the carbon skeleton and shield it from any attack by microorganisms. These observations strongly suggest that the substance will not biodegrade.

3.1.2.1 Biodegradation in aqueous media or aqueous environment

3.1.2.1.1 Estimated data

The EPI Suite tool (US EPA, 2000) includes several BIOWIN models that provide degradation timeframes for primary and ultimate degradation of chemicals. According to REACH Guidance Chapter R.11. (ECHA, 2017a) the combination of estimates from BIOWIN 2, 3 and 6 can be used as screening criteria that indicate whether compounds are potentially (very) persistent. If the BIOWIN 2 or 6 score is less than 0.5 in combination with a BIOWIN 3 score less than 2.25, one should conclude that the substance is potentially (very) persistent.

For the two constituents of the substance the following estimates are found:

- BIOWIN 2: 0.0000 (<0.5) ➔ Does not biodegrade fast;
- BIOWIN 3: 0.2682 (<2.25) ➔ Ultimate biodegradation longer than months;
- BIOWIN 6: 0.0000 (<0.5) ➔ Not readily degradable.

The estimated values are far below the screening criteria and it is concluded that the substance is potentially (very) persistent. Furthermore, these models estimate the ether and the tertiary amine functionalities in the substance to decrease the biodegradation potential compared with perfluorinated compounds without nitrogen or oxygen in their carbon chain.

On the other hand, these BIOWIN models cannot be expected to predict the biodegradability of perfluorinated compounds with high reliability. The reason is that the training data set is not fully implemented for perfluorinated compounds. In particular, there is no fragment coefficient for $-CF_2-$ moieties in models 2 and 3 and perfluorinated compounds are not represented in the training set.

It is noted that the Biodegradation/Biocatalysis Pathway Prediction System from EAWAG (EAWAG BBD software, 2010) does not present a result for the substance's constituents. Apparently, biodegradation of perfluorinated compounds is hardly or not reported in scientific literature. This observation suggests that it is highly unlikely that biodegradation of perfluorinated substances takes place under environmentally relevant conditions.

3.1.2.1.2 Screening tests

For EC 473-390-7 only one experimental biodegradation study is available: a ready biodegradation test according to OECD Test Guideline 310, i.e., a sealed bottle test with a headspace.

Overall, the approach as recommended in the Test Guideline was applied: 4 sets of bottles are used: 1) test vessels containing the test item; 2) blank controls containing only the test medium plus inoculum; 3) vessels containing sodium benzoate as reference substance; 4) vessels for checking a possible inhibitory effect (toxicity control). All bottles contained mineral medium inoculated with activated sludge from a predominantly domestic source. Test duration was 28 days. In this test the recommended headspace to liquid ratio 1:2 was applied and not decreased, although the Henry's law constant of the test item is higher than the threshold value mentioned in § 11 of the OECD Test Guideline 310. Not adapting the headspace to liquid ratio is considered to lower the reliability of the test. On the other hand, the validity criteria (§ 66) for the test are fulfilled: less than 3 mg/L inorganic carbon was produced in the blank bottles and the reference substance sodium benzoate was degraded for more than 60% by day 14. Therefore, this test is considered to be reliable with restrictions.

Assuming that all inorganic carbon in the toxicity control was due to sodium benzoate, there was no statistical difference between the positive control and the toxicity control. Therefore, it is concluded that the test item does not inhibit the activated sludge. As the concentration of inorganic carbon in the bottles with test item was lower than in the blank bottles, it is concluded that in this study 0% biodegradation is found after 28 days and consequently EC 473-390-7 should be considered as not readily biodegradable.

Moreover, the total lack of biodegradation in this test is fully in line with the overall observation that all perfluorinated compounds are extremely stable and that they all resist to biodegradation.

3.1.2.1.3 Simulation tests

A simulation study is not available for EC 473-390-7.

3.1.2.2 Biodegradation in soil

A biodegradation study in soil is not available for EC 473-390-7.

3.1.2.3 Summary and discussion on biodegradation

In general, the stability of organic fluorine compounds has been described by Siegemund *et al.* (Siegemund, 2012). This author concludes that *"when all valences of a carbon chain are satisfied by fluorine, the zigzag-shaped carbon skeleton is twisted out of its plane in the form of a helix. This situation allows the electronegative fluorine substituents to envelop the carbon skeleton completely and shield it from chemical attack. Several other properties of the C-F bond contribute to the fact that highly fluorinated compounds belong to the most stable organic compounds. These include polarizability and high bond energies, which increase with increasing substitution by fluorine. The influence of fluorine is greatest in highly fluorinated and perfluorinated compounds."*

The fluorine atoms of EC 473-390-7 completely envelop the carbon skeleton and shield it from any attack by microorganisms. These observations strongly suggest that the substance will not biodegrade.

Modelling and screening data support the above findings. Indeed, BIOWIN predictions (low reliability) indicate that EC 473-390-7 screens as potentially persistent (P) or very persistent (vP) and this is confirmed by a screening study (OECD TG 310, reliable with restrictions) where no degradation was observed for EC 473-390-7.

3.1.3 Field data

Measured field data on the presence of EC 473-390-7 are not available.

3.1.4 Summary and discussion of degradation

Experimental data on the abiotic degradation of EC 473-390-7 itself are not available. Nevertheless, based on a read-across approach with the structural analogue perfluoro-N-methylmorpholine, no indications are found that the substance can degrade to a relevant extent by abiotic processes under environmental conditions. Based on structural similarity, persistence in the air compartment is expected for EC 473-390-7 as analogous substances like perfluorocyclobutane show half-lives of more than 1000 years.

It is to be noted that many perfluorinated substances have been extensively examined (e.g., PFCAs and PFASs) and for none of them a relevant abiotic degradation process was found.

Regarding biotic degradation, the ready biodegradation study according to OECD TG 310 (reliable with restrictions) indicates no degradation of the substance. This finding is consistent with the QSAR predictions (low reliability) which point out that (bio)degradation is not expected for EC 473-390-7.

Perfluoroalkyl compounds all share high resistance to environmental and metabolic degradation. This resistance to degradation is primarily due to the high electronegativity and low polarisability of fluorine, which results in the strongest covalent bond known in organic chemistry: the C-F bond (Kissa, 2001). The C-F bond is resistant to acids, bases, oxidation and reduction, and also high temperatures. Multiple C-F bonds on the same geminal carbon lead to additional strengthening of the C-F bond. The strong electron withdrawing effect of the fluorine atoms in perfluoroalkyl moieties also strengthens the skeletal bonds in the carbon chain (O'Hagan, 2008). It is not expected that the length or the shape of the perfluoroalkyl chain has any major impact on the inherent stability of PFASs.

Furthermore, the following perfluorinated compounds that were assessed in the framework of the REACH Regulation were concluded to meet the vP criterion of REACH Annex XIII: PFOA (ECHA, 2013), C₉-C₁₄ PFCAs (ECHA, 2015; ECHA, 2012a; ECHA, 2012b; ECHA, 2012c; ECHA, 2012d; ECHA, 2012e), PFDA (ECHA, 2016) and PFHxS (ECHA, 2017b).

Consequently, based on a weight-of-evidence approach, EC 473-390-7 is considered to be very persistent in all environmental compartments as no indications are found that it can undergo abiotic or biotic degradation under relevant environmental conditions. Half-lives are expected to largely exceed the triggers for 'persistence' (P) and 'very persistent' (vP) criteria (degradation half-life >60 days in water and degradation half-lives >180 days in sediment or soil) of REACH Annex XIII.

3.2 Environmental distribution

A reliable determination of key physicochemical properties is of paramount importance in the assessment of the distribution of substances in environmental compartments. In contrast to other organic substances, the uncharged perfluorinated compounds tend to be at the same time very hydrophobic and also rather lipophobic what makes that their concentrations in all condensed environmental compartments (water, sediment and soil) probably remain quite low. Because of the unusual properties of these compounds, it is often difficult to execute the usual physicochemical tests in a reliable way and the resulting values should be used with care.

The following observations in relation to key physicochemical properties are made. Values for the individual constituents are not available. Considering their chemical structures, it is reasonable to accept that the values in the tables in this section are valid for the individual constituents as well as for the substance as a whole.

3.2.1 Adsorption/desorption

An experimental adsorption/desorption study to determine the K_{oc} value is not available as the practical execution of the test is very challenging. In absence of an experimentally determined K_{oc} , it is best to use a QSAR method to assess the adsorption potential.

EPI Suite (US EPA, 2000) provides two approaches to estimate the K_{oc} . In general, the Molecular Connectivity Index (MCI) method seems to be more reliable than the method based on the $\log K_{ow}$. The MCI method predicts a K_{oc} of 21930 L/kg ($\log K_{oc} = 4.34$) for EC 473-390-7 thus indicating a high potential for adsorption.

3.2.2 Volatilisation

The vapour pressure of the substance was examined in two studies and the study according to OECD Test Guideline 104 is considered to be the most reliable one. Based on this study the vapour pressure was found to be 6750 Pa at 20 °C. The other study according to a US protocol resulted in a value of 5070 Pa and is thus in line with the study according to OECD Test Guideline 104. Also, the estimation with EPI Suite (US EPA, 2000) is in line with the key study as it predicts a vapour pressure of 31200 Pa at 25 °C.

A vapour pressure of 6750 Pa (at 20 °C) is accepted as a reliable and correct estimate. This vapour pressure corresponds with a concentration in air of 1105 g/m³ (= 2.77 mol/m³). Based on this high vapour pressure, the substance is considered to be highly volatile.

Partitioning air-water

The dimensionless Henry's law constant (HL_{Ct}) was measured experimentally by analytically quantifying the concentration of the substance in both the headspace and the water phase of a sealed vial after equilibration. The resulting measured dimensionless HL_{Ct} of 42400 (= 1030 atm·m³/mole) is rather high given the measured values for the volatility (2.77 mol/m³) and the water solubility (1.66×10⁻⁴ mol/m³). Based on the separate values, one would expect a dimensionless HL_{Ct} of 16700.

Because the dimensionless Henry's Law constant is greater than 10000, one may expect that the substance readily evaporates from water bodies.

Partitioning octanol-air

The log K_{oa}-value is not experimentally measured but can be derived from the relationship $K_{oa} = K_{ow}/K_{aw}$ or $\log K_{oa} = \log K_{ow} - \log K_{aw}$. Based on the measured dimensionless Henry's law constant one can derive a log K_{oa}-value of 1.07 (= 5.7-4.63).

3.2.3 Distribution modelling

The distribution of the substance in environmental compartments can be assessed with different modelling programs. All these models have in common that they are based on the methodology developed by Donald Mackay and co-workers (Mackay *et al.*, 2006). One such program is the fugacity module embedded in EPI Suite (US EPA, 2000). This is a rather simple model that does not allow to change default parameters that describe the environmental compartments. More flexible and thus more complex models are the new EQC model developed by the Canadian Environmental Modelling Centre (CEMC, Trent University) and EUSES (ECHA). In the last two programs the assessor has more options to change default values and can adapt the assessment taking into account the use of the substance under investigation.

The three programs were used to examine quantitatively the distribution of the substance in the environment.

EPI Suite

In one of the submodules of EPI Suite (US EPA, 2000), the volatilisation rate and the corresponding half-lives for standardised rivers and lakes are estimated. The half-life in a standard river is estimated to be 2 hours, and the estimated half-life in a standard lake is predicted to be 8 days. These half-lives cannot be used to evaluate the distribution in the environment as the deposition process from air to water or soil is not considered.

In the framework of distribution modelling the level III fugacity module is much more instructive. Such a model predicts the partitioning of a chemical between air, soil, water and sediment using a combination of default environmental parameters and an initial release pattern that can be chosen by the user. In this way, the probable distribution of the substance is examined and as could be expected, the predicted distribution depends on the compartment to which the substance is initially released. Three scenarios were developed, namely initial release to respectively only air, only water and only soil. Taking into account the use scenarios that are described in the registration dossier, the first scenario seems by far to be the most realistic one. The various resulting mass distributions are provided in table 7.

Table 7: EPI Suite distribution modelling (Level III Fugacity model)

Only release to air (ppm)			
Air	Water	Soil	Sediment
999,960	< 1	40	< 1
Only release to water (ppm)			
Air	Water	Soil	Sediment
62,000	260,000	2	678,000
Only release to soil (ppm)			
Air	Water	Soil	Sediment
979,000	< 1	21,000	< 1

If direct releases are only to the air, the substance will stay in the air compartment and its presence in other compartments will be negligible. If direct releases take place to surface water, the sediment is estimated to form the main sink. If the release is to soil, the majority of the substance will evaporate into the air compartment. It should be noted that according to the use of the substance as mentioned in the registration dossier the last two scenarios, i.e., release to water and soil are unlikely to occur in practice.

NewEQC Level III fugacity model

NewEQC incorporates advances in the science of chemical partitioning and reactivity as compared to the original EQC fugacity model. The NewEQC model specifically includes improved treatment of input partitioning and reactivity data, temperature dependence, and sensitivity/uncertainty analysis, as well as providing full user control over a range of substance partitioning parameters.

Based on the assumption that 100% of the emission is directed to the air compartment and assuming a production volume of 250 t/y (i.e., the highest volume reported in the past) the relative distribution between compartments is provided in table 8.

Table 8: NewEQC Level III Fugacity modelling

Air (gas phase)	99.996%
Aerosol in gas phase	$2 \times 10^{-6}\%$
Water	$5 \times 10^{-6}\%$
Soil (gas filled pores)	$4 \times 10^{-3}\%$
Adsorbed to soil	$5 \times 10^{-4}\%$
Sediment	$4 \times 10^{-5}\%$
Biota	$1 \times 10^{-7}\%$

The half-time for transport from soil to air was predicted to be 1.59 hours, which is many orders of magnitude shorter than transport from air to soils (1610 days) or from air to water (461,000 years).

As already indicated, this analysis is based on the reasonable assumption that all emissions are to the atmosphere.

EUSES

In order to verify the analysis made with the NewEQC fugacity model, the environmental distribution was also estimated with EUSES.

EUSES is a user-friendly computer program that allows to estimate the risks posed by chemicals to man and the environment in a quantified manner. To achieve this purpose, several submodules are implemented in the program, one of them being a method to predict the environmental distribution based on the estimated releases and emissions of substances and this on different spatial scales. Therefore, EUSES can be used to get an estimation of to what extent the various environmental compartments will be impacted by the release of the substance. EUSES also allows to assess the influence of the assumptions that are made regarding the emission pattern.

The emission pattern described in EUSES for the most prominent use of the substance is taken as a starting point, namely use as a heat transfer agent. The emission patterns for the production step as well as for the industrial use step were considered. EUSES provides different release fractions for these two steps. For the production step the TGD/EUSES provides the following release fractions : air = 0.05; wastewater = 0.003; industrial soil = 0.0001, while for the industrial use step the release fractions are : air = 0.001; wastewater = 0.005; industrial soil = 0.01. By considering both scenarios separately, one can assess the impact of the underlying assumptions on the quantitative prediction of the distribution.

EUSES allows to estimate the environmental distribution on different spatial scales going from the local scale in a sewage treatment plant (STP) up to the global scale. For the smallest scale (i.e., an STP) EUSES predicts the distribution as follows: air = 33%; water = 4%; sludge = 63%. This result is substantially determined by the adsorption behaviour of a substance and unfortunately that property is not experimentally examined for the substance. So, substantial uncertainty remains on the reliability of this specific estimation.

When considering the distribution estimation for the larger scales, the initial assumptions on the release pattern become less and less influential, and at the largest scale the release patterns do not make a difference anymore.

For the various spatial scales EUSES predicts the relative mass distribution of the substance in percentage as shown in table 9.

Table 9: EUSES environmental distribution modelling

	Air	Agricultural soil	Natural soil	Freshwater	Sediment
Regional scale	82	18	0.4	3×10^{-4}	8×10^{-3}
Continental scale (=EU)	99.74	0.23	0.03	4×10^{-6}	9×10^{-5}
Global scale	99.9	/	0.09	9×10^{-3}	7×10^{-4}

It is concluded that the environmental distribution estimated with EUSES is fully in line with the predictions from the NewEQC model. Over time, when a steady state situation is established, more than 99% of the substance will reside in the air and less than 1% will be found in condensed states. As indicated by the EPI Suite model (US EPA, 2000), the sediment compartment could only form temporarily the main sink in case that direct releases take place to surface water.

3.2.4 Field data

Measured data on the presence of EC 473-390-7 in environmental compartments are not available.

3.2.5 Summary and discussion of environmental distribution

EC 473-390-7 is hydrophobic with a low water solubility (66.2 µg/L), a high log K_{ow} (5.7) and a high potential for adsorption with an estimated log K_{oc} of 4.34.

Based on its vapour pressure (6750 Pa at 20 °C) and its dimensionless HLCT (>10000), the substance is expected to have a high potential for volatilisation to the atmosphere.

Based on the use of the substance as reported in the registration dossier, releases to the air compartment is the most realistic scenario. Distribution modelling indicate that over time, when a steady-state situation is established, more than 99% of EC 473-390-7 will reside in the air and less than 1% will be found in condensed states. As indicated by the EPI Suite model, the sediment compartment could only form temporarily the main sink in case that direct releases take place to surface water.

3.3 Data indicating potential for long-range transport

In order to assess the potential for long-range transport, quantitative half-life values in air, water and soil must be available. In absence of measured data, it is only appropriate to state qualitatively that EC 473-390-7 meets the vP criterion in water, sediment and soil and that the half-life in air is expected to be greater than 2 days based on information on analogue substances (see section '3.1.1.3.1 Phototransformation in air'). In combination with the observation that EC 473-390-7 distributes significantly to the air compartment, it is reasonable to conclude that the substance shows considerable potential for long-range atmospheric transport.

3.4 Bioaccumulation

3.4.1 Bioaccumulation in aquatic organisms (pelagic & sediment organisms)

Screening information

The Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11, v3.0 (pages 68 and 82; ECHA, 2017a), points out that if the log K_{ow} of a substance is greater than 4.5, the substance is potentially (very) bioaccumulative for aquatic organisms.

For EC 473-390-7 a log K_{ow} value of 5.7 has been calculated based on its solubility in water and in n-octanol. Further EPI Suite v4.1 (US EPA, 2000) predicts log K_{ow} values for the isopropyl and n-propyl constituent of respectively 4.55 and 4.70. The small difference between these two values can be attributed to the fact that the perfluorinated isopropyl fragment is not recognised by the model while on the contrary the perfluorinated n-propyl fragment is recognised. As these values are greater than 4.5, it is concluded that both constituents screen as potentially (very) bioaccumulative for aquatic organisms.

QSAR estimations

It is verified whether QSAR models could deliver useful estimations of the bioaccumulation potential of the substance.

At this moment the BCFBAF module in EPI Suite (US EPA, 2000) is not recommended for perfluorinated substances and the maximum number of fluorine atoms in any individual compound is 8, while FC-770 contains 15 fluorine atoms. None of the BCF models in VEGA (VEGA HUB, 2022) can be applied due to a lack of similar substances in the training sets. The BCF baseline model of CATALOGIC (LMC, 2022) cannot be used as FC-770 is out of the structural and mechanistic domain.

Therefore, it is concluded that at the moment QSAR estimations do not provide reliable information on the bioaccumulation potential of the substance.

Experimental information

In the framework of the Substance Evaluation process, a Decision was sent to the registrant(s) of the substance requesting to perform a bioaccumulation study on aquatic organisms according to OECD Test Guideline 305 (OECD, 2012). The registrant(s) carried out a pilot BCF study that was not executed under GLP conditions and which is indicated in the registration dossier to be reliable with restrictions. This study is also considered to be reliable with restrictions.

The pilot BCF study with the substance was performed in closed glass aspirator bottles with a volume of 13.2 L without a headspace. Considering the extremely high measured dimensionless Henry's law constant for the substance, namely 42400, it was clear that avoiding headspaces in the test bottles would be essential in order to be able to establish appropriate substance concentrations in the water phase. One can calculate that employing 13.2 L aspirator bottles a headspace volume of 300 μ L already causes the substance concentration to drop with ca 50% in the water medium. So, one foresaw that relatively minute headspace volume variations in the test bottles will lead to substantially varying substance concentrations in the water phase. In order to find out how an appropriate stable substance concentration could be achieved in the test system three preliminary tests were run proceeding to the BCF study. Whatever test set-up was applied in these preliminary tests, one found that time weighted average concentrations in water were systematically 3 to 6 times lower than the nominal starting concentration. In view of this observation, it was decided to run the BCF study at a nominal substance concentration of 100 μ g/L.

The actual BCF study was carried out with freshwater under flow-through conditions using *Lepomis macrochirus* (common name: bluegill). The test substance was not radiolabelled as specific chemical analysis by gas chromatography was considered to be effective. The uptake duration was 28 days, with fish being sampled on exposure days 7, 14, 21, 27 and 28. A 14-day depuration phase followed with sampling on days 3, 7 and 14. Control chambers were sampled on exposure day 28 and depuration day 14 only.

The test conditions during the study are described in table 10.

Table 10: Test conditions in OECD 305 study

Nominal test item concentration	100 µg/L; Purity 98.5%; No radiolabelling.
Vehicles	Methyl tert-butyl ether (2.4 µL/L); Dimethylformamide (100 µg/L).
Temperature	21.8 – 22.3 °C
Flow rate	38 exchanges/day
pH	7.8
Dissolved oxygen	7.5 - 9.2 mg/L
Hardness	140 - 144 mg CaCO ₃ /L
TOC	< 1 mg/L (in 4 weeks prior to the test)
Apparatus	13.2 L glass bottles without headspace
Number of fish per vessel	6
Acclimation period	14 days
Uptake period	28 days
Depuration period	14 days
Fish weight at study initiation	2.24 g
Fish weight at study termination	2.45 g
Biomass loading rate	ca. 1 g/L

The applied nominal test concentration was thus 100 µg/L while it is expected that the concentrations to which the fish are exposed in reality are lower. Indeed, it is in practice difficult to reduce the headspace to 0 and to avoid all leaks in the test chambers and one has to open the test system from time to time for feeding, cleaning and sampling operations. Based on these observations the test item concentrations in water as given in table 11 are considered to be accurate.

The measured concentrations in fish and in the water medium at the various sampling points are reported in table 11.

Table 11: Measured tissue and water concentrations

Sampling day	Mean tissue concentration and standard deviation (µg/kg wet weight)	Mean water concentration and standard deviation (µg/L)
Uptake day 0, hour 0	-	24.1 ± 4.1
Uptake day 0, hour 4	-	14.6 ± 2.1

Uptake day 1	-	14.8 ± 0.8
Uptake day 7	66300 ± 8500	11.8 ± 4.0
Uptake day 14	52700 ± 22010	6.0 ± 0.32
Uptake day 21	132800 ± 7500	30.7 ± 3.2
Uptake day 27	116500 ± 18300	7.0 ± 2.1
Uptake day 28	94000 ± 18300	7.9 ± 5.6
Depuration day 3	88800 ± 36700	-
Depuration day 7	76100 ± 16500	-
Depuration day 14	36300	-

In a first instance these raw data were used to determine a kinetic BCF. In order to do so, the sequential method approach (OECD TG 305 (2012), annex 5, § 4 & 5) using non-linear regression was applied and resulted in a depuration rate constant k_2 of 0.0633/d. It is noted that in this study fish growth was minimal and corresponds with a growth dilution rate constant k_g of 0.0012/d. Using the depuration rate constant (k_2) in combination with the measured fish tissue concentrations from the uptake phase, an uptake rate constant k_1 of 607/d was calculated. Combination of these two rate constants leads to a BCF_k (k_1/k_2) of 9585 with a 95% confidence interval of 5492-16726. One can also use the simultaneous method (OECD TG 305 (2012), annex 5, § 6) to calculate a BCF_k . Proceeding in this way a BCF_k of 8901 with a 95% confidence interval of 6775-11027 is found.

It is noted that the substance concentrations in the water medium in the various test bottles differed a lot. The lowest concentration in water was 6.0 µg/L and the highest value was 30.7 µg/L. The simple mean of the daily water concentrations was 14.6 µg/L and the time weighted average 13.84 µg/L. In the BCF calculation the simple mean is used as this represents the less conservative approach. One of the validity criteria of the OECD 305 test with aqueous exposure (OECD 305, § 24) states that the concentration of the test substance should be maintained within 20% of the mean value. Despite the fact that a stable test concentration could not be generated, the results of the study are considered to be relevant and should be used in the determination of the BCF. In this study, the substantial variation in exposure concentration between the bottles is caused by subtle differences in the bottle set-up and their operation conditions and not by erroneous analysis of the water samples. Although the precision is rather poor, the calculated BCF_k is estimated to be accurate and not biased. Because the lowest boundary of the 95% confidence intervals is calculated to be 5492 and thus still greater than the very bioaccumulative (vB) criterion ($BCF > 5000$) for aquatic organisms, it is appropriate to conclude that the substance meets the vB criterion for aquatic organisms.

Besides a kinetic BCF_k also a steady-state BCF_{ss} could be determined. In this experiment it is not clear when steady-state can be considered to be reached or whether steady-state is reached at all, but comparing the concentrations in water and in the fish at all sampling points during uptake (i.e. at day 7, 14, 21, 27, 28), regardless whether steady-state would be established or not, one comes to the following average BCFs: arithmetic mean = 9454 L/kg; geometric mean = 8418 L/kg; median value = 8783 L/kg. It is to be noted that the real BCF_{ss} can only be greater than the BCFs derived in this way and so this confirms that the substance meets the vB criterion for aquatic organisms.

In ECHA's PBT/vPvB guidance (ECHA, 2017a, § 4.1.2.9) it is stated that uptake rates are rather similar for neutral organic compounds and as a result the elimination rate is the

discriminating factor in the bioaccumulation potential of such compounds. It is also recognised that the uptake rate constant depends on the fish weight and in ECHA's Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7c, v3.0 (page 37) (ECHA, 2017c, § 7.10.4.1), the following formula is given to establish the expected uptake rate constant: $k_1 = 520 \cdot \text{fish wet weight}^{(-0.32)}$ L/kg/d. Assuming linear growth during the test, the fish weight at the start of depuration is estimated here at 2.38 g. Based on this fish weight, one can calculate the uptake rate constant to be 394 L/kg/d. Consequently, one can conclude that if the depuration rate constant is less than 0.0788/d (= 394/5000), the very bioaccumulative criterion would be fulfilled. In this study the depuration rate constant was found to be 0.0633/d and so this observation confirms that the substance meets the very bioaccumulative criterion for aquatic organisms. Besides, it should be noted that in this analysis the variable exposure conditions employed in the test do not affect the result, and as such it represents a reliable additional argument in assessing the bioaccumulation potential.

It is noted that in this study fish mortality is observed in the test chambers and even to a greater extent in the control chambers without test item. Mortality also did not associate with measured exposure concentrations. Therefore, it is reasonable to assume that fish mortality is not caused by the test item but is triggered by the experimental set-up. In order to check whether the circumstances that caused fish mortality also had an influence on the determined BCFs, the BCFs were recalculated omitting those replicates where some fish did not survive (i.e., replicates for exposure days 14 and 27 and depuration days 7 and 14). Proceeding in this way an arithmetic mean BCF of 7281 L/kg and a depuration rate constant k_2 of 0.019/d was found. It is noted that based on this alternative approach the vB criterion is still met and consequently that the observed mortality in some replicates is not a reason to reject the study or its results.

In the determination of a BCF it is the customary approach to take into account the lipid content of the fish that are employed in the study. Paragraph 2 of the OECD TG 305 mentions that the BCF should be expressed on a 5% lipid content basis. Unfortunately, it was in practice not possible to find out the lipid content of the fish used in this test and thus the estimated BCF_k of 9585 represents a non-normalised value. It is noted that normalisation of the BCF would only lead to a different end conclusion regarding the fulfilment of the very bioaccumulative criterion if the mean lipid content of the fish had been greater than 9.585%. This condition is considered to be highly unlikely, especially since the observed mortality and morbidity indicate stressful conditions for the fish.

Based on this study, one cannot definitively conclude which mechanism (passive diffusion driven by hydrophobicity versus specific binding to proteins) causes the observed bioaccumulation. It is reasonable to assume that storage in lipids is the most likely route because the $\log K_{ow}$ of FC-770 is 5.7 and one may reasonably assume that organisms are not at all able to metabolise these very stable perfluorinated compounds. Although FC-770 is an amine it is a very weak base because of the great electron withdrawing effect of the fluorine atoms. Being predominantly a neutral molecule FC-770 is unlikely to bind to proteins.

3.4.2 Bioaccumulation in terrestrial organisms (soil dwelling organisms, vertebrates)

Based on the calculated $\log K_{ow}$ and the measured dimensionless Henry's law constant a $\log K_{oa}$ value of 1.07 is determined for the substance. As the $\log K_{oa}$ is far less than the threshold value set in the PBT guidance (ECHA, 2017a) for bioaccumulation in air-breathing organisms ($\log K_{oa} = 5$), one may assume that the bioaccumulation potential for these species is very low.

This conclusion is in line with the results of a non GLP toxicokinetic study. In this study three single doses (100, 300 and 1000 mg/kg bw) of EC 473-390-7 were administered to

male Sprague-Dawley rats by gavage. Monitoring of serum, liver, urine and faeces took place up to 48 hours after administration. In serum, liver and urine no quantifiable levels of EC 473-390-7 or other fluorinated metabolites were found. EC 473-390-7 was quantifiable in the fecal samples but only up to 27% of the administered dose. Because the concentration in fat tissues was not measured and most of the administered dose was not retrieved analytically, this study does not allow to provide a full picture of the bioaccumulation potential of the substance in mammals.

3.4.3 Field data

Measured data on the presence of EC 473-390-7 in aquatic or terrestrial organisms are not available.

3.4.4 Summary and discussion of bioaccumulation

The substance screens as bioaccumulative according to REACH Guidance Chapter R.11 (ECHA, 2017a) based on its $\log K_{ow} > 4.5$.

Based on an experimental bioaccumulation study with fish via aqueous exposure (reliable with restrictions), it is concluded that the substance shows a high potential for bioaccumulation in aquatic organisms with BCF_k and $BCF_{ss} > 5000$ and a low depuration rate constant (k_2 of 0.0633 d^{-1}) which is indicative of a $BCF > 5000$. Based on a weight-of-evidence approach, it is concluded that EC 473-390-7 meets the 'bioaccumulation' criterion (B) and the 'very bioaccumulative' criterion (vB) of REACH Annex XIII ($BCF > 5000$) for aquatic organisms.

Regarding the bioaccumulation potential for terrestrial organisms one can refer to the screening criterion, namely the $\log K_{oa}$. The estimated $\log K_{oa}$ of the substance is far less than the threshold value mentioned in the PBT guidance. Therefore, EC 473-390-7 is not expected to be bioaccumulative for air-breathers. However, this screening information cannot be fully confirmed by available information on toxicological and pharmacokinetic studies in mammals as uncertainties remain regarding available toxicokinetic data.

4. Human health hazard assessment

Not relevant for the identification of the substance as a SVHC in accordance with Article 57(e) of the REACH Regulation.

5. Environmental hazard assessment

5.1 Aquatic compartment (including sediment)

5.1.1 Fish

5.1.1.1 Short-term toxicity to fish

A semi-static short-term fish test with *Danio rerio* was carried out according to OECD Guideline 203 using 10 litre sealed glass containers with a fill volume of 9.5 litres. The loading rate of the test substance was 100 mg/L which is far above its water solubility (i.e., 0.066 mg/L). Test solutions were prepared daily by stirring for approximately 1 hour in air-tight vessels. After a stabilisation period of 5-25 minutes, the Water Accommodated Fraction (WAF) was collected by siphoning and used for the test. The final test solutions were all clear and colourless.

Concentrations of the substance, in the freshly prepared solutions, were 0.159 mg/L and 0.214 mg/L at 0 and 72 hours, respectively. The substance concentrations in the test solutions after 24 hours were all below the limit of quantitation (LoQ). As the rate at which the substance disappears from the test vessel is not monitored, it is also not possible to estimate a reliable time weighted average and to present a sensible value for LC₅₀. One can only conclude qualitatively that in this test no mortality is observed.

5.1.1.2 Long-term toxicity to fish

A long-term test with fish is not available for EC 473-390-7.

5.1.2 Aquatic invertebrates

5.1.2.1 Short-term toxicity to aquatic invertebrates

A semi-static acute immobilisation test was performed with *Daphnia magna* according to OECD Guideline 202 using 100-mL sealed glass containers. A limit test was conducted with an initial loading rate of 100 mg/L which is far above the substance's water solubility (i.e., 0.066 mg/L). The test solutions were prepared each day by stirring for approximately 1 hour in air-tight vessels. After a stabilisation period of 5-25 minutes, the Water Accommodated Fraction (WAF) was collected by siphoning and used for the test. The final test solutions were all clear and colourless.

The actual substance concentrations to which the *Daphnia* were exposed are unknown since the substance concentrations in the test solutions after 24 hours were all below the limit of quantitation (LoQ). The concentration of Substance in the freshly prepared solutions were 0.1 mg/L and in one case <LoQ. As the rate at which the substance disappears from the test vessel is not monitored, it is also not possible to estimate a reliable time weighted average and to present a sensible EC₅₀ value. One can only conclude that in this test limited immobilisation (5%) is observed in the exposed organisms.

5.1.2.2 Long-term toxicity to aquatic invertebrates

A long-term test with fish is not available for EC 473-390-7.

5.1.3 Algae and aquatic plants

An algae growth inhibition test was performed using *Pseudokirchnerella subcapitata* in freshwater under static conditions (OECD Guideline 201) using 100 mL septum-sealed glass bottles. The substance concentration corresponded to an initial loading rate of 100 mg/L which is far above its water solubility (i.e., 0.066 mg/L).

The test solutions were prepared by stirring a loading rate of 100 mg/L for approximately 1 hour in air-tight vessels. After a stabilisation period of 5-20 minutes, the Water Accommodated Fraction (WAF) was collected by siphoning and used for the test. The final test solutions were all clear and colourless. The substance concentration on day 0 was 0.479 mg/L but the samples after 24 hours were <LoQ. As the rate at which the substance disappears from the test vessel is not monitored, it is also not possible to estimate a reliable time weighted average and to present a sensible value for EC₅₀.

Growth during the 0-24 hour period was 29% inhibited versus the controls but recovered by 48 hours. Overall, no significant effects on the algae growth rate were observed at 48 hours.

5.1.4 Sediment organisms

Experimental studies on sediment organisms are not available for EC 473-390-7.

5.1.5 Other aquatic organisms

Experimental studies on other aquatic organisms are not available for EC 473-390-7.

5.2 Terrestrial compartment

Experimental studies on terrestrial organisms are not available for EC 473-390-7.

5.3 Atmospheric compartment

No data available.

5.4 Microbiological activity in sewage treatment systems

In a static respiration inhibition test, performed with activated sludge of predominantly domestic sewage (study according to OECD Guideline 209), no reduction in respiration rate was recorded. The nominal concentration of the test item was 1000 mg/L, which is far above the water solubility of the substance (i.e., 0.066 mg/L). Therefore, it is concluded that the substance shows no toxicity for microorganisms at saturation. EC₅₀ (3h) is considered to be >0.066 mg/L.

5.5 Toxicity to birds

Experimental studies on birds are not available for EC 473-390-7.

5.6 Mammalian wildlife

No data available.

5.7 Endocrine disruption (Environment)

Not relevant for the identification of the substance as SVHC in accordance with Article 57(e) of the REACH Regulation.

5.8 Other effects

Not relevant for the identification of the substance as SVHC in accordance with Article 57(e) of the REACH Regulation.

5.9 Summary and discussion of the environmental hazard assessment

Short-term toxicity tests are available for fish and aquatic invertebrates. In these tests, it was not possible to create stable substance concentrations, and therefore reliable LC₅₀ or EC₅₀ values could not be determined. One can only qualitatively conclude that no mortality and limited immobilisation is observed in the exposed test organisms. No long-term toxicity tests are available and therefore, it cannot be ruled out that effects would occur after long-term exposure as it is most likely that the substance does not have time to reach steady-state in a short time period.

An algae growth inhibition test was performed and overall, no significant effects on the growth rate were observed at 48 hours. The substance shows no toxicity for microorganisms at saturation.

6. Conclusions on the SVHC Properties

6.1 CMR assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57(e) of the REACH Regulation.

6.2 PBT and vPvB assessment

6.2.1 Assessment of PBT/vPvB properties

A weight-of-evidence determination according to the provisions of Annex XIII of REACH is used to identify the substance as vPvB. All available information such as the results of standard tests, information from the application of the analogue approach (read-across) and (Q)SAR results was considered together in a weight-of-evidence approach. EC 473-390-7 is a substance that consists of two constituents whose chemical structures are very similar. Therefore, the vPvB assessment performed for EC 473-390-7 is also valid for the two individual constituents.

6.2.1.1 Persistence

The substance as such is registered under REACH, but substance specific studies relating to its degradation behaviour are very scarce. No indications are found that the substance can degrade to a relevant extent by abiotic processes under environmental conditions. Based on structural similarity, persistence in the air compartment is expected for EC 473-390-7 as analogous substances like perfluorocyclobutane show half-lives of more than 1000 years. Regarding biotic degradation, in a ready biodegradation test according to OECD TG 310 (reliable with restrictions) no degradation whatsoever is found. The lack of biodegradation is supported by QSAR predictions (low reliability) with EPI Suite (US EPA, 2000). A simulation study according to OECD TG 307, 308 or 309 is not available. Nevertheless, it is concluded that EC 473-390-7 meets the very persistent criterion (vP) in water, sediment and soil of REACH Annex XIII (degradation half-life >60 days in water and degradation half-lives >180 days in sediment or soil). This conclusion is underpinned by the following argumentation.

Perfluoroalkyl compounds all share high resistance to environmental and metabolic degradation. This resistance to degradation is primarily due to the high electronegativity and low polarisability of fluorine, which results in the strongest covalent bond known in organic chemistry: the C-F bond (Kissa, 2001). The C-F bond is resistant to acids, bases, oxidation and reduction, and also high temperatures. Multiple C-F bonds on the same geminal carbon lead to additional strengthening of the C-F bond. The strong electron withdrawing effect of the fluorine atoms in perfluoroalkyl moieties also strengthens the skeletal bonds in the carbon chain (O'Hagan, 2008). It is not expected that the length of the perfluoroalkyl chain has any major impact on the inherent stability of PFASs. Several perfluorinated substances have already been assessed in the framework of the REACH Regulation and concluded as very persistent (vP), e.g., PFOA (ECHA, 2013), C₉-C₁₄ PFCAs (ECHA, 2015), PFDA (ECHA, 2016), PFHxS and its salts (ECHA, 2017b), HFPO-DA (ECHA, 2019a), PFBS and its salts (ECHA, 2019b). For none of these compounds, potential degradation under relevant environmental conditions is demonstrated.

6.2.1.2 Bioaccumulation

According to the Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11, v3.0 (page 68, ECHA, 2017a), EC 473-390-7 meets the bioaccumulation screening criterion for aquatic organisms ($\log K_{ow} > 4.5$).

Based on the results from an experimental bioaccumulation study with aquatic organisms (reliable with restrictions) both kinetic and steady state BCFs were determined for EC 473-390-7. Detailed analysis of the available test data leads to a kinetic BCF_k of 9585. The lower and upper boundaries of the 95% confidence interval are respectively 5492 and 16726. The determination of a steady-state BCF_{ss} from the study is less robust, as it is not clear whether steady-state is actually reached at termination of the study. Assuming that steady-state was reached in the study, and applying the least conservative mathematical approach, a BCF of 8418 L/kg is calculated. Taking into account the underlying assumption, it is concluded that the real BCF_{ss} can only be greater than 8418 L/kg and that this value represents a minimal estimation. The very low depuration rate constant (k_2 of 0.0633 d^{-1}) derived from this bioaccumulation test further confirms the bioaccumulation potential of EC 473-390-7.

Experimental data on the bioaccumulation potential in terrestrial organisms is not available. However, it is noted that the screening criterion for air-breathing organisms/terrestrial bioaccumulation is not met. However, this screening information cannot be fully confirmed by available information on toxicological and pharmacokinetic studies in mammals as uncertainties remain regarding available toxicokinetic data.

Using a weight-of-evidence approach and considering that the lower limit of the 95% confidence interval for the kinetic BCF_k (i.e., 5492) and the minimal steady-state BCF_{ss} (i.e., 8418 L/kg) are greater than 5000 and the low depuration rate constant (k_2 of $0.0633/\text{d}$) of EC 473-390-7 is indicative of a $BCF > 5000$, it is concluded that EC 473-390-7 meets the 'bioaccumulation' criterion (B) and the 'very bioaccumulative' criterion (vB) in accordance with Annex XIII, points 1.2.1. and 1.2.2., of the REACH Regulation.

6.2.1.3 Toxicity

Relating to the T criterion for the environment only short-term toxicity tests with aquatic organisms are carried out. Based on the results from these tests with fish, aquatic invertebrates and algae there is no indication that the T criterion for the environment is met. However, long-term tests are not performed with the substance and so a definitive conclusion cannot be drawn. Indeed, it cannot be ruled out that effects would occur after long-term exposure as it is most likely that the substance does not have time to reach steady-state in a short-term test.

Further, it is noted that the substance does not meet any of the T criteria for human health since it is not classified for the endpoints: carcinogenicity, mutagenicity or reproductive toxicity. In the oral repeated dose study, a NOAEL of 1000 mg/kg bw/d was established and the substance is not classified as STOT RE.

6.2.2 Summary and overall conclusions on the PBT and vPvB properties

A weight-of-evidence determination according to the provisions of Annex XIII of REACH has been used to identify reaction mass of 2,2,3,3,5,5,6,6-octafluoro-4-(1,1,1,2,3,3,3-heptafluoro-propan-2-yl)morpholine and 2,2,3,3,5,5,6,6-octafluoro-4-(heptafluoropropyl)morpholine (referred to as 'EC 473-390-7' in this document) as vPvB. All available information such as the results of standard tests, information from the application of the analogue approach (read-across) and (Q)SAR results was considered together in a weight-of-evidence approach.

EC 473-390-7 is a substance that consists of two main constituents that are structural isomers. Their chemical structures are very similar. Therefore, the vPvB assessment performed for EC 473-390-7 is also valid for the two individual constituents.

Persistence

Based on a weight-of-evidence approach and considering assessment information in accordance with REACH Annex XIII Section 3.2.1.(d), it is concluded that EC 473-390-7 is very persistent due to its C-F bonds which cannot be broken under environmental conditions, and the abundant presence of fluorine atoms shields the carbon skeleton from other transformation reactions. This is supported by a ready biodegradation study (OECD TG 310; reliable with restrictions) which showed no degradation of EC 473-390-7 and by QSAR predictions (low reliability). No abiotic degradation is expected for this substance. Based on structural similarity, persistence in the air compartment is expected for EC 473-390-7 as analogous substances like perfluorocyclobutane show half-lives of more than 1000 years.

In summary, EC 473-390-7 is considered to be very persistent in all environmental compartments as no indications are found that it can undergo abiotic or biotic degradation under relevant environmental conditions. Half-lives are expected to largely exceed the triggers for 'persistence' (P) and 'very persistent' (vP) criteria (degradation half-life >60 days in water and degradation half-lives >180 days in sediment or soil) of REACH Annex XIII, exhibiting extreme persistence beyond current regulatory criteria.

Bioaccumulation

The substance screens as bioaccumulative according to REACH Guidance Chapter R.11 based on its $\log K_{ow} > 4.5$. Based on the results from an experimental bioaccumulation study (reliable with restrictions) with EC 473-390-7, a kinetic BCF_k and a steady-state BCF_{ss} were determined. Detailed analysis of the available test data leads to a kinetic BCF_k of 9585 with a 95% confidence interval of 5492–16726. Assuming that steady-state was reached in the study and applying the least conservative mathematical approach a BCF_{ss} of 8418 L/kg is calculated. Taking into account the underlying assumption, it is concluded that the real BCF_{ss} can only be greater than 8418 L/kg, and that this value represents a minimal estimation. The very low depuration rate constant (k_2 of 0.0633 d^{-1}) derived from this bioaccumulation test further confirms the bioaccumulation potential of EC 473-390-7.

Using a weight-of-evidence approach and considering that the lower limit of the 95% confidence interval for the kinetic BCF_k (i.e., 5492) and the estimation of the minimal steady-state BCF_{ss} (i.e., 8418 L/kg) are greater than 5000 and the low depuration rate constant (k_2 of 0.0633 d^{-1}) of EC 473-390-7 is indicative of a $BCF > 5000$, it is concluded

that EC 473-390-7 meets the 'bioaccumulation' criterion (B) and the 'very bioaccumulative' criterion (vB) in accordance with Annex XIII, points 1.2.1. and 1.2.2. of the REACH Regulation.

Conclusion on the P and B properties

Based on the information available and using a weight-of-evidence determination, it is concluded that EC 473-390-7 meets the criteria for a vPvB substance in accordance with Annex XIII of the REACH Regulation, and thereby it fulfils the criteria set out in REACH Article 57(e).

6.3 Assessment under Article 57(f)

Not relevant for the identification of the substance as SVHC in accordance with Article 57(e) of the REACH Regulation.

Part II

7. Registration and C&L notification status

7.1 Registration status

Table 12: Registration status

From the ECHA dissemination site ¹	
Registrations	☒ Full registration(s) (Art. 10) ☐ Intermediate registration(s) (Art. 17 and/or 18)

7.2 CLP notification status

Table 13: CLP notifications

	CLP Notifications ²
Number of aggregated notifications	2
Total number of notifiers	1

8. Total tonnage of the substance

Table 14: Tonnage status

Total tonnage band for the registered substance (excluding the volume registered under Art 17 or Art 18) ³	10-100 t/a
Tonnage information from public sources other than registration dossiers (if available)	not available

¹ Registration dossier, <https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/3563> (accessed 27 July 2022)

² C&L Inventory database, <https://echa.europa.eu/nl/information-on-chemicals/cl-inventory-database/-/discli/details/19953> (accessed 27 July 2022)

³ Registration dossier, <https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/3563> (accessed 27 July 2022)

9. Information on uses of the substance

Table 15: Uses

	Use(s)	Registered use	Use <u>likely</u> to be in the scope of Authorisation
Uses as intermediate	-	No	No
Formulation or repacking	Use name: re-packaging of substance. Transfer of substance or mixture (charging and discharging) at dedicated facilities. Formulation into mixture.	Yes	Yes
Uses at industrial sites	Use name: industrial use in closed systems. Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions. Transfer of substance or mixture (charging and discharging) at dedicated facilities. Use as laboratory reagent. Use as functional fluid at industrial site.	Yes	Yes
Uses by professional workers	Use name: professional use in closed systems. Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions. Transfer of substance or mixture (charging and discharging) at dedicated facilities. Use as laboratory reagent. Widespread use of functional fluid indoor.	Yes	Yes
Consumer uses	-	No	No
Article service life	Service life name: Article service life of filled equipment. Low energy manipulation of substance bound in materials and/or articles. Widespread use of articles with low	Yes	Yes

	release (outdoor). Widespread use of articles with low release (indoor).		
--	---	--	--

10. Information on structure of the supply chain

No information available.

11. Additional information

11.1 Substances with similar hazard and use profiles on the Candidate List

A series of perfluorinated substances is already identified as SVHC (PFHxS and its salts, PFBS and its salts, HFPO-DA, PFOA, C₉-C₁₄ PFCAs). For some of these substances, i.e., C₁₁-C₁₄ PFCAs, PFHxS and its salts, the identification as SVHC was (also) based on Article 57(e) of the REACH Regulation.

The technical function(s) of EC 473-390-7 as described in the registration dossier (i.e., confidential business information) are not mentioned in the publicly available use information on the perfluorinated substances identified as SVHC.

11.2 Alternatives

Information on potential alternatives is not available.

11.3 Existing EU legislation

EC 473-390-7 is at the moment not covered by EU legislation.

11.4 Previous assessments by other authorities/ongoing regulatory activities

EC 473-390-7 is not assessed by other authorities.

REFERENCES

References for Part I

- CEMC. EQUilibrium Criterion Model, developed by the Canadian Environmental Modelling Centre, Trent University, Peterborough, Ontario, Canada.
- EAWAG BBD software, accessible via <http://eawag-bbd.ethz.ch/index.html> ; Gao J., Ellis L.B.M., Wackett L.P. (2010). The University of Minnesota Biocatalysis/Biodegradation Database: improving public access, *Nucleic Acids Research*, 38, D488-491.
- ECHA Disseminated dossier 2022. Disseminated dossier for reaction mass of 2,2,3,3,5,5,6,6-octafluoro-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)morpholine and 2,2,3,3,5,5,6,6-octafluoro-4-(heptafluoropropyl)morpholine. Information on registered substances, published on ECHA's website <https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/3563>
- ECHA. EUSES v2.2.0, accessible via <https://echa.europa.eu/en/support/dossier-submission-tools/euses>
- ECHA 2012a. Member State Committee support document for identification of henicosafuoroundecanoic acid as a substance of very high concern because of its vPvB properties. Helsinki, Finland.
- ECHA 2012b. Member State Committee support document for identification of heptacosafuorotetradecanoic acid as a substance of very high concern because of its vPvB properties. Helsinki, Finland.
- ECHA 2012c. Member State Committee support document for identification of nonadecafluorodecanoic acid and its sodium and ammonium salts as a substance of very high concern because of its toxic for reproduction and PBT properties. Helsinki, Finland.
- ECHA 2012d. Member State Committee support document for identification of pentacosafuorotridecanoic acid as a substance of very high concern because of its vPvB properties. European Chemicals Agency. Helsinki, Finland.
- ECHA 2012e. Member State Committee support document for identification of tricosafuorododecanoic acid as a substance of very high concern because of its vPvB properties. European Chemicals Agency. Helsinki, Finland.
- ECHA 2013. Member State Committee support document for identification of pentadecafluorooctanoic acid (PFOA) as a substance of very high concern because of its CMR and PBT properties. Helsinki, Finland.
- ECHA 2015. Member State Committee support document for identification of perfluorononan-1-oic acid (PFNA) and its sodium and ammonium salts as a substance of very high concern because of its toxic for reproduction, PBT properties. Helsinki, Finland.
- ECHA 2016. Member State Committee support document for identification of nonadecafluorodecanoic acid (PFDA) and its sodium and ammonium salts as a substance of very high concern because of its toxic for reproduction (Article 57c) and persistent, bioaccumulative and toxic (PBT) (Article 57d) properties. Helsinki, Finland.
- ECHA 2017a. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB assessment Version 3.0. June 2017.
- ECHA 2017b. Member State Committee Support Document for identification of

- perfluorohexane-1-sulphonic acid and its salts as substances of very high concern because of their vPvB (article 57e) properties. Helsinki, Finland.
- ECHA 2017c. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7c: Endpoint specific guidance Version 3.0. June 2017.
- ECHA 2019a. Member State Committee Support Document for identification of 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propionic acid, its salts and its acyl halides (covering any of their individual isomers and combinations thereof) as substances of very high concern because of their hazardous properties which cause probable serious effects to human health and the environment which give rise to an equivalent level of concern to those of CMR and PBT/vPvB substances (article 57f). Helsinki, Finland.
- ECHA 2019b. Member State Committee Support Document for identification of perfluorobutane sulphonic acid and its salts as substances of very high concern because of their hazardous properties which cause probable serious effects to human health and the environment which give rise to an equivalent level of concern to those of CMR and PBT/vPvB substances (article 57f). Helsinki, Finland.
- Kissa E., 2001. Fluorinated surfactants and repellents, CRC Press.
- LMC 2022. BCF base-line model developed by the Laboratory of Mathematical Chemistry, Burgas, Bulgaria.
- Mackay D., Shiu W.Y., Ma K.-C., Lee S.C. (2006). Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals. <https://doi.org/10.1201/9781420044393>
- OECD 2012. Test No. 305: Bioaccumulation in Fish: Aqueous and Dietary Exposure. <https://doi.org/10.1787/2074577x>
- O'Hagan D., 2008. Understanding organofluorine chemistry. An introduction to the C-F bond. Chemical society reviews, 37, p. 308-319.
- Prather M., Ehhalt D., Dentener F., Derwent R., Duglokencky E., Holland E., Isaksen I., Katima J., Kirchhoff V., Matson P., Midgley P., Wang M., Atmospheric Chemistry and Greenhouse Gases, Chapter 4 of the IPCC Third Assessment Report Climate Change 2001: the scientific basis.
- Siegemund G., Schwertfeger W., Feiring A., Smart B., Behr F., Vogel H., McKusick B., (2012), Fluorine Compounds, Organic. Ullmann's Encyclopedia of Industrial Chemistry. Weinheim, Germany, Wiley-VCH Verlag GmbH & Co., KGaA.
- US EPA (2000). Estimation Programs Interface (EPI) Suite™, v4.1., developed by United States Environmental Protection Agency, Washington, DC, USA.
- VEGA HUB 2022. Developed by Laboratory of Environmental Chemistry and Toxicology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy.

References for Part II

- ECHA (2022): reaction mass of 2,2,3,3,5,5,6,6-octafluoro-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)morpholine and 2,2,3,3,5,5,6,6-octafluoro-4-(heptafluoropropyl)morpholine. Information on registered substances, published on ECHA's website <https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/3563> (accessed on 27 July 2022).
- ECHA (2022): reaction mass of 2,2,3,3,5,5,6,6-octafluoro-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)morpholine and 2,2,3,3,5,5,6,6-octafluoro-4-(heptafluoropropyl)morpholine. C&L Inventory database, published on ECHA's website <https://echa.europa.eu/nl/information-on-chemicals/cl-inventory-database/-/discli/details/19953> (accessed on 27 July 2022).